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Ligand-Free Palladium-Catalyzed Direct Arylation of Thiazoles at Low Catalyst Loadings

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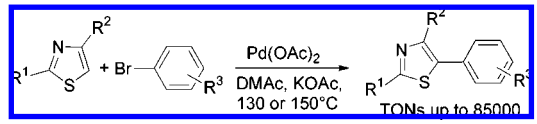

Ligand-free $Pd(OAc)_2$ was found to catalyze very efficiently the direct arylation of thiazole derivatives under very low catalyst concentration. By using activated aryl bromides, the reaction can be performed employing as little as 0.1−0.001 mol % catalyst. With such substrates, this procedure is economically and environmentally attractive. On the other hand, in the presence of more challenging substrates, such as some strongly deactivated or highly congested aryl bromides, in some cases, disappointing results were obtained.

Introduction

The arylation of heteroaromatics, such as thiophenes, furans, pyrroles, thiazoles, or oxazoles, is an important field for research in organic synthesis due to the biological and physical properties of such compounds.[1] Palladium-catalyzed Suzuki,[2] Stille,[3] or Negishi[4] cross-couplings are among the most important methods to perform such reactions. However, they require the preparation of an organometallic derivative and provide an organometallic salt (MX) as byproduct. Therefore, these reactions are not economically and environmentally attractive. In 1990, Ohta et al. reported the direct arylation of thiophenes, furans, or thiazoles with aryl halides via a C−H bond activation in moderate to good yields using 5 mol % of $Pd(PPh_3)_4$ as catalyst.[5] Since these exciting results, the palladium-catalyzed direct arylation of heteroaryl derivatives with aryl halides or triflates has proved to be a powerful method for the synthesis of arylated heterocycles.[6,7] This method provides a cost-effective and environmentally attractive procedure for the preparation of arylated heteroaromatics due to the reduced number of steps, reduced amount of waste, and the wider diversity of available compounds. The major drawback of the reported procedures is that they generally require 5−10 mol % of palladium catalyst associated with 5−20 mol % of mono-[8] or bidentate[9] phosphine ligands. Only a few examples of such reactions with low catalyst loadings have been reported to date.[10]

De Vries and co-workers have recently described extremely promising results for the Heck and Suzuki reactions under low

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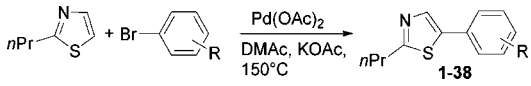
TABLE 1. Direct Arylation of 2-*n*-Propylthiazole with Para-Substituted Bromobenzenes (Scheme 1)[b]

Entry	Aryl bromide	Substrate-catalyst ratio	Product	Yield (%)
1	MeOC–Br	10000	MeOC–(thiazole)–*n*Pr **1**	100 (94)
2		100000		79
3	EtOC–Br	1000	EtOC–(thiazole)–*n*Pr **2**	100 (89)
4		10000		54
5	OHC–Br	1000	OHC–(thiazole)–*n*Pr **3**	100 (95)
6		10000		55
7	MeO_2C–Br	250	MeO_2C–(thiazole)–*n*Pr **4**	100
8		1000		80 (72)
9	PhOC–Br	1000	PhOC–(thiazole)–*n*Pr **5**	100 (94)
10		10000		67
11	F_3C–Br	10000	F_3C–(thiazole)–*n*Pr **6**	100 (93)
12		100000		14
13	NC–Br	10000	NC–(thiazole)–*n*Pr **7**	94 (89)
14		100000		54
15	O_2N–Br	1000	O_2N–(thiazole)–*n*Pr **8**	53 (46)[a]
16	F–Br	10000	F–(thiazole)–*n*Pr **9**	95 (90)
17	Me–Br	1000	Me–(thiazole)–*n*Pr **10**	96 (89)
18	*t*Bu–Br	1000	*t*Bu–(thiazole)–*n*Pr **11**	75 (71)
19	MeO–Br	100	MeO–(thiazole)–*n*Pr **12**	88 (77)
20		1000		88 (79)
21	Me_2N–Br	100	Me_2N–(thiazole)–*n*Pr **13**	52 (42)
22		250		40
23		1000		52 (44)

[a] Reaction temp 120 °C. [b] Conditions: catalyst $Pd(OAc)_2$, aryl bromide (1 mmol), 2-*n*-propylthiazole (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, under argon, GC and NMR yields, yields in parentheses are isolated.

