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Pd(II)-catalyzed regioselective direct arylation of uracil via oxidative Heck reaction using arylboronic acids

Biplab Mondal, Somjit Hazra, B. Roy *

Department of Chemistry, University of Kalyani, Kalyani, Nadia, West Bengal, India

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ABSTRACT

A palladium catalyzed regioselective synthesis of 6-aryl uracils via oxidative Heck reaction (C–H bond functionalization) of uracils and arylboronic acids is reported. The method is simple, atom-economical, and high yielding.

C-Aryl pyrimidines exhibit a wide range of bioactivities.[1] 5-Aryl uracil is used as biosensor[2] and in labeling of nucleotides as well as DNA.[3] Likewise, 6-aryl uracils also attract the biochemists due to their various potential bioactivities (Fig. 1).[4]

For example, 6-aryl uracil derivatives (**I** and **II**) are two classes of sirtuin inhibitors which show antitumor activity.[1c] 5-Halo-6-phenyl pyrimidines (**III** and **IV**) demonstrate cardioregulatory and anti-inflammatory activities.[4d] Various 6-aryl thiouracils are also impending therapeutics such as antiviral, anticancer, and antimicrobial agents.[4e] 6-Aryl-5-cyano thiouracil quinoxaline hybrid **V** shows strong inhibitory effect on EBV-EA activation without cytotoxicity on Raji cells.[5] **VI** possesses inhibitory property against hepatitis C viral NS5B RNA-dependent RNA polymerase.[6]

C-Aryl uracils are usually synthesized by heterocyclic cyclization,[7] cross coupling of halouracil with arylboronic acid, or via metallated uracil which couples with aryl halides.[8] Though there are many available methodologies for the synthesis of 5-aryl uracils, known methodologies for the synthesis of 6-aryl uracils are scanty due to inaccessibility of 6-halouracil. In recent years, a range of direct arylation by C–H bond functionalization reactions has been developed to synthesize *C*-arylated heterocycles with high efficiency.[9] In 2009, Hocek et al. reported that *N*-substituted uracil could be arylated at C-6 position with aryl iodides using $Pd(OAc)_2$ as catalyst in the presence of CuI.[10] In 2012 Kim et al. described another methodology for the generation of C-6 aryl uracil via double

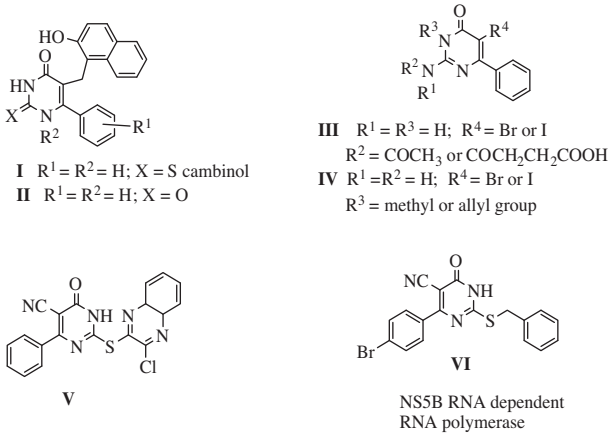

Figure 1. Some examples of pharmaceutically active C-6 aryl pyrimidines.

C–H activation between 1,3-dimethyluracil (1,3-DMU) and arenes, which were used as solvent, in the presence of catalytic amount of $Pd(TFA)_2$.[11] But they isolated 5-arylated uracil and dimeric byproducts also together with the 6-arylated uracil in the reaction condition. Organoboron-mediated oxidative Heck type reactions for C–C bond formation have received much attention in the past few years. The commercial accessibility, functional group tolerance, low toxicity, and general applicability of boron reagent increase its importance in industrial research.[12] In 2013, Cheng et al. reported Cu(I)-mediated C-6 arylation of uracil using 4 equiv of LiO^tBu in DMF with aryl iodides, but this reaction shuts down

* Corresponding author. Tel.: +91 3325828750; fax: +91 3325828282.
E-mail addresses: broy@klyuniv.ac.in, broybsku@gmail.com (B. Roy).

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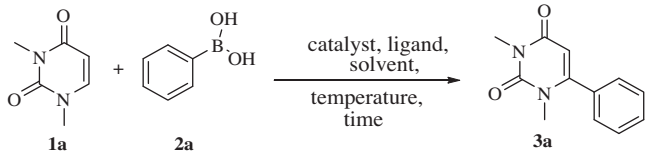
Table 1
Optimization of the reaction condition for direct C–H arylation



