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Palladium bis(2,2,6,6-tetramethyl-3,5-heptanedionate): an efficient catalyst for regioselective C-2 arylation of heterocycles

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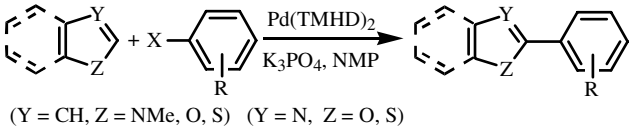
Abstract

Palladium bis(2,2,6,6-tetramethyl-3,5-heptanedionate), a structurally well defined O-containing transition metal complex is reported as an efficient catalyst for regioselective direct C-2 arylation of heterocycles with aryl halides. The present protocol is applicable to a wide variety of heterocycles providing good to excellent yields of products.

Keywords: C-Arylation; Heterocycles; Aryl halides; Palladium complex; Regioselectivity

Heteroaromatics are important structural units frequently found in natural products,[1] pharmaceutically active substances,[2] agrochemicals,[3] compounds used to treat endoparasitic diseases of domestic animals[4] and organic functional materials such as liquid crystals and fluorescent dyes.[5] The direct arylation of heterocycles has received considerable interest among synthetic chemists as it would eliminate the need for establishing a reactive functionality (halogenation or stoichiometric metalation) prior to C–C coupling, enabling direct elaboration and expansion of the core motif. The pioneering work in this field was performed by Ohta and co-workers.[6] Subsequently, other groups extended this methodology to arylation of a number of heterocycles with aryl halides employing catalysts such as $[RhCl(coe)_2]_2/PR_3$,[7] $[RuCl_2(p\text{-cymene})]_2/(1\text{-Ad})_2PHO$,[8] $Pd(OAc)_2/BuAd_2P$,[9] $PdCl_2/PCy_3$,[10] $Pd(OAc)_2/CuI$, [11] $PdCl_2(PPh_3)/CuI$[12] and $Pd(I_2)PPh_3$–NHC.[13] In spite of their utility, the use of expensive, air sensitive and toxic phosphine ligands, the addition of stoichiometric amounts of copper salt additives, use of sealed reaction vessels and substrate incompatibility limit their applications. Moreover, very few methods employ a structurally well defined and stable Pd-complex as catalyst.[13] Thus, there is a need to develop an efficient protocol, which could catalyze directly the arylation of a wide range of heterocycles employing a single-component Pd-complex as catalyst.

Previously, we reported N-arylation of aliphatic, aromatic and heteroaromatic amines with aryl halides using preformed copper bis(2,2,6,6-tetramethyl-3,5-heptane dionate) as the catalyst.[14] The use of 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) as a ligand resulted in excellent yields of products and such reactivity could be attributed to the fact that a good balance exists between the steric and electronic properties of the complex. Herein, we report a facile C-2 arylation of heterocycles with aryl halides catalyzed by a well defined and stable O-containing transition metal complex, viz Pd bis(2,2,6,6-tetramethyl-3,



(Y = CH, Z = NMe, O, S) (Y = N, Z = O, S)
(X = I, Br) (R = Me, OMe, NO_2)

Scheme 1. C-Arylation of heterocycles with aryl halides.

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Table 1
Effect of catalyst, base and solvent on the arylation of benzothiazole with iodobenzene[a]

Entry	Catalyst	Base	Solvent	Yield (%)
1	$Pd(TMHD)_2$	K_3PO_4	NMP	86
2	$Cu(TMHD)_2$	K_3PO_4	NMP	20
3	$Ru(TMHD)_3$	K_3PO_4	NMP	—
4	$Co(TMHD)_2$	K_3PO_4	NMP	—
5	$Pd(TMHD)_2$	Cs_2CO_3	NMP	80
6	$Pd(TMHD)_2$	KO^{t}Bu	NMP	10
7	$Pd(TMHD)_2$	K_2CO_3	NMP	76
8	$Pd(TMHD)_2$	KOH	NMP	17
9	$Pd(TMHD)_2$	K_3PO_4	Toluene	22
10	$Pd(TMHD)_2$	K_3PO_4	DMF	28
11	$Pd(TMHD)_2$	K_3PO_4	Dioxane	11
12	$Pd(TMHD)_2$	K_3PO_4	DMSO	83

[a] Reaction conditions: benzothiazole (1 mmol), iodobenzene (1.5 mmol), catalyst (10 mol %), base (2 mmol), solvent (5 mL), 36 h at 125 °C.

