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Reactivity of Antipyrine and Haloantipyrines in Pd-Catalyzed C–H Bond Arylations

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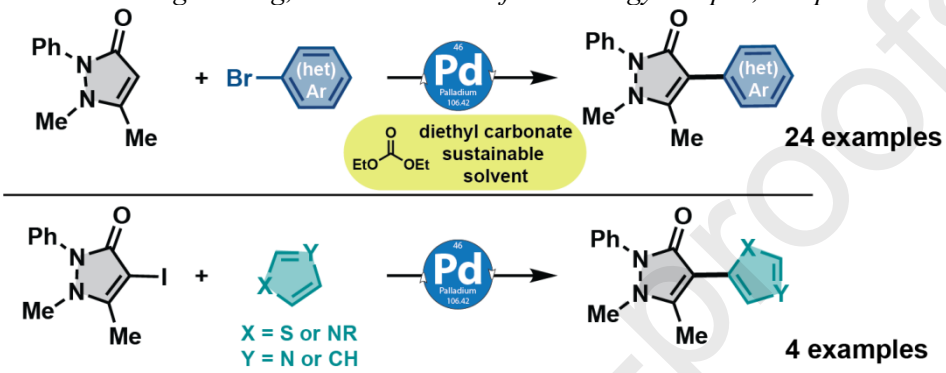

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Reactivity of Antipyrine and Haloantipyrines in Pd-Catalyzed C–H Bond Arylations

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ABSTRACT

We reported herein the Pd-catalyzed direct arylation of antipyrine using $Pd(OAc)_2$ as catalyst associated with KOAc as inexpensive base. In most cases, diethyl carbonate was used a sustainable solvent. The reaction tolerated a wide range of functional groups on the aryl bromide partners (e.g., nitrile, nitro, chloro, fluoro, formyl, acetyl, propionyl, benzoyl, ester, methyl, methoxy). In addition, some nitrogen-containing heteroaryl bromides were also efficiently coupled with antipyrine. We also demonstrated that in contrast to 4-bromoantipyrine, 4-iodoantipyrine could be employed as an efficient heteroaryl source in Pd-catalyzed C–H bond arylation of 5-membered ring heteroarenes.

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1. Introduction

Pyrazolone derivatives are important heterocycles, which often exhibit important pharmacological properties. Among them 1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (antipyrine) and its derivatives (e.g., Aminophenazone, Piperylone or Morazone) are used as non-steroidal anti-inflammatory drugs (Figure 1). Moreover, Adavosertib, which contains a pyrazolone skeleton, is an experimental anti-cancer drug candidate (Figure 1). Some pyrazolones also found applications in agricultural chemistry as herbicides.[1] Therefore, the development of new methods to prepare well-decorated pyrazolones under sustainable conditions at an affordable cost is a hot topic for both industrial and academic points of view.

