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Pyrazole-directed, fluoroalcohol-free arylation of C-H bonds

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ABSTRACT

Directed arylation of sp^2 C–H bonds is often considered one of the most convenient methods to rapidly increase the complexity of organic molecules. However, most of the available methods utilized fluoroalcohols such as hexafluoroisopropanol (HFIP) as the solvent. Herein we report a simple method for palladium-catalyzed, directed arylation of arene C–H bond using acetic acid solvent. The successful functionalization relies on the use of pyrazole directing group.

1. Introduction

Recent decades have witnessed tremendous development of methods for directed functionalization of C–H bonds as the tactic is perhaps one of the most universal methods to rapidly increase the complexity of organic molecules [1-3]. Among the available examples, those for arylation of C–H bonds have attracted substantial attention since aryl electrophiles are often inert [4-6]. Encouraged by pioneering works [7-9], more attempts are devoted to developing general scope of substrates and/or practical reaction conditions. Notably, most successes have relied on the use of well-designed anionic bidentate directing groups [10,11].

It is scarcely rare for using a removable, neutral, and monodentate directing groups for directed arylation of C–H bonds [12-15]. Daugulis and co-workers reported two exemplary methods for arylation of sp^2 and sp^3 C–H bonds using pyrazole directing groups [14,16]. The approaches are considerably helpful in functionalization of C–H bonds in amines. Despite certain successes, the methods still suffer from the use of expensive, unpleasantly smelling solvent hexafluoroisopropanol (HFIP). Given that HFIP solvent plays the important role in many transformations [17,18], it is still more beneficial if directed arylation of arene C–H bonds proceeds without the requirement of such solvent. It should be noted that early examples for directed functionalization of C–H bonds showed that arylation could feasibly occur in the present of acetic acid solvent [7,8]. As such, herein we would like to develop a method for pyrazole-directed, HFIP-free arylation of sp^2 C–H bonds which utilized palladium acetate ($Pd(OAc)_2$) catalyst, silver acetate (AgOAc) promoter, and acetic acid as the sole solvent. Our successes would offer an convenient tactic to obtain *ortho*-arylation without handling fluoroalcohol solvents.

2. Experimental

Chemicals were obtained from AK Scientific, Bidepharm, Acros, and Sigma-Aldrich and used without further purification. Synthesis of derivatives of 3,5-dimethyl-1-phenyl-1*H*-pyrazole **1a** followed a known procedure [14]. For the *ortho*-arylation, a typical experiment was as follows: a mixture of 3,5-dimethyl-1-phenyl-1*H*-pyrazole **1a** (17.2 mg, 0.1 mmol),

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iodobenzene **2a** (61.2 mg, 0.3 mmol), $Pd(OAc)_2$ (1.2 mg, 5 µmol), AgOAc (34.8 mg, 0.15 mmol), and acetic acid (0.5 mL) was added to a 4-mL dried vial equipped with a magnetic stir bar. The mixture was then heated at 140 °C for 48 h. The crude mixture was diluted with ethyl acetate (EtOAc, 10 mL) and extracted with $NaHCO_3$ (saturated aqueous solution, 3x10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. For GC analyses, diphenyl ether (17.0 mg, 0.1 mmol) as the internal standard was added, then the mixture was further diluted with ethyl acetate (5 mL) before GC determination. Characterization was carried out on a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (inner diameter = 0.25 mm and film thickness = 0.25 µm). For isolation, the aforementioned crude mixture was purified by column chromatography (eluent hexanes/EtOAc 20:1) to obtain 20.3 mg (82% yield) the desired product **3aa**. The structure of **3aa** was determined by NMR (recorded on a Bruker AV 500 spectrometer). The results were in agreement with that previously reported [13] and as shown below:

1-([1,1'-Biphenyl]-2-yl)-3,5-dimethyl-1*H*-pyrazole **3aa**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.52 – 7.40 (m, 4H), 7.26 – 7.24 (m, 3H, overlapping with $CHCl_3$ signal), 7.12 – 7.09 (m, 2H), 5.73 (s, 1H), 2.29 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 148.6, 140.5, 139.0, 138.6, 137.4, 130.4, 129.1, 129.0, 128.7, 128.3, 128.2, 127.1, 105.5, 13.6, 11.1.