1a **2a** **3a**

Entry	Catalyst	Ligand	Solvent	Temperature (°C)	Conversion (%)	Yield[a] (%)
1	$Cu(OTf)_2$	—	Toluene	110	0	0
2	$Pd(OAc)_2$	—	DMF	rt-100	0	0[b]
3	$Pd(OAc)_2$	TMEDA	DMF	rt	20	5
4	$Pd(OAc)_2$	TMEDA	DMF	60	54	30
5	$Pd(OAc)_2$	DMEDA	DMF	60	25	10
6	$Pd(OAc)_2$	DMAP	DMF	60	45	25
7	$Pd(OAc)_2$	Phen	DMF	60	90	70
8	Pd(OAc)2	L-Proline	DMF	60	100	N.D
9	$Pd(OAc)_2$	Phen	Toluene	60	0	N.R
10	$Pd(OAc)_2$	Phen	DMSO	60	20	5
11	Pd(OAc)2	Phen	DMA	60	80	50
12	$Pd(OAc)_2$	Phen	DCE	60	50	20
13	$Pd(OAc)_2$	Phen	CH_3CN	60	100	N.D
14	PdCl2	Phen	DMF	60	55	15
15	$Pd(PPh_3)_2Cl_2$	Phen	DMF	60	64	20
16	**$Pd(OAc)_2$**	**Phen**	**DMF**	**90**	**100**	**82**
17	Pd(OAc)2	Phen	DMF	110	100	65
18	$Pd(OAc)_2$	Phen	DMF	90	75	60[c]
19	$Pd(OAc)_2$	Phen	DMF	90	100	80[d]
20	Pd(OAc)2	Phen	DMF	90	60	50[e]
21	$Pd(OAc)_2$	Phen	DMF	90	80	65[f]
22	$Pd(OAc)_2$	Phen	DMF	90	0	0[g]
23	Pd(OAc)2	Phen	DMF	90	0	0[h]

Reactions condition: 1,3-DMU **1a** (1 equiv), phenylboronic acid **2a** (3 equiv), Pd catalyst (10 mol %), ligand (15 mol %), O_2 balloon in the mentioned solvent (10 ml) heated for 16 h.
Bold line indicates the optimized condition.
[a] Yields were calculated after flash chromatography.
[b] Na_2CO_3 (2 equiv) used as base.
[c] Catalyst used 5 mol %.
[d] Catalyst used 15 mol %.
[e] Reaction continued for 8 h.
[f] Reaction continued for 12 h.
[g] Reaction performed under N_2 atmosphere.
[h] Reaction performed under open air. Phen = 1,10-Phenanthroline; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine DMEDA = *N*,*N*′-dimethylethylenediamie. N.D = no desired product (complicated result). N.R = no reaction (conversion of starting material is zero).

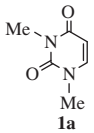
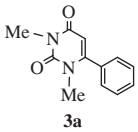
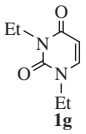
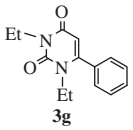
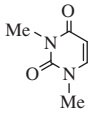
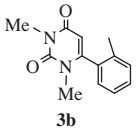
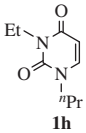
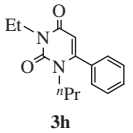
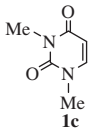
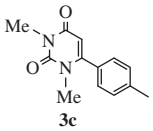
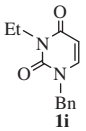
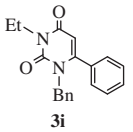
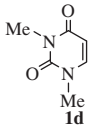
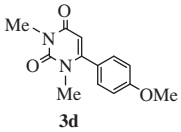
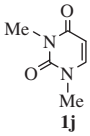
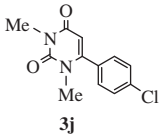
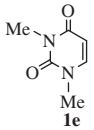
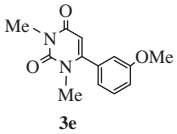
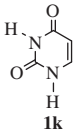
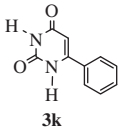
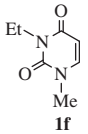
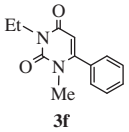
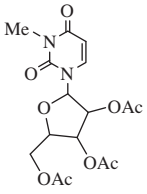
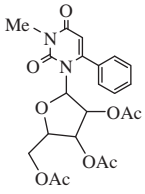
when arylboronic acid was used as coupling partner.[13] Very recently, we developed a route for the synthesis pyrrolo[3, 2-*d*]pyrimidine derivatives that involves activation of uracil C6-H bond.[14] In this context, we opted to explore an alternative way for uracil C6-H bond functionalization via boronic acid-mediated oxidative Heck reaction. Herein, we report the synthesis of 6-aryl uracil through organoboron-mediated oxidative Heck reaction and to the best of our awareness, this is the first Letter of C-6 arylation of uracil by Pd(II)-catalyzed organoboron-mediated oxidative Heck reaction.

Taking a clue from our previous work,[14] we carried out a preliminary experiment where 1,3-dimethyluracil (1,3-DMU) (**1a**) and phenylboronic acid (**2a**) in toluene were refluxed in the presence of 20 mol % of $Cu(OTf)_2$ for 12 h (Table 1, entry 1). But we failed to obtain any product. On changing the catalyst to $Pd(OAc)_2$ (10 mol %) and introducing Na_2CO_3 (2 equiv) as base[12b] in DMF at room temperature under oxygen atmosphere (Table 1, entry 2), we obtained the same result. A sign of progress was recorded when we used a ligand (20 mol % of TMEDA) at room temperature (Table 1, entry 3) and a further improvement was observed at 60 °C (Table 1, entry 4), as the reaction afforded 30% yield of only C-6 arylated product (after 16 h). This result prompted us to optimize this oxidative Heck reaction.