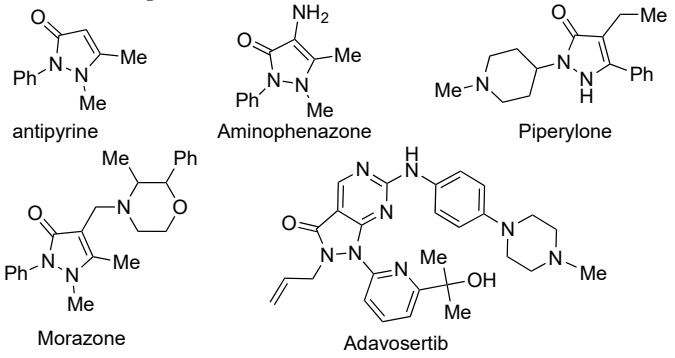

Figure 1. Representative pyrazolones in pharmaceuticals

Recently, transition metal catalyzed-regioselective C–H bond functionalization has emerged as a suitable method to build-up a library of compounds in a minimum of steps.[2-19] Few methods have been dedicated to the late-stage modification of antipyrine. In 2013, Kwang and co-workers reported the first example of C4 modification of antipyrine using Pd-catalyzed C–H bond alkenylation using activated alkenes (Figure 2a).[20] In the same year, they also developed Pd-catalyzed C–H bond arylation using aryl iodides as aryl source. They found that a silver base is required to get a good yield in favor of C4 arylated antipyrine (Figure 2b).[21] They also reported three examples using cheaper aryl bromides as aryl source. In 2017, during their investigations on Ru-catalyzed C–H bond alkenylation of arene rings using pyrazolone as directing group, Ma, Ackermann and co-workers reported that in the presence disulfides and a silver catalyst, thiolation of antipyrine occurred at C4-position (Figure 2c).[22] Replacing disulfide by diselenides, they also achieved the direct selenations of antipyrine. In 2018, Yotphan and co-workers succeeded in C–H acylation of antipyrine using carboxylic acid derivatives under oxidative conditions and copper catalysis (Figure 2d).[23] Later, a similar protocol was used by Sun and co-workers, albeit they employed aldehydes as acyl source.[24] In 2018, Xia and co-workers reported one example of Au-catalyzed C–H bond alkynylation of antipyrine using silylethynyl-1,2-benziodoxol-3(1H)-one (silyl-EBX) as alkynyl source (Figure 1e).[25] Owing the importance of (hetero)biaryl units in pharmaceuticals, we decided to reinvestigate the Pd-catalyzed C–H bond arylation of antipyrine to find greener conditions allowing the use of aryl bromides, including electron-rich one, in the absence of silver base which is expensive and difficult to remove. (Figure 1f). Besides, we also investigated the reactivity of haloantipyrine in Pd-catalyzed C–H bond arylation of 5-membered ring heterocycles to access to bis-heteroaryl derivatives in one step.