SCHEME 1. Direct Arylation of 2-*n*-Propylthiazole



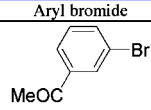
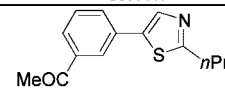
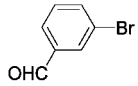
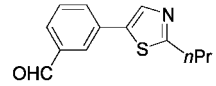
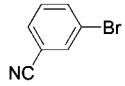
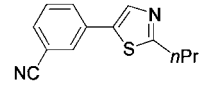
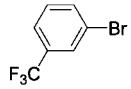
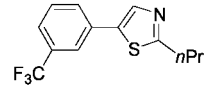
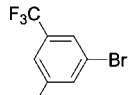
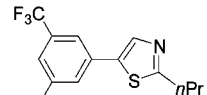
catalyst loading (0.1−0.01 mol %) using ligand-free catalyst $Pd(OAc)_2$.[11,12] They have demonstrated that, at elevated temperature, when $Pd(OAc)_2$ is employed as the catalyst precursor, soluble palladium(0) colloids or nanoparticles are formed, and that the Heck or Suzuki reaction takes place via the interaction of the arylating agent with the palladium atoms in the outer rim of the nanoparticles. This leads to the formation of the monomeric or dimeric anionic palladium complexes that undergo the usual steps of the Heck or Suzuki mechanisms.

To our knowledge, so far, only one procedure using ligand-free palladium catalyst for the 5-arylation of thiazoles via C−H bond activation has been described.[13] Fagnou and co-workers have reported the 5-arylation of thiazole with 4-bromotoluene in 71% yield in the presence of 10 mol % of $Pd(OH)_2/C$ as catalyst.[13] The use of ligand-free $Pd(OAc)_2$ for the direct arylation of heteroaromatics has been reported for the 2-arylation of pyrroles or indoles. For these reactions, 1 mol % of catalyst was employed.[14] Therefore, the discovery of more effective conditions, for the direct coupling of thiazole derivatives with aryl bromides using a ligand-free catalyst, especially under low catalyst loading conditions (less than 0.1 mol %), would be a considerable advantage for industrial applications and also for sustainable development. We have already reported preliminary results for the 5-arylation of thiazole, furans, or thiophene derivatives using ligand-free palladium catalyst.[15] Here, we wish to report on the reaction of a set of thiazoles using a very wide variety of electronically and sterically diverse aryl or heteroaryl bromides at low catalyst loadings.

Results and Discussion

First, we studied the coupling of 4-bromoacetophenone with 2-*n*-propylthiazole employing the "de Vries low catalyst loading procedure": elevated reaction temperature, polar solvent, acetate as base, no ligand on palladium, and a low concentration of

TABLE 2. Direct Arylation of 2-*n*-Propylthiazole with Meta-Substituted Bromobenzenes (Scheme 1)[a]

Entry	Aryl bromide	Substrate-catalyst ratio	Product	Yield (%)
1		10000	 **14**	100 (90)
2		1000	 **15**	100 (91)
3		10000		50
4		1000	 **16**	100 (93)
5		10000		65
6		1000	 **17**	100 (93)
7		10000		95
8		1000		100 (92)
9		10000		93

[a] Conditions: catalyst $Pd(OAc)_2$, aryl bromide (1 mmol), 2-*n*-propylthiazole (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, under argon, GC and NMR yields, yields in parentheses are isolated.

$Pd(OAc)_2$. We observed that using such conditions in the presence of as little as 0.01 mol % of catalyst, the selective formation of 1-[4-(2-propylthiazol-5-yl)phenyl]ethanone **1** was observed with complete conversion of the aryl bromide and a very high isolated yield (Scheme 1, Table 1, entry 1). No formation of side products was detected during the course of this reaction. With this procedure, the priority for the arylation or 2-substituted thiazoles is clearly the 5-position. The 4-arylation product, which was formed with another procedure,[8e] was not detected. Moreover, the homocoupling product of 4-bromoacetophenone, which is often observed in palladium-catalyzed reactions, was not observed.