3. Results and discussion

We firstly studied the arylation of phenylpyrazole **1a** by iodobenzene **2a**. The arylation product **3aa**, as shown in Fig. 1, could be observed by GC (later confirmed by results of GC-MS and NMR).

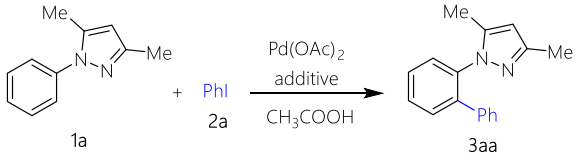

Fig. 1: Pyrazole-directed arylation of C–H bond in acetic acid solvent

Reaction temperature was pivotal to the successful coupling. As seen in Fig. 2, *ortho*-arylation of **1a** hardly proceeded at the temperature lower than 120 °C. A 15% yield of **3aa** was obtained at 120 °C. Running the arylation at 140 °C furnished **3aa** in 68% yield. However, increasing the temperature above 140 °C led to significant drops of yields as acetic acid rapidly evaporated. It should be noted that the reasonable yield of **3aa** was obtained only if $Pd(OAc)_2$ catalyst was used. A 42% yield of **3aa** was observed in case $PdCl_2$ catalyst, while no product was detected if $Pd(dppf)Cl_2$ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) was used.

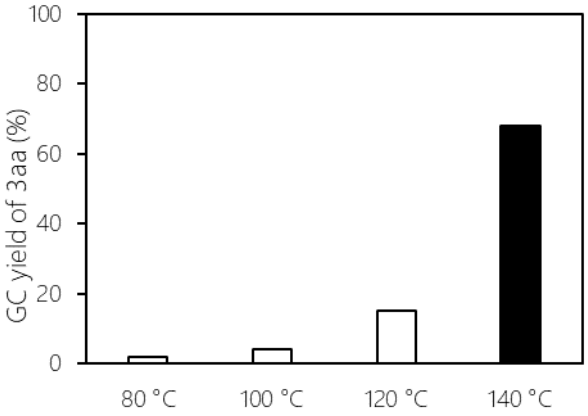

Fig. 2: Effect of reaction temperature. Reactions followed the general procedure except 10 mol% $Pd(OAc)_2$ (0.01 mmol) was used

We next turned our attention to the effect of additives. The results are shown in Table 1. The arylation could proceed in the presence of $Cu(OAc)_2$ additive, albeit affording **3aa** in moderate yield (33%). Better yields were obtained if silver salts were used. Among those, AgOAc was superior. Omitting the additive did not furnish the product, confirming the crucial role of those salts.

Table 1: Effect of additives

Additive	Yield of **3aa** (%)
$Cu(OAc)_2$	33
Ag_2CO_3	46
Ag_2O	57
AgOAc	68
no additive	< 5

Reactions followed the general procedure except 10 mol% $Pd(OAc)_2$ (0.01 mmol) was used.

Investigation on how solvents affect the arylation was next studied. The results are shown in Table 2. Most of polar aprotic solvents including DMF, DMSO, and DMAc were not suitable for the reaction. Aromatic solvents were examined, as *m*-xylene gave the product **3aa** in 53% yield. The solvent-free arylation afforded **3aa** in 20% yield. We also studied the effect of $Pd(OAc)_2$ concentration on the reaction yield. It could

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be observed that no improvement was obtained if more than 5 mol% $Pd(OAc)_2$ was used (70% yield of **3aa** was obtained in the presence of 7.5 mol% $Pd(OAc)_2$). Meanwhile, omitting $Pd(OAc)_2$ did not furnish **3aa**, confirming the pivotal role of Pd(II) in this arylation. As such, 5 mol% of $Pd(OAc)_2$ was used for further studies.