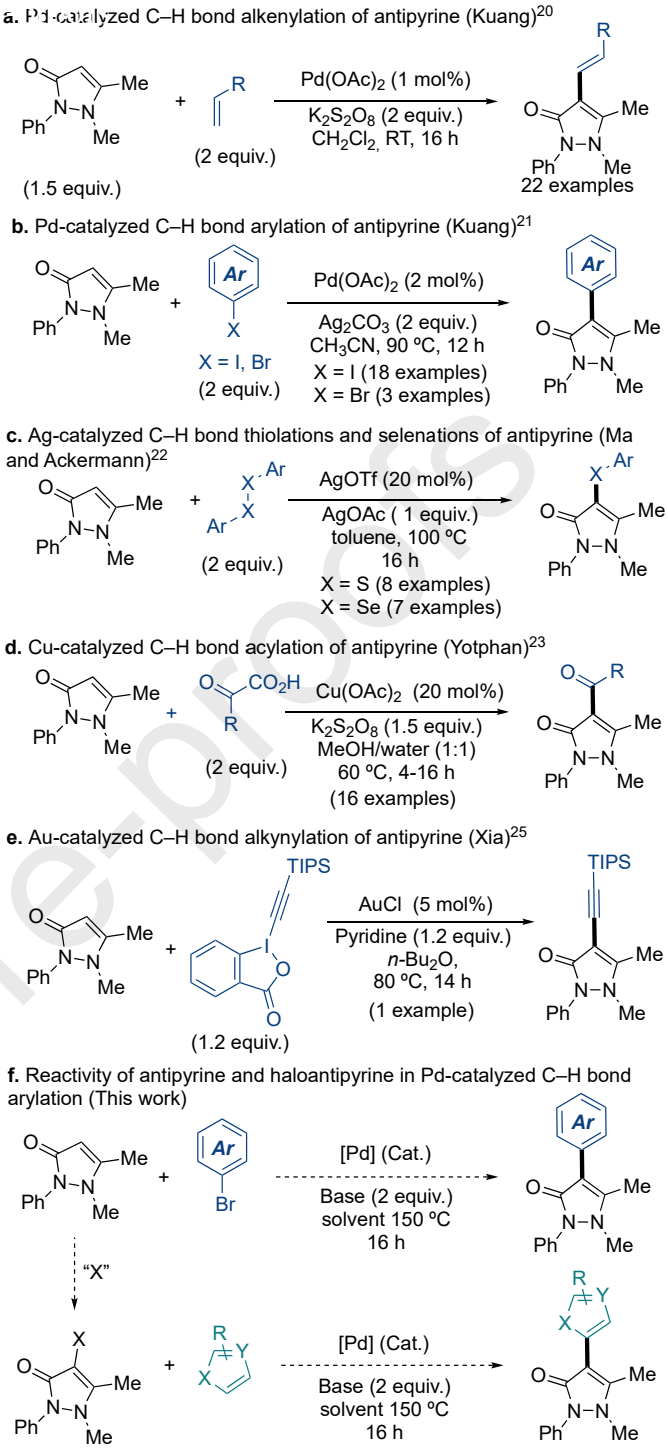

Figure 2. Methods for the C–H bond functionalization of antipyrine

2. Results/Discussion

We began our investigation by screening different inexpensive bases to replace Ag_2CO_3 in Pd-catalyzed C–H bond arylation of antipyrine with 4-bromobenzonitrile. Based on our previous work on direct arylation of heterocycles,[26-28] we selected phosphine-free $Pd(OAc)_2$ as catalyst and DMA as the solvent. No reaction occurred when K_2CO_3 or K_3PO_4 were employed. In the presence of $NaHCO_3$ as base the desired arylated antipyrine **1** was obtained in 23% yield (Table 1, entry 3). A lower yield was observed using KOH as base; however, the desired arylated product **1** was isolated in 85% yield using KOAc as the base (Table 1, entries 4 and 5).

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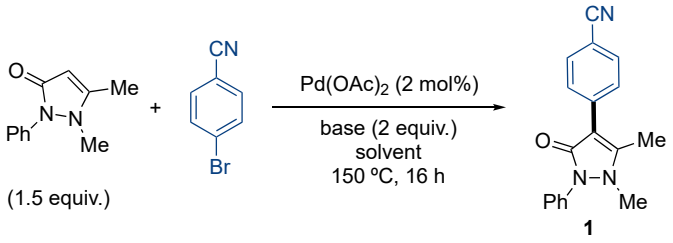
The use of other acetate bases (e.g., KOPiv or NaOAc) did not afford a better yield in **1** (Table 1, entries 6 and 7). We have previously shown that DMA can be replaced in some cases by greener solvents in Pd-catalyzed C–H bond arylation.[29, 30] Therefore, we investigated the outcome of this reaction using water, pentan-1-ol, CPME [= cyclopentyl methyl ether], and DEC [= diethyl carbonate] (Table 1, entries 8-11). Among them, DEC, which is a polar, aprotic, non-toxic, biodegradable, and bio-sourced solvent,[31-36] proved to be the best choice to replace DMA, as the arylated antipyrine **1** was isolated in 78% yield. More interestingly, using DEC as solvent, the palladium loading could be decreased to 0.5 mol% or even 0.25 mol% without greatly affecting the yield (Table 1, entries 12-14).