Then, we examined the scope and limitations of this procedure using para-, meta-, or ortho-substituted aryl bromides (Tables 1−3) and also heteroaryl bromides (Table 4). Electron-deficient aryl bromides, 4-trifluoromethylbromobenzene and 4-bromobenzonitrile also gave selectively arylated products **6** and **7** in very high yields of 93% and 89% and turnover numbers (TONs) of 14 000 and 54 000, respectively (Table 1, entries 11−14). 4-Bromopropiophenone, 4-bromobenzaldehyde, methyl 4-bromobenzoate, or 4-bromobenzophenone were found to be slightly less reactive and TONs of 800−6700 were obtained. With these substrates, in all cases, good isolated yields of target compounds **2**−**5** were obtained employing only 0.1 mol % of catalyst (Table 1, entries 3−10). Using this substrate/catalyst ratio, 4-bromonitrobenzene gave **8** in moderate yield. This is probably due to the partial poisoning of the catalyst in the presence of this substrate (Table 1, entry 15). Activated aryl bromide, 4-fluorobromobenzene reacted with 2-*n*-propylthiazole gave the expected product **9** in high TON of 9000 and in high yield (90%) (Table 1, entry 16). Deactivated aryl bromides, 4-bromotoluene, 4-*tert*-butylbromobenzene, or 4-bromoanisole gave **10**−**12** in 89%, 71%, and 79% yields, respectively, using 0.1 mol % of catalyst (Table 1, entries 17−20). On the other hand, using the strongly deactivated aryl bromide, 4-bromo-*N*,*N*-dimethylaniline, in the presence of 0.1 mol % of catalyst, **13** was obtained in only 44% yield (Table 1, entry 23). For this reaction the oxidative addition of aryl bromide to palladium appears to be the rate-limiting step of the catalytic cycle. Interestingly, for the reactions with 4-bromoanisole or 4-bromo-*N*,*N*-dimethylaniline, the yields of **12** and **13** were not improved by an increase of the catalyst loading from 0.1 to 0.4 or 1 mol %, revealing that the concentration of active Pd species is relatively similar with these three different concentrations of $Pd(OAc)_2$. For this ligand-free procedure, under relatively high palladium concentrations, so-called "palladium black" forms more rapidly. This "palladium black" is generally inactive for such catalyzed reactions. Consequently the conversions of aryl bromides and the yields of coupling products are not increased by a higher catalyst loading.

Next, we examined the reactivity of meta-substituted aryl bromides with 2-*n*-propylthiazole (Table 2). As expected, the electron-deficient aryl bromides, 3-bromoacetophenone, 3-bromobenzaldehyde, 3-bromobenzonitrile, or 3-trifluoromethylbromobenzene could be reacted by using similar substrate/catalyst ratios as the para-substituted aryl bromides. In all cases, using only 0.1−0.01 mol % of catalyst, the desired products **14**−**17** were obtained in good yields and TONs of 6500−10000.

Ortho substituents on the aryl bromides generally have a more important effect on the reactions rates and yields of Heck

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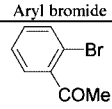
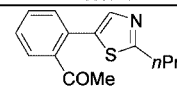
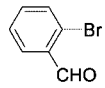
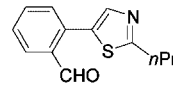
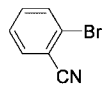
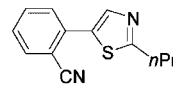
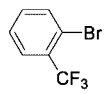
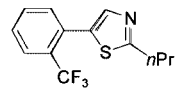
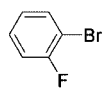
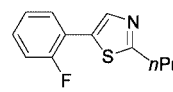
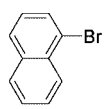
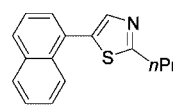
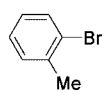
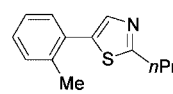
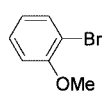
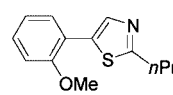
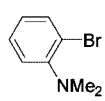
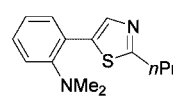
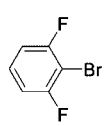
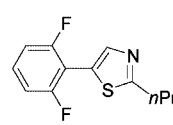
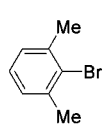
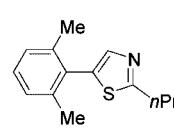
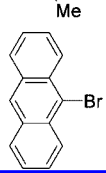
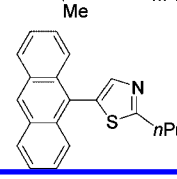
TABLE 3. Direct Arylation of 2-*n*-Propylthiazole with Ortho-Substituted Bromobenzenes (Scheme 1)[a]

