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Graphical Abstract

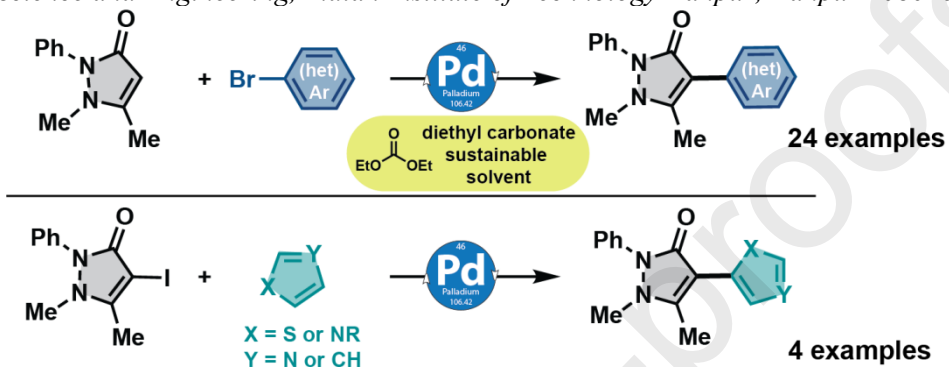
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Reactivity of Antipyrine and Haloantipyrines in Pd-Catalyzed C–H Bond Arylations

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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 as 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.

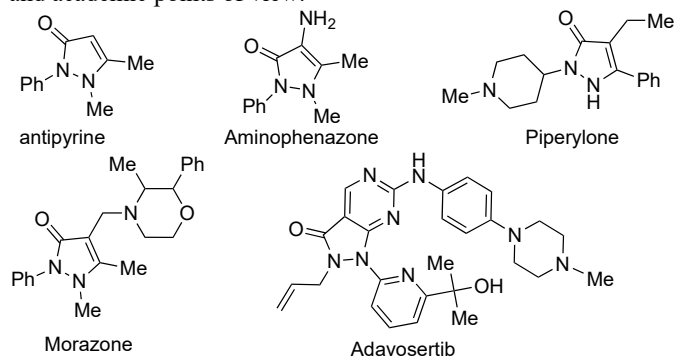
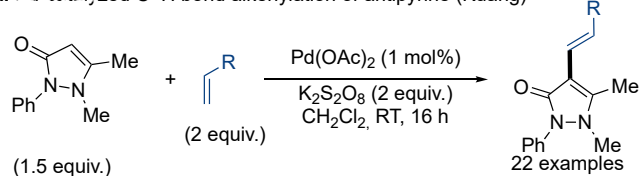
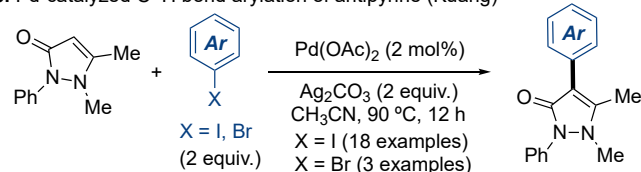
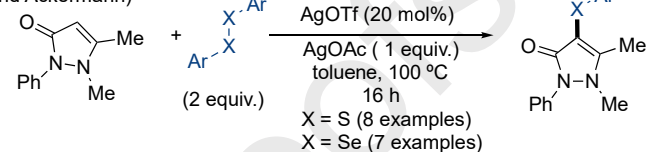
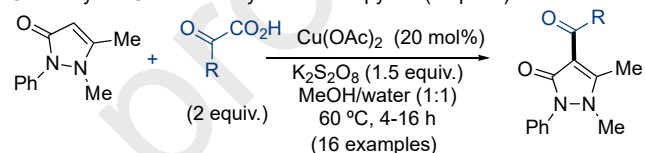
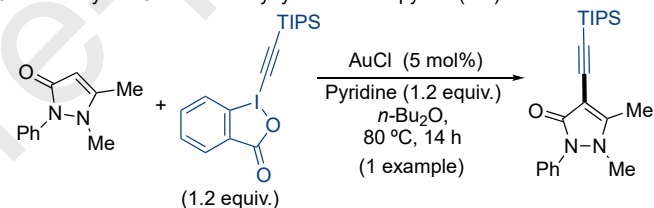


Figure 1. Representative pyrazolones in pharmaceuticals

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 of 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.