Table 1. Optimization of Pd-catalyzed C–H bond arylation of antipyrine

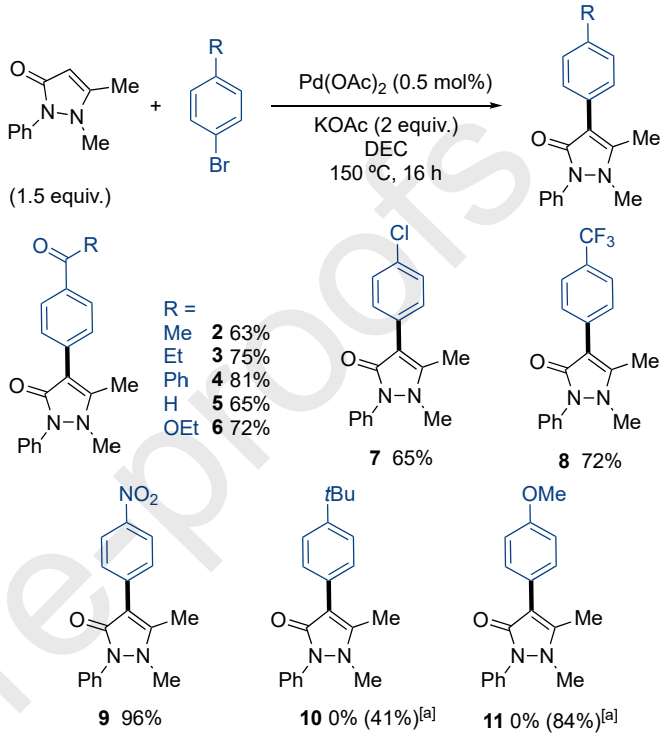


Entry	Base	Solvent	Yield in **1** (%)[a]
1	K_2CO_3	DMA	0
2	K_3PO_4	DMA	0
3	$NaHCO_3$	DMA	23
4	KOH	DMA	12
5	KOAc	DMA	85
6	KOPiv	DMA	75
7	NaOAc	DMA	45
8	KOAc	water	0
9	KOAc	Pentan-1-ol	38
10	KOAc	CPME	43
11	KOAc	DEC	78
12[b]	KOAc	DEC	80
13[c]	KOAc	DEC	89 (85)
14[d]	KOAc	DEC	80

[a] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard, isolated yield is shown in parentheses; [b] using 1 mol% of $Pd(OAc)_2$; [c] using 0.5 mol% of $Pd(OAc)_2$; [d] using 0.25 mol% of $Pd(OAc)_2$. [CPME = Cyclopentyl methyl ether, DEC = Diethylcarbonate]

With the optimized conditions in hand to perform direct arylation of antipyrine without the use of a silver salt as base in renewable DEC as greener solvent, we investigated the aryl bromides scope. Firstly, the reactivity of a set of *para*-substituted aryl bromides was surveyed (Scheme 1). From 4-bromo substituted acetophenone, propiophenone and benzophenone, the desired arylated products **2**-**4** were obtained in good yields. The reaction was also tolerant to aldehyde function, as from 4-bromobenzaldehyde, the coupling product **5** was obtained in 65% yield without the formation of deformylated product. Ethyl 4-bromobenzoate nicely reacted with antipyrine to afford **6** in 72% yield. From 4-bromo-1-chlorobenzene the reaction was selective and only occurred *via* the activation of C–Br bond to give the chloro-substituted arylated antipyrine **7** in 65% yield. The reaction was also compatible with aryl bromides bearing a strong electron-withdrawing group (*i.e.*, CF_3 or NO_2), affording the desired products **8** and **9** in 72% and 96% yield, respectively. Phosphine-free palladium conditions are often more challenging with electron-rich aryl bromides such as 1-bromo-4-(*tert*-butyl)benzene and 4-bromoanisole. Indeed, when the reactions were carried out in DEC, no reaction occurred; but the use of DMA as more polar and coordinating solvent promoted the C–H bond arylation affording the arylated products **10** and **11** in good yields.

Scheme 1. Scope of *para*-substituted aryl bromides in direct arylation of antipyrine using $Pd(OAc)_2$/KOAc



[a] Reaction performed in DMA.

Next, we examined the reactivity of various *meta*-substituted aryl bromides (Scheme 2). Aryl bromides bearing an electron-withdrawing group such as trifluoromethyl, cyano, methyl ester, or nitro reacted with antipyrine to afford selectively the arylated products **12**-**15** in 49-66% yields. From 1,3-bis(trifluoromethyl)-5-bromobenzene, the coupling product **16** was isolated in 60% yield. The reaction with 2-bromonaphtalene was more sluggish and required the use of DMA as the solvent to obtain **17** in good yield.

Scheme 2. Scope of *meta*-substituted aryl bromides in direct arylation of antipyrine using $Pd(OAc)_2$/KOAc