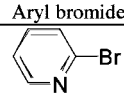
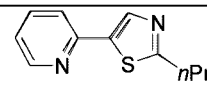
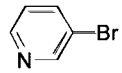
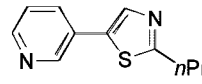
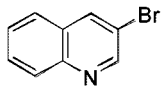
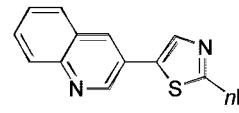
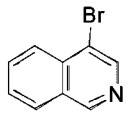
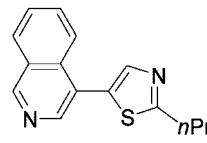
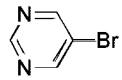
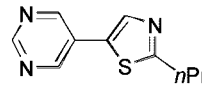
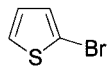
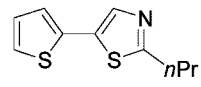
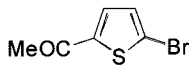
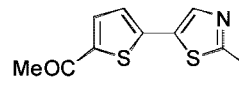
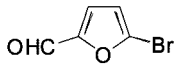
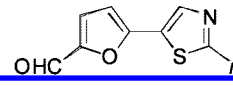
Entry	Aryl bromide	Substrate-catalyst ratio	Product	Yield (%)
1		250	 **19**	mixture
2		1000		0
3		1000	 **20**	98 (90)
4		10000	 **21**	97 (91)
5		1000	 **22**	100 (91)
6		1000	 **23**	78 (74)
7		1000	 **24**	100 (92)
8		10000		97
9		1000	 **25**	90 (82)
10		250	 **26**	0
11		1000		0
12		250	 **27**	0
13		1000		0
14		1000	 **28**	72 (66)
15		100	 **29**	0
16		250		0
17		1000		0
18		250	 **30**	100 (75)

[a] Conditions: catalyst $Pd(OAc)_2$, aryl bromide (1 mmol), 2-*n*-propylthiazole (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, under argon, GC and NMR yields, yields in parenthesis are isolated.

reactions due to their steric or coordination properties. In some cases, similar yields, as in the presence of the para-substituted aryl bromides, were obtained (Table 3). We observed that the coupling of 2-bromobenzonitrile or 1-bromonaphthalene with 2-*n*-propylthiazole proceeds nicely with only 0.01 mol % of catalyst to give **21** and **24** in very high yields (Table 3, entries 4, 7, and 8). On the other hand, in the presence of 2-bromobenzaldehyde, 2-trifluoromethylbromobenzene, and 2-fluorobromobenzene, 0.1 mol % of catalyst had to be employed, instead of 0.01 mol % with the para-substituted aryl bromides, in order to obtain high conversions of the starting material (Table 3, entries 3, 5, and 6). 2-Bromoacetophenone was found to be unreactive or gave unidentified products, even with 0.4 mol % of catalyst (Table 3, entries 1 and 2). This is probably due to the coordination of the acetyl function to palladium. The reactivity of a few electron-rich ortho-substituted aryl bromides has also been examined. 2-Bromotoluene gave **25** in good yield with 0.1 mol % of catalyst (Table 3, entry 9), whereas 2-bromoanisole and 2-bromo-*N*,*N*-dimethylaniline were recovered unreacted (Table 3, entries 10−13).

Next, we tried to evaluate the difference in the reactivity between mono- and di-ortho-substituted aryl bromides, and we observed that 2,6-difluorobromobenzene and even the highly hindered aryl bromide (9-bromoanthracene) could be employed

TABLE 4. Direct Arylation of 2-*n*-Propylthiazole with Heteroaryl Bromides (Scheme 1)[a]

Entry	Aryl bromide	Substrate-catalyst ratio	Product	Yield (%)
1		250	 **31**	0
2		1000		0
3		10000	 **32**	100 (96)
4		100000		85
5		1000	 **33**	100 (94)
6		10000		51
7		1000	 **34**	83 (74)
8		1000	 **35**	94 (87)
9		250	 **36**	85 (62)
10		1000		60
11		1000	 **37**	70 (61)
12		1000	 **38**	90 (82)

[a] Conditions: catalyst $Pd(OAc)_2$, aryl bromide (1 mmol), 2-*n*-propylthiazole (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, under argon, GC and NMR yields, yields in parentheses are isolated.