a. Pd-catalyzed C–H bond alkenylation of antipyrine (Kuang)²⁰b. Pd-catalyzed C–H bond arylation of antipyrine (Kuang)²¹c. Ag-catalyzed C–H bond thiolations and selenations of antipyrine (Ma and Ackermann)²²d. Cu-catalyzed C–H bond acylation of antipyrine (Yotphan)²³e. Au-catalyzed C–H bond alkynylation of antipyrine (Xia)²⁵

f. Reactivity of antipyrine and haloantipyrine in Pd-catalyzed C–H bond arylation (This work)

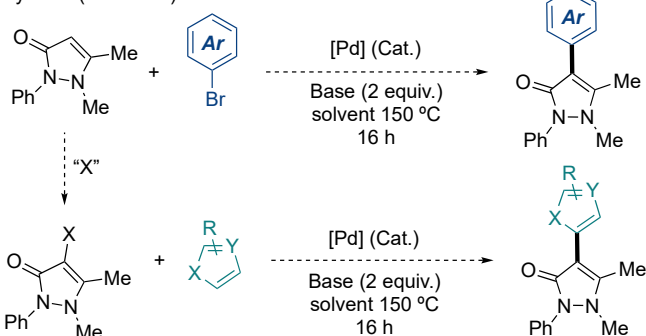


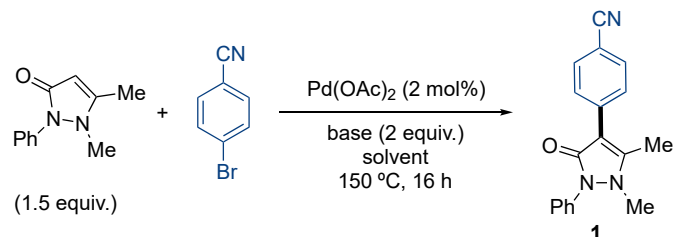
Figure 2. Methods for the C–H bond functionalization of antipyrine

2. Results/Discussion

We began our investigation by screening different inexpensive bases to replace Ag₂CO₃ 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 K₂CO₃ or K₃PO₄ were employed. In the presence of NaHCO₃ 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).

The use of other acetate bases (e.g., KO₂Piv 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



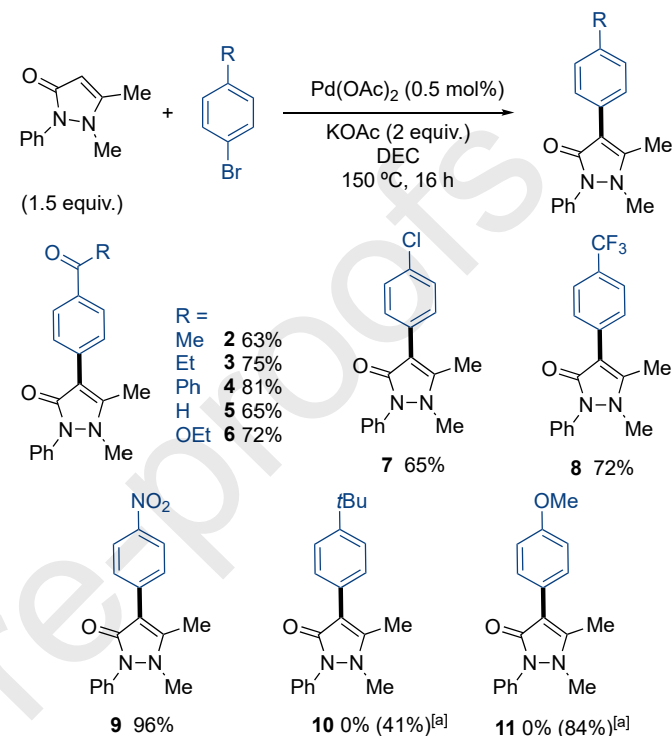
Entry	Base	Solvent	Yield in 1 (%) ^[a]
1	K ₂ CO ₃	DMA	0
2	K ₃ PO ₄	DMA	0
3	NaHCO ₃	DMA	23
4	KOH	DMA	12
5	KOAc	DMA	85
6	KOPiv	DMA	75
7	NaOAc	DMA	45
8	KOAc	water	0
9	KOAc	Pentan-1-ol	38
10	KOAc	CPME	43
11	KOAc	DEC	78
12 ^[b]	KOAc	DEC	80
13 ^[c]	KOAc	DEC	89 (85)
14 ^[d]	KOAc	DEC	80

[a] Determined by ¹H 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.*, CF₃ or NO₂), 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.