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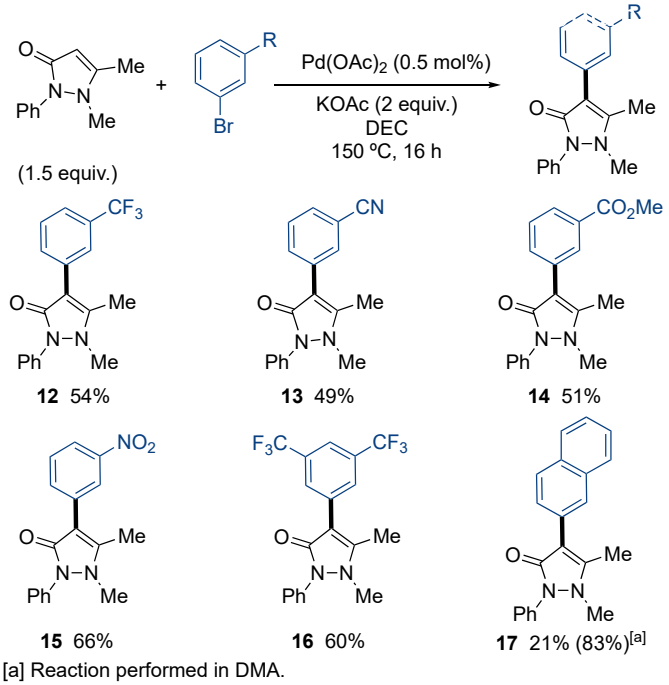
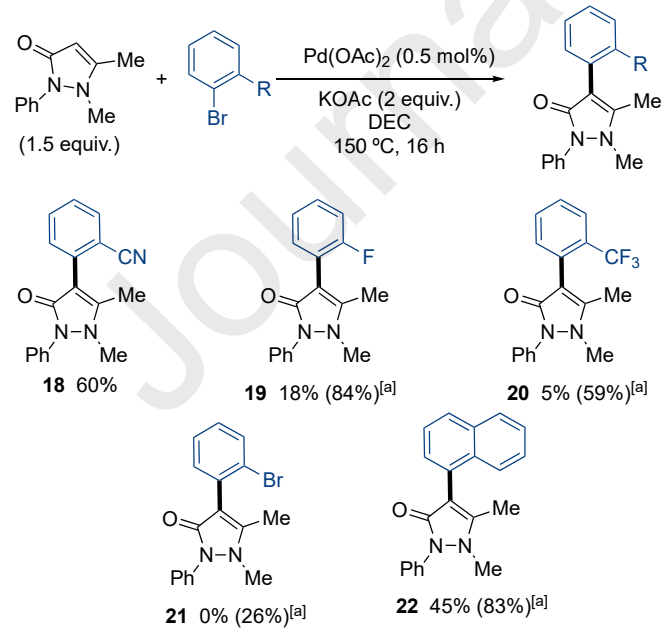


[a] Reaction performed in DMA.

Ortho-substituted aryl bromides often display lower reactivities in palladium catalysis due to the steric hindrance or the formation of stable chelate complexes. Therefore, we evaluated the reactivity of a few *ortho*-substituted aryl bromides (Scheme 3). From 2-bromobenzonitrile, the antipyrine was arylated to afford the compound **18** in 60% yield. The reactions with aryl bromide *ortho*-substituted by fluoro or trifluoromethyl group required the use of DMA as the solvent to give the arylated antipyrine **19** and **20** in 84% and 59% yield, respectively. 1,2-Dibromobenzene underwent mono-coupling to afford the product **21** bearing an *ortho*-bromophenyl group at the C4-position in 26% yield. Reaction with sterically hindered 2-bromonaphthalene led to the formation of **22** in 45% yield in DEC and 83% in DMA.

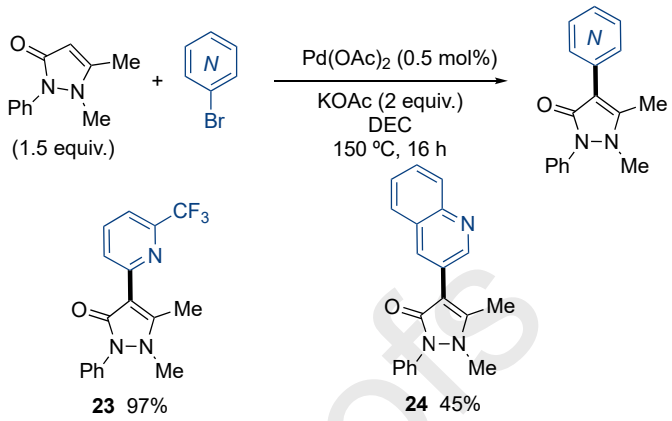
Scheme 3. Scope of *ortho*-substituted aryl bromides in direct arylation of antipyrine using $Pd(OAc)_2$/KOAc



[a] Reaction performed in DMA.