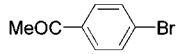
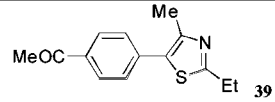
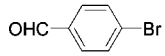
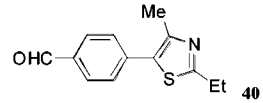
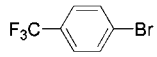
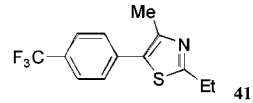
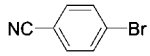
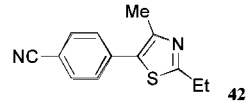
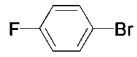
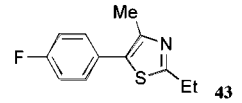
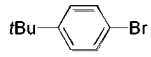
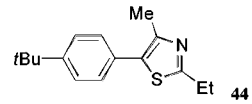
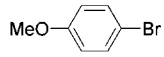
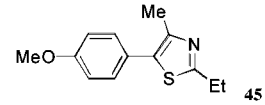
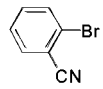
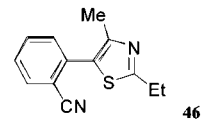
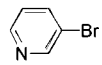
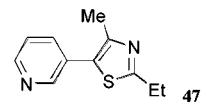
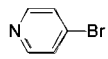
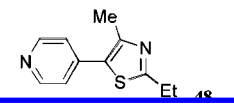
successfully (Table 3, entries 14 and 18). By using these substrates, the products **28** and **30** were isolated in 66% and 75% yields, respectively. On the other hand, in the presence of sterically congested 2,6-dimethylbromobenzene, no coupling product was obtained (Table 3, entries 15−17). With this substrate, we have employed substrate/catalyst ratios of 100, 250, or 1000, but in all cases, the target product **29** was not detected.

This ligand-free procedure is not limited to aryl bromides. Heteroaryl bromides are also suitable reactants (Table 4). Pyridines are π-electron deficient and therefore the oxidative addition of bromopyridines to palladium is, in general, relatively easy. With 3-bromopyridine, 3-bromoquinoline, or 4-bromoisoquinoline, **32**−**34** were obtained in high TONs of 830−85000 by using only 0.1−0.001 mol % of catalyst (Table 4, entries 3−7). A high yield was also obtained with 5-bromopyrimidine (Table 4, entry 8). These reactions are extremely clean, and very high isolated yields were obtained in most cases. On the other hand, 2-bromopyridine gave no coupling product **31** (Table 4, entries 1 and 2). This result seems to indicate that, with this substrate, an interaction between the heteroelement and the palladium complex has a poisoning effect. Furans and thiophenes are π-electron excessive and their oxidative addition to palladium is generally slower than that with pyridines. However, 2-bromothiophene and 2-acetyl-5-bromothiophene gave **36** and **37** in 62% and 61% yields, respectively, using 0.4 and 0.1 mol % of catalyst (Table 4, entries 9 and 10). The formation of unidentified side products was also observed in the course of these reactions. 5-Bromofuraldehyde gave **38** in a high yield of 82% with a TON of 900 (Table 4, entry 12).

Sterically hindered 2-ethyl-4-methylthiazole has been employed to determine the influence of a 4-substitution on thiazole on the reaction rates with this ligand-free procedure (Table 5). In most cases, this substrate was found to be less reactive than 2-*n*-propylthiazole by a factor of 10. For example, using electron-deficient aryl bromides such as 4-bromoacetophenone or 4-bromobenzonitrile TONs of 6600 and 2600 were obtained with 2-ethyl-4-methylthiazole, whereas with 2-*n*-propylthiazole, TONs of 79 000 and 54 000 had been obtained (compare Table 5 entries 2 and 6 with Table 1 entries 2 and 14). A very similar trend was observed with 4-fluorobromobenzene (TONs of 930 instead of 9500; compare Table 5 entry 7 and Table 1 entry 16) or 2-bromobenzonitrile (TONs of 1000 instead of 9700; compare Table 5 entry 11 and Table 3 entry 4). However, in most cases, high yields of target coupling products **39**−**48** were obtained by using as little as 0.1 mol % of catalyst. Therefore, with this substrate also, this ligand-free procedure is very attractive in terms of catalyst cost.