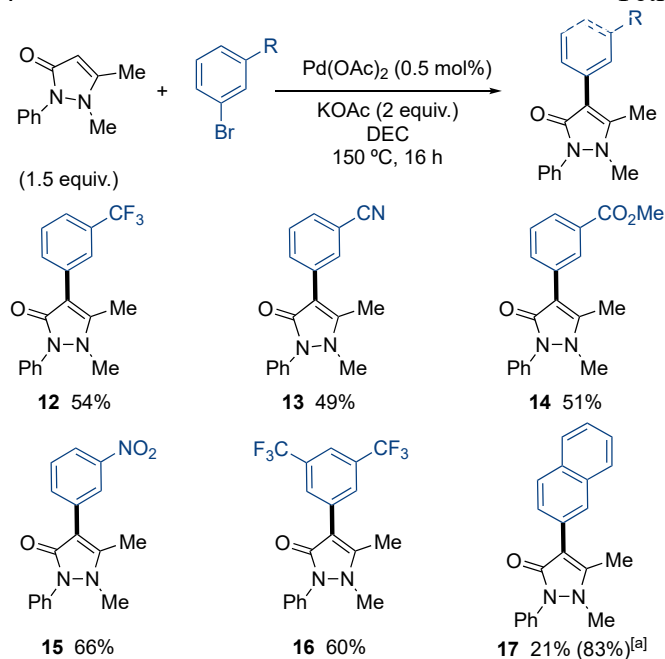
Scheme 1. Scope of *para*-substituted aryl bromides in direct arylation of antipyrine using Pd(OAc)₂/KOAc



[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-bromonaphthalene was more sluggish and required the use of DMA as the solvent to obtain **17** in good yield.

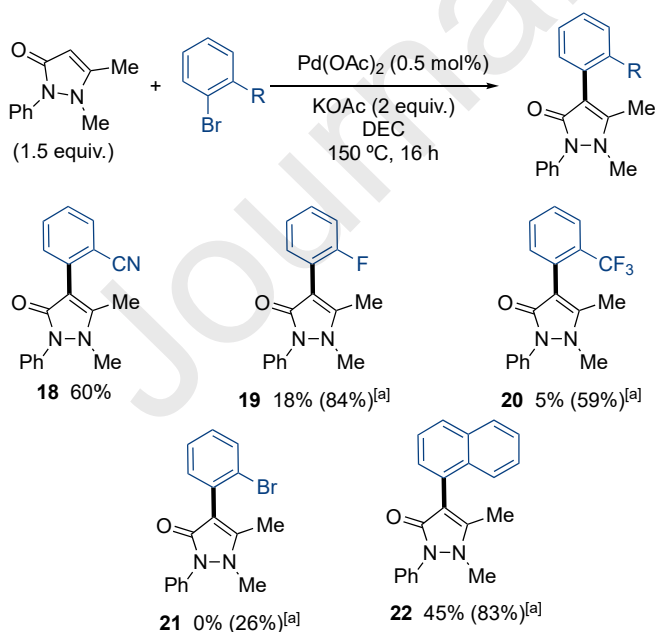
Scheme 2. Scope of *meta*-substituted aryl bromides in direct arylation of antipyrine using Pd(OAc)₂/KOAc



[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 $\text{Pd}(\text{OAc})_2/\text{KOAc}$

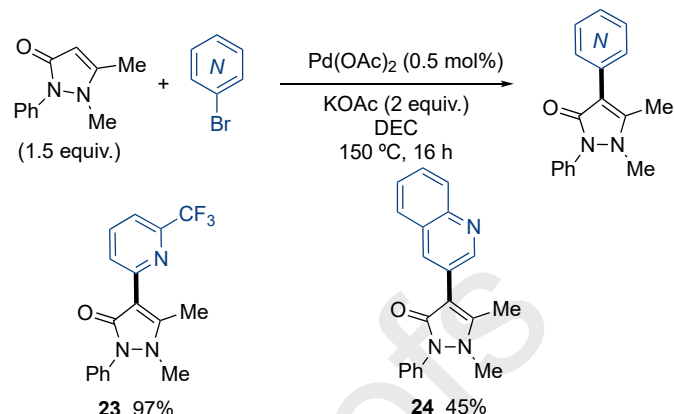


[a] Reaction performed in DMA.