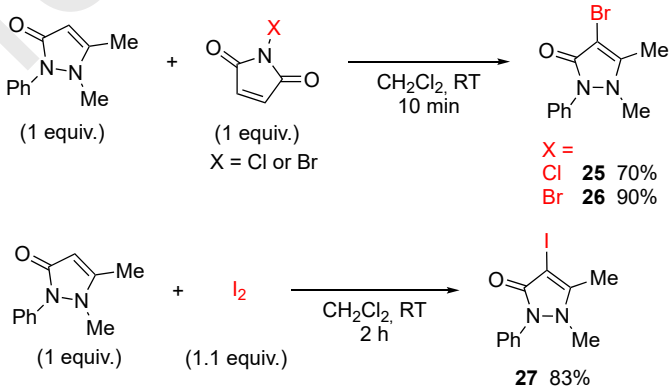
We also investigated the reactivity of nitrogen-containing heterocycles, as many pharmaceuticals include such motifs (Scheme 4). 2-Bomo-6-trifluoromethylpyridine and 3-bromoquinoline nicely reacted with antipyrine to deliver the C4-arylated products **23** and **24** in 97% and 45% yield, respectively.

Scheme 3. Scope of heteroaryl bromides in direct arylation of antipyrine using $Pd(OAc)_2$/KOAc



Next, we decided to halogenate the C4–H bond of antipyrine to latter use it as heteroaryl halide sources in Pd-catalyzed C–H bond arylation of 5-membered ring heterocycles to access quickly to higher molecular diversity. The chlorinated and brominated antipyrines **25** and **26** were obtained in 70% and 90% yields, respectively using only *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) in CH_2Cl_2 (Scheme 4, up). Notably, there is no need of a photoredox system, as previously reported.[37] Similarly, the iodinated antipyrine **27** was obtained in 83% yield using I_2.

Scheme 4. Selective halogenation of antipyrine



We then employed these halogenated antipyrines **25-27** as aryl sources in Pd-catalyzed C–H bond arylation of 2-ethyl-4-methylthiazole (Table 2). The *bis*-heteroaryl product **28** was not formed using 4-bromoantipyrine **26** as aryl source whatever the palladium sources [i.e., $Pd(OAc)_2$ or air-stable $PdCl(C_3H_5)(dppb)$], the base [i.e., KOAc, PivOK, or Ag_2CO_3)] (Table 2, entries 1-4). Sometimes aryl iodides, especially electron-rich ones, were more easily coupled than aryl bromides. Therefore, we tried to employ 4-iodoantipyrine **26** as the aryl source. Again under classical conditions, namely 1 mol% $Pd(OAc)_2$ associated with KOAc in DMA, no reaction occurred (Table 2, entry 5). The use of PivOK of the base had no effect, but when the reaction was set-up with Ag_2CO_3 as the base, the desired arylated thiazole **27** was obtained in 45% yield (Table 2, entries 6 and 7). The use of air-stable diphosphine palladium catalyst $[PdCl(C_3H_5)(dppb)]$ failed to improve the yield, as the desired product **27** was obtained in only 35% yield (Table 1, entry 8). No reaction occurred using 4-chloroantipyrine **25** as aryl source (Table 1, entry 9). It is important to note that the presence of silver slats is critical for this

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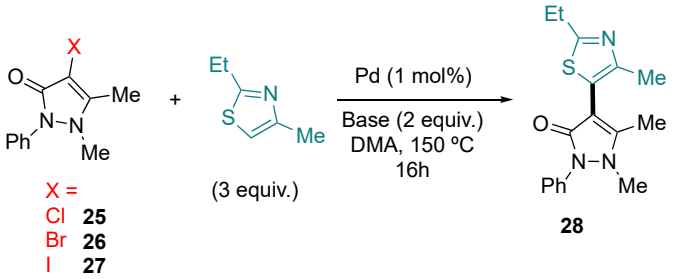
transformation and might be involved in C–H bond cleavage as previously reported.[38-40]