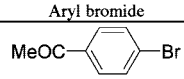
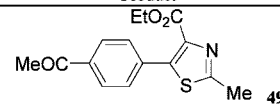
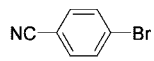
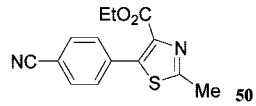
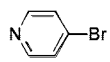
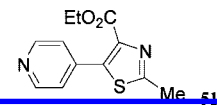
This procedure also tolerates functionalized thiazole derivatives. For example, ethyl 2-methylthiazole-4-carboxylate has been coupled successfully with 4-bromoacetophenone, 4-bromobenzonitrile, or 4-bromopyridine (Table 6). In the course of

TABLE 5. Direct Arylation of 2-Ethyl-4-Methylthiazole with Bromobenzene Derivatives (Scheme 2)[b]

Entry	Aryl bromide	Substrate-catalyst ratio	Product	Yield (%)
1		1000	 **39**	100 (93)
2		10000		66
3		1000	 **40**	100 (90)
4		1000	 **41**	100 (90)
5		1000	 **42**	100 (88)
6		10000		26
7		1000	 **43**	93 (87)
8		250	 **44**	82 (74)
9		250	 **45**	85 (76)
10		1000		15
11		1000	 **46**	100 (90)
12		1000	 **47**	100 (91)
13		250	 **48**	100[a]
14		1000		99 (89)[a]

[a] 4-Bromopyridine hydrochloride was used with 3 mmol of KOAc. [b] Conditions: catalyst $Pd(OAc)_2$, aryl bromide (1 mmol), 2-ethyl-4-methylthiazole (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, under argon, GC and NMR yields, yields in parentheses are isolated.

TABLE 6. Direct Arylation of Ethyl 2-Methylthiazole-4-carboxylate with Bromobenzene Derivatives (Scheme 3)[b]

Entry	Aryl bromide	Product	Yield (%)
1		 **49**	78 (68)
2		 **50**	63 (54)
3		 **51**	80 (70)[a]

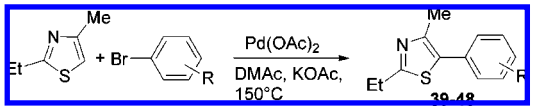
[a] 4-Bromopyridine hydrochloride was used with 3 mmol of KOAc. [b] Conditions: catalyst $Pd(OAc)_2$ (0.004 mmol), aryl bromide (1 mmol), ethyl 2-methylthiazole-4-carboxylate (2 mmol), KOAc (2 mmol), DMAc, 3 h, 150 °C, under argon, GC and NMR yields, yields in parentheses are isolated.

TABLE 7. Direct Arylation of Thiazole or 4-Methylthiazole with Bromobenzene Derivatives (Scheme 4)[a]

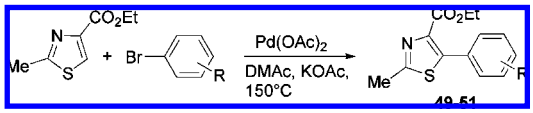
Entry	Aryl bromide	Thiazole	Substrate-catalyst ratio	Product	Yield (%)
1	MeOC–C$_6$H$_4$–Br		250		100 (90)
2			1000	**52**	38
3	NC–C$_6$H$_4$–Br		250		100 (88)
4			1000	**53**	50
5	MeOC–C$_6$H$_4$–Br		1000		100 (89)
6			10000	**54**	70
7	NC–C$_6$H$_4$–Br		1000		100 (90)
8			10000	**55**	95
9	Br–C$_5$H$_4$N		1000		100 (86)
10			10000	**56**	82

[a] Conditions: catalyst $Pd(OAc)_2$, aryl bromide (1 mmol), thiazole or 4-methylthiazole (2 mmol), KOAc (2 mmol), DMAc, 20 h, 130 °C for the reactions with thiazole, 150 °C for the reactions with 4-methylthiazole, under argon, GC and NMR yields, yields in parentheses are isolated.

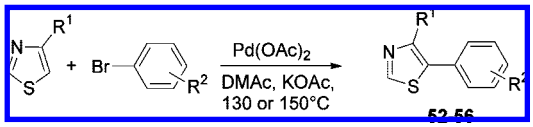
SCHEME 2. Direct Arylation of 2-Ethyl-4-methylthiazole



SCHEME 3. Direct Arylation of Ethyl 2-Methylthiazole-4-carboxylate



SCHEME 4. Direct Arylation of Thiazole or 4-Methylthiazole



this reaction, some decarboxylation of thiazole was observed when long reaction times were employed. However, the reactions are quite clean when they are stopped after 3 h, and relatively high yields of products **49**−**51** were isolated. These reactions were performed with only 0.4 mol % of catalyst.