5-heptanedionate) [$Pd(TMHD)_2$] in an efficient manner. The ease of preparation of the complex,[15] its high solubility in organic solvents, indefinite shelf life, stability towards air and compatibility with a wide variety of heterocycles makes it an ideal complex for direct C-2 arylation of heterocycles (Scheme 1).

Initially, the direct arylation of benzothiazole with iodobenzene was chosen as a model reaction and the roles of various metal–TMHD complexes, bases and solvents were investigated (Table 1). Complexes of Ru and Co were found to be completely ineffective using the present conditions, whereas $Cu(TMHD)_2$ was found to give only a 20% yield. In comparison, $Pd(TMHD)_2$ was found to be highly active providing an excellent yield (86%) of the desired product.

The influence of various organic and inorganic bases such as K_3PO_4, Cs_2CO_3, KO^{t}Bu, K_2CO_3 and KOH was studied for the standard reaction (entries 1, 5–8). It was observed that the bases K_2CO_3, Cs_2CO_3 and K_3PO_4 afforded good yields of the desired product. However, due to cost considerations K_3PO_4 was preferred over Cs_2CO_3. The effect of various solvents on the reaction system was

Table 2
Arylation of heterocycles with aryl halides[a]

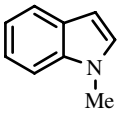
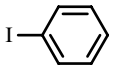
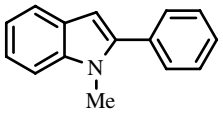
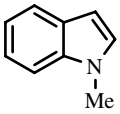
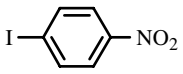
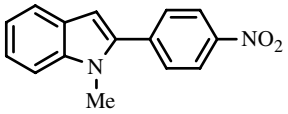
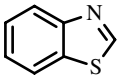
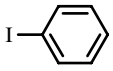
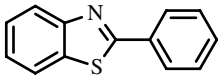
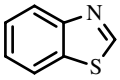
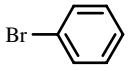
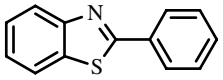
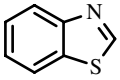
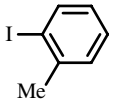
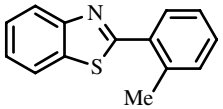
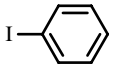
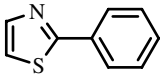
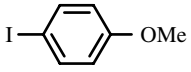
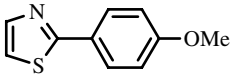
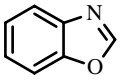
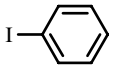
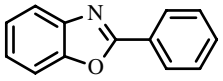
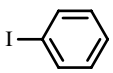
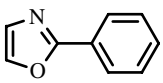
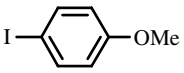
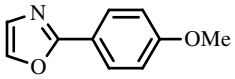
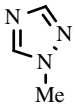
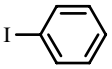
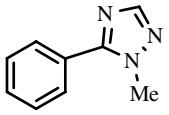
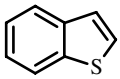
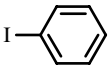
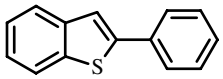
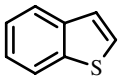
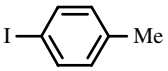
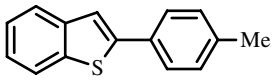
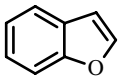
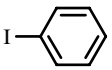
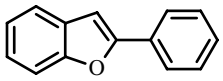
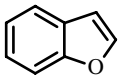
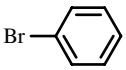
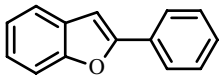
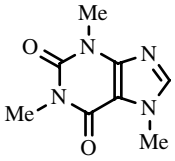
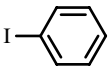
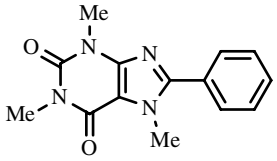
Entry	Heterocycle	Aryl halide	Product	Yield (%)
1				96
2				67
3				86
4[b]				60
5				45
6				67
7				40
8				55
9				62