We also investigated the reactivity of nitrogen-containing heterocycles, as many pharmaceuticals include such motifs (Scheme 4). 2-Bromo-6-trifluoromethylpyridine and 3-

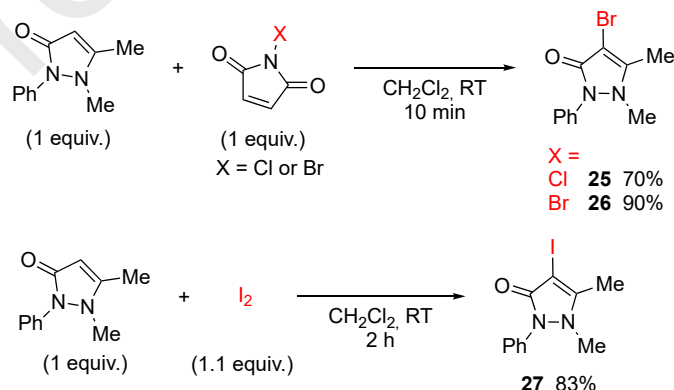
bromoquinoline nicely reacted with antipyrine to deliver the C4-arylated products **23** and **24** in 97% and 45% yield, respectively.

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



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 CH₂Cl₂ (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 I₂.

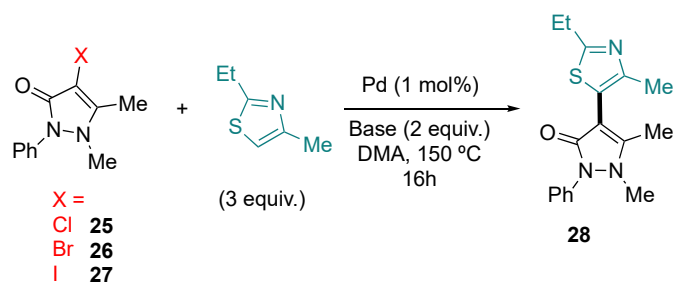
Scheme 4. Selective halogenation of antipyrine



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., $\text{Pd}(\text{OAc})_2$ or air-stable $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$], 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% $\text{Pd}(\text{OAc})_2$ 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 [$\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$] 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

transformation and might be involved in C–H bond cleavage as previously reported.^{38–40}

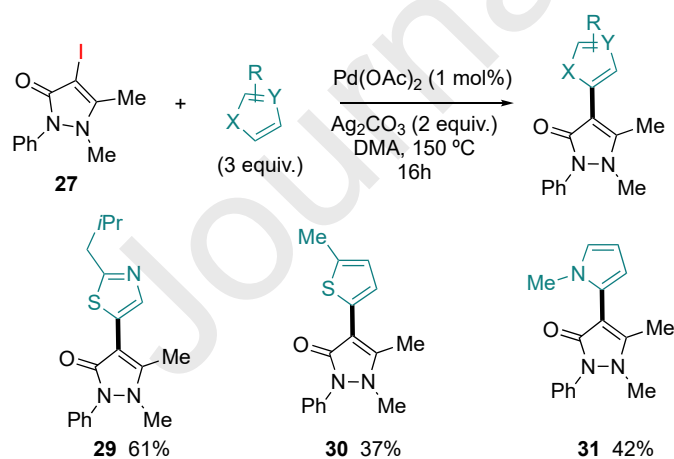
Table 2. Optimization of the Pd-catalyzed C–H bond arylation of 2,4-diethylthiazole with 4-haloantipyrine



Entry	X	Pd	Base	Yield in 28 (%)
1	Br	Pd(OAc) ₂	KOAc	0
2	Br	PdCl(C ₃ H ₅)(dppb)	KOAc	0
3	Br	PdCl(C ₃ H ₅)(dppb)	PivOK	0
4	Br	PdCl(C ₃ H ₅)(dppb)	Ag ₂ CO 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 ₂ CO ₃	45
8	I	PdCl(C ₃ H ₅)(dppb)	Ag ₂ CO ₃	35
9	Cl	Pd(OAc) ₂ (2.5)	Ag ₂ CO 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/Ag₂CO₃/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 heteroarylation 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 CH₃CN), 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 ^1H NMR, ^{13}C NMR, and ^{19}F NMR charts

Journal Pre-proofs

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