Finally, we studied this reaction using thiazole or 4-methylthiazole (Scheme 4, Table 7). With these two substrates, we could have observed the 2- or the 5-arylation products. However, in all cases, only the 5-arylation products were formed. The 2-arylated or 2,5-diarylated thiazoles were not detected. Such regioselective 5-arylation of thiazole had already been reported by Fagnou and co-workers.[13] Using the "$Pd(OAc)_2$ ligand-free procedure", the reactions with thiazole and 4-bromoacetophenone or 4-bromobenzonitrile at 130 °C allow the formation of products **52** and **53** in 90% and 88% yields, respectively (Table 7, entries 1−4). With this reactant substrate/catalyst ratios of 250 or 1000 were employed. Coupling reactions using 4-methylthiazole with 4-bromoacetophenone, 4-bromobenzonitrile, or 3-bromopyridine were performed at 150 °C in the presence of only 0.1−0.01 mol % of catalyst (Table 7, entries 5−10). Again, only the 5-arylation products were formed, and compounds **54**−**56** were obtained in 86−90% yields.

Conclusion

In summary, we have demonstrated that the "de Vries ligand-free palladium procedure" is not limited to Heck or Suzuki reactions. By using as little as 0.4−0.001 mol % of $Pd(OAc)_2$ as catalyst precursor, the direct 5-arylation via C−H bond activation of thiazole derivatives proceeds in moderate to very high yields. With this ligand-free procedure, an increase of the catalyst loading to 1 mol % generally led more rapidly to aggregation of palladium to form so-called "palladium black" and no improvement in the yield of coupling products was observed. Therefore, this procedure is limited to activated and some deactivated aryl bromides. However, it should be noted that a wide range of functions such as acetyl, benzoyl, formyl, nitro, nitrile, fluoro, methoxy, or trifluoromethyl on the aryl bromide are tolerated. Satisfactory results were also obtained with use of some sterically congested aryl bromides and heteroaryl bromides. This low catalyst loading procedure is economically and environmentally attractive. The only byproducts are AcOH/KBr instead of metallic salts with classical coupling procedures such as Suzuki, Stille, or Negishi reactions. Moreover, no preparation of an organometallic derivative is required, reducing the number of steps and consequently the amount of waste to prepare these compounds.

Experimental Section

General Procedure. As a typical experiment, the reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-*n*-propylthiazole (0.254 g, 2 mmol), and KOAc (0.196 g, 2 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $Pd(OAc)_2$ (0.0224 mg, 0.0001 mmol) under argon affords the corresponding product 1-[4-(2-propylthiazol-5-yl)phenyl]ethanone[9d] (**1**) after extraction with dichloromethane, evaporation, and filtration on silica gel (pentane/ether) in 94% (0.231 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.90 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H), 3.01 (t, J = 7.4 Hz, 2H), 2.58 (s, 3H), 1.85 (sext., J = 7.4 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H).

1-[4-(2-Propylthiazol-5-yl)phenyl]propan-1-one (2) (Table 1, entry 3). The reaction of 4-bromopropiophenone (0.213 g, 1 mmol), 2-*n*-propylthiazole (0.254 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.224 mg, 0.001 mmol) in DMAc at 150 °C affords the corresponding product **2** in 89% (0.231 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H),

7.50 (d, $J = 8.0$ Hz, 2H), 2.91 (m, 4H), 1.78 (sext., $J = 7.4$ Hz, 2H), 1.15 (t, $J = 7.1$ Hz, 3H), 0.96 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.6, 171.9, 138.8, 137.1, 135.9, 128.7, 126.3, 35.6, 31.7, 23.2, 13.6, 8.2. Anal. Calcd for $C_{15}H_{17}NOS$ (259.36): C 69.46, H 6.61. Found: C 69.47, H 6.50.