Table 2 (*continued*)

Entry	Heterocycle	Aryl halide	Product	Yield (%)
10				63
11				76
12				35
13				30
14				83
15[b]				65
16[b]				60

[a] Reaction conditions: heterocycle (1 mmol), aryl halide (1.5 mmol), Pd $(TMHD)_2$ (10 mol %), K_3PO_4 (2 mmol), NMP (5 mL), 36 h at 125 °C.
[b] 48 h at 140 °C.

also examined (entries 1, 9–12). It was observed that non-polar solvents such as toluene gave a low yield of product probably due to the poor solubility of reactant and catalyst in the reaction medium. It was also observed that prolonged reaction of the catalyst in toluene led to decomposition of the catalyst and precipitation of Pd metal. The use of polar solvents such as NMP and DMSO led to an increase in the yield without any catalyst deactivation. However, *N*-methyl-2-pyrrolidine (NMP) was found to give the best results and was used for further studies.

Thus, using $Pd(TMHD)_2$ as catalyst, K_3PO_4 as base and NMP as solvent, a wide variety of heterocycles possessing different steric and electronic properties were coupled with aryl iodides or bromobenzene under mild reaction conditions (Table 2).[16]

N-Methylindole was found to react smoothly with iodobenzene providing an excellent yield (96%) of the C-2 arylated product. The reaction also worked well with an electron withdrawing substituent such as nitro on the aryl iodide (entry 2). To check the generality of the procedure the system was extended to various azoles including benzothiazole, thiazole, benzoxazole, oxazole and triazole (entries 3–11). Benzothiazole was found to react efficiently with both iodo and the less reactive bromoarene providing good yields of the desired product. Also, electron donating groups such as methyl and methoxy at the *ortho* or *para* positions of the iodoarene were viable partners under the present conditions (entries 5, 7, and 10). 1-Methyltriazole was found to be arylated selectively at the more active C-5 position (entry 11). We also tested the applicability of this method with other heteroarenes such as benzothiophene and benzofuran (entries 12–15). However, reaction of benzothiophene was found to be sluggish using the present catalytic system, while benzofuran was found to react efficiently with both iodo and bromobenzene providing good yields of the desired product. Encouraged with the above results, the system was further extended to the aryaltion of caffeine, as the products are of interest as adenosine receptor antagonists.[17] Caffeine was arylated effectively under the present conditions providing an excellent yield of 60% of product (entry 16). If C–H activation methodology is not used, the synthetic sequence leading to these compounds requires several steps instead of a single step.[17]

In summary, the first example of the direct, regioselective C-2 arylation of heterocycles catalyzed by the cheap, air stable and well defined $Pd(TMHD)_2$ complex as a catalyst is described. The system works equally well for a wide variety of heterocycles and tolerates various functional groups.

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15. *Typical procedure for the preparation of Pd(TMHD)$_2$*: Palladium chloride (1.8 g, 10 mmol) and sodium chloride (0.59 g, 10 mmol) were dissolved in methanol (50 mL) and stirred at room temperature overnight. The solution was filtered into a 100 mL volumetric flask and diluted with methanol to give a solution of 0.1 M palladium(II) concentration. A mixture of this solution (100 mL), the ligand 2,2,6,6-tetramethyl-3,5-heptanedione (4.6 g), and sodium carbonate (1.06 g, 10 mmol) was stirred overnight. The resulting yellow precipitate was filtered and dried, mp 238–240 °C.
16. *General procedure*: Under a N_2 atmosphere, heterocycle (1 mmol), aryl halide (1.5 mmol), $Pd(TMHD)_2$ (10 mol %) and K_3PO_4 (2 mmol) in NMP (5 mL) were stirred at room temperature. The reaction mixture was then heated in an oil bath at 125 °C for 36 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography (silica gel 60–120 mesh) using petroleum ether (60/80)/ethyl acetate as eluent to afford the pure product. All the products are known compounds and were characterized by GCMS and ^{1}H NMR.
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