Table 2: Effect of solvents

Solvent	Yield of **3aa** (%)
DMF, DMSO, DMAc	< 5
m-xylene	53
acetic acid	68
no solvent	20

Reactions followed the general procedure except 10 mol% $Pd(OAc)_2$ (0.01 mmol) was used.

With the reaction conditions in hands, we wondered if obtaining other derivatives of *ortho*-arylated 3,5-dimethyl-1-phenyl-1*H*-pyrazole **1a** was feasible. To our expectation, 4-nitro-1-iodobenzene **2b** could afford the arylation product **3ab** in moderate yield (54%, equation 1, Fig. 3). Meanwhile, methoxy-substituted pyrazole **1b** only gave the arylation product **3ba** given that two *ortho* C–H bonds are possibly functionalized (equation 2, Fig. 3). Expansion of substrate scope is ongoing in our lab.

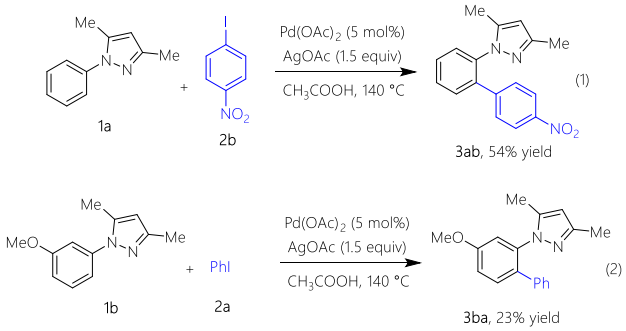

Fig. 3: Preliminary results of substrate scope. Reaction conditions: **1a**/**1b** (0.1 mmol), **2a**/**2b** (0.3 mmol), $Pd(OAc)_2$ (5 µmol), AgOAc (0.15 mmol), CH_3COOH (0.5 mL), 140 °C, 48 h. Yields are isolated yields

We proposed the possible mechanism as that shown in Fig. 4. Coordination of substrate **1a** to $Pd(OAc)_2$ followed by a directed *ortho* C–H functionalization (**1a** → **4** → **5**) would afford the palladacycle **5**. Oxidative addition of iodobenzene **2a** to **5** gave the Pd(IV) complex **6**. Reductive elimination on **6** would furnish the desired product **3aa** and the palladium adduct **7**. Regeneration perhaps occurred in the presence of AgOAc to deliver $Pd(OAc)_2$ for the next catalytic cycle.

To somewhat support our hypothesis of Pd(II)/Pd(IV) mechanism, we examined the arylation of 1a with chlorobenzene and phenyl tosylate. To our expectation, no product **3aa** was obtained, confirming that a catalytic cycle of Pd(0)/Pd(II) was unlikely.

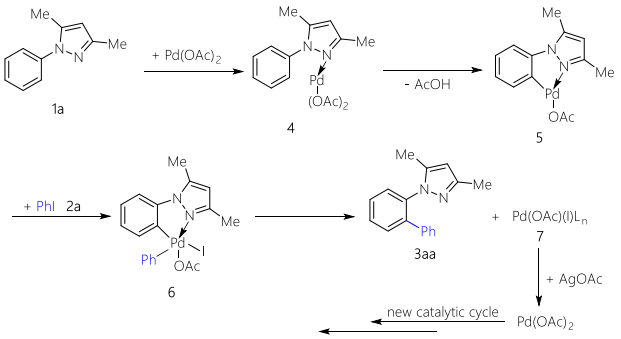

Fig. 4: Plausible mechanism

4. Conclusion

In conclusion, we have developed a convenient method for *ortho*-arylation of $C(sp^2)$–H bonds in *N*-aryl pyrazoles with aryl iodides. Notably the conditions did not require the use of HFIP solvent. Momentarily, the reaction mechanism was proposed to follow a Pd(II)/Pd(IV) catalytic cycle. Studies regarding substrate scope are of our next attention.

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