1-[3-(2-Propylthiazol-5-yl)phenyl]ethanone (14) (Table 2, entry 1). The reaction of 3-bromoacetophenone (0.199 g, 1 mmol), 2-*n*-propylthiazole (0.254 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.0224 mg, 0.0001 mmol) in DMAc at 150 °C affords the corresponding product **14** in 90% (0.221 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.81 (s, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 2.92 (t, $J = 7.6$ Hz, 2H), 2.56 (s, 3H), 1.80 (sext., $J = 7.6$ Hz, 2H), 1.00 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.4, 171.3, 138.2, 137.7, 137.2, 132.2, 130.8, 129.3, 127.7, 126.0, 35.5, 26.6, 23.3, 13.6. Anal. Calcd for $C_{14}H_{15}NOS$ (245.34): C 68.54, H 6.16. Found: C 68.57, H 6.19.

2-(2-Propylthiazol-5-yl)benzaldehyde (20) (Table 3, entry 3).[9d] The reaction of 2-bromobenzaldehyde (0.185 g, 1 mmol), 2-*n*-propylthiazole (0.254 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.224 mg, 0.001 mmol) in DMAc at 150 °C affords the corresponding product **20** in 90% (0.208 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.55 (m, 2H), 7.44 (m, 2H), 2.98 (t, $J = 7.1$ Hz, 2H), 1.82 (sext., $J = 7.1$ Hz, 2H), 1.01 (t, $J = 7.1$ Hz, 3H).

3-(2-Propylthiazol-5-yl)pyridine (32) (Table 4, entry 3). The reaction of 3-bromopyridine (0.158 g, 1 mmol), 2-*n*-propylthiazole (0.254 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.0224 mg, 0.0001 mmol) in DMAc at 150 °C affords the corresponding product **32** in 96% (0.196 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.54 (d, $J = 4.2$ Hz, 1H), 7.87 (s, 1H), 7.84 (d, $J = 7.2$ Hz, 1H), 7.33 (dd, $J = 7.2$ and 4.2 Hz, 1H), 3.01 (t, $J = 7.5$ Hz, 2H), 1.88 (sext., $J = 7.5$ Hz, 2H), 1.05 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 149.4, 147.9, 139.1, 134.9, 134.0, 128.3, 124.1, 36.0, 23.7, 14.1;. Anal. Calcd for $C_{11}H_{12}N_2S$ (204.29): C 64.67, H 5.92. Found: C 64.87, H 5.90.

1-[4-(2-Ethyl-4-methylthiazol-5-yl)phenyl]ethanone (39) (Table 5, entry 1). The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-ethyl-4-methylthiazole (0.254 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.224 mg, 0.001 mmol) in DMAc at 150 °C affords the corresponding product **39** in 93% (0.228 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (d, $J = 7.1$ Hz, 2H), 7.45 (d, $J = 7.1$ Hz, 2H), 2.95 (q, $J = 7.1$ Hz, 2H), 2.56 (s, 3H), 2.44 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.1, 171.1, 148.1, 137.3, 135.7, 129.7, 128.9, 128.6, 26.9, 26.5, 16.4, 14.2. Anal. Calcd for $C_{14}H_{15}NOS$ (245.34): C 68.54, H 6.16. Found: C 68.64, H 6.10.

Ethyl 5-(4-Acetylphenyl)-2-methylthiazole-4-carboxylate (49) (Table 6, entry 1). The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), ethyl 2-methylthiazole-4-carboxylate (0.342 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.896 mg, 0.004 mmol) in DMAc at 150 °C during 3 h affords the corresponding product **49** in 68% (0.197 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.2$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.76 (s, 3H), 2.63 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.4, 165.1, 161.8, 144.7, 140.5, 137.1, 135.4, 130.2, 128.0, 61.5, 26.7, 19.3, 14.1. Anal. Calcd for $C_{15}H_{15}NO_3S$ (289.35): C 62.26, H 5.23. Found: C 62.40, H 5.31.

5-(4-Acetylphenyl)thiazole (52) (Table 7, entry 1).[16] The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), thiazole (0.170 g, 2 mmol), and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (0.896 mg, 0.004 mmol) in DMAc at 130 °C during 20 h affords the corresponding product **52** in 90% (0.183 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.15 (s, 1H), 7.96 (d, $J = 8.3$ Hz, 2H), 7.62 (d, $J = 8.3$ Hz, 2H), 2.59 (s, 3H).

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Supporting Information Available: Graphical ^{1}H and ^{13}C NMR spectra of new compounds and ^{1}H NMR of known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Jensen, J.; Skjaerbaek, N.; Vedso, P. *Synthesis* **2001**, 128.