Table 2. Optimization of the Pd-catalyzed C–H bond arylation of 2,4-diethylthiazole with 4-haloantipyrine



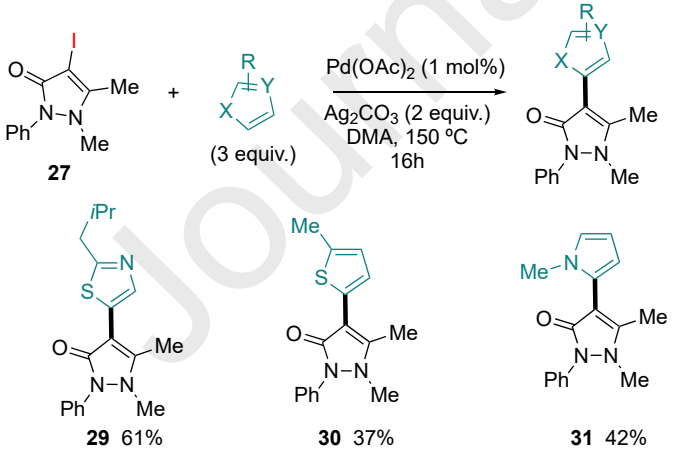
X = Cl **25**, Br **26**, I **27**

28

Entry	X	Pd	Base	Yield in **28** (%)
1	Br	$Pd(OAc)_2$	KOAc	0
2	Br	$PdCl(C_3H_5)(dppb)$	KOAc	0
3	Br	$PdCl(C_3H_5)(dppb)$	PivOK	0
4	Br	$PdCl(C_3H_5)(dppb)$	Ag_2CO_3	0
5	I	$Pd(OAc)_2$ (2.5)	KOAc	0
6	I	$Pd(OAc)_2$ (2.5)	PivOK	0
7	I	$Pd(OAc)_2$ (2.5)	Ag_2CO_3	45
8	I	$PdCl(C_3H_5)(dppb)$	Ag_2CO_3	35
9	Cl	$Pd(OAc)_2$ (2.5)	Ag_2CO_3	0

After having optimized the reaction conditions to couple 4-iodoantipyrine **27** with 2-ethyl-4-methylthiazole, we then explored the reactivity of a couple of heteroarenes using $Pd(OAc)_2/Ag_2CO_3$/DMA system (Scheme 5). 2-Isobutylthiazole was heteroarylated at the C4 position to afford **29** in 61% yield. The reaction was not limited to thiazoles, as heteraoarylation of 2-methylthiophene occurred at the C5 position to deliver **30** in 37% yield. From 4-iodoantipyrine **27** and *N*-methylpyrrole**,** the C2-heteroarylated pyrrole **31** was isolated in 42% yield.

Scheme 5. Scope of heteroarenes in Pd-catalyzed C–H bond heteroarylation with 4-iodoantipyrine.



3. Conclusion

In summary, we have developed silver-free conditions for the C4-arylation of antipyrine using $Pd(OAc)_2$ as catalyst. In most cases, the reaction can be performed in renewable solvent DEC. The advantage to previous nitrogen-containing solvent (i.e., DMA or CH_3CN), is that DEC does not lead to NO_x emissions upon incineration; therefore, the environmental concerns are reduced. A broad range of *para*-, *meta*-, and *ortho*-substituted electron-poor aryl bromides (*e.g.*, nitro, nitrile, formyl, ester, acetyl, benzoyl, propionyl, halo, trifluoromethyl) were successfully coupled. With electron-rich or bulky aryl bromides, better yields were observed in DMA as the solvent. We also demonstrated that 4-iodoantipyrine could be used as heteroaryl sources in Pd-catalyzed C–H bond arylation of thiazole, thiophene, and pyrrole derivatives.

Acknowledgments

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Supplementary Material

Copy of ^{1}H NMR ,^{13}C NMR, and ^{19}F NMR charts

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights.

- Antipyrine can be efficiently coupled with halide halides
- 4-Iodopyrine was employed in Pd-catalyzed C–H bond arylation of heterocycles.
- C–H bond activation was developed instead of classical Suzuki-reaction.
- Sustainable solvent and silver-free conditions have been developed

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