At first we decided to explore various ligands in the initial reaction condition. By changing the ligand to DMEDA and DMAP, the 6-arylated product was isolated (table-1, entry-5, 6) in 10% and 25% yields, respectively. A significant improvement was observed with 1,10-phenanthroline which afforded 70% yield of **3a** (Table 1, entry 7), but in case of L-proline no arylated product was found (Table 1, entry 8). The above results showed that ligand played an important role and 1,10-phenonthroline ligand appeared to be the best. The solvent effect for this coupling reaction was also tested. No product was obtained with toluene and acetonitrile (Table 1, entry 9, 13). A poor to moderate yield of **3a** was observed for the solvents DMSO, DMA, and DCE (Table 1, entry 10–12). DMF gave the most satisfactory result and it was selected as the preferred solvent. The maximum yield (82%) of 6-phenyl-1,3-DMU **3a** was isolated when the temperature was increased to 90 °C and the reaction continued for 16 h (Table 1, entry 16). A further increase in temperature resulted in lowering of the desired product **3a**, (Table 1, entry 17). With $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ as catalyst, the yield of **3a** was inadequately low (Table 1, entry 14, 15). When we changed the reaction atmosphere from oxygen to nitrogen or open air no reaction took place (Table 1, entry 22, 23). This finding indicated that molecular oxygen played an important role in this reaction. After the survey of different reaction conditions a combination of 10 mol % $Pd(OAc)_2$ as catalyst, 15 mol % 1,10-phenonthroline as ligand in DMF under oxygen atmosphere at 90 °C (Table 1, entry 16) temperature was found to be optimal.

Encouraged by these results, we next investigated the applicability of this methodology to several uracil derivatives (Table 2). The result indicates that *N*-substitution has some effect on the

Table 2
Palladium-catalyzed direct C-6 arylation of different uracil derivatives **1** with different boronic acids **2**[a]

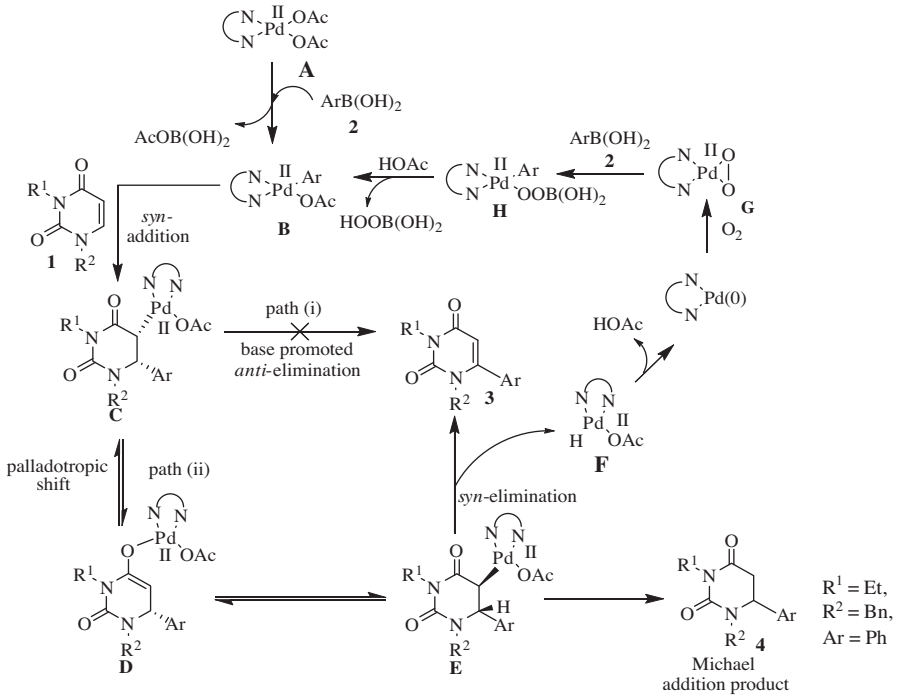
Entry	Starting	Product	Yield (%)	Entry	Starting	Product	Yield (%)
1	 **1a**	 **3a**	82	7	 **1g**	 **3g**	70
2	 **1b**	 **3b**	70	8	 **1h**	 **3h**	64
3	 **1c**	 **3c**	78	9	 **1i**	 **3i**	56[*]
4	 **1d**	 **3d**	82	10	 **1j**	 **3j**	69
5	 **1e**	 **3e**	78	11	 **1k**	 **3k**	0
6	 **1f**	 **3f**	75	12	 **1l**	 **3l**	0

[a] Reaction condition: Uracil **1** (1 equiv), aryl boronic acid **2** (3 equiv), $Pd(OAc)_2$ (10 mol %), 1,10-phenthroline (15 mol %), O_2 balloon in 10 ml dry DMF heated in a round bottom flask at 90 °C for 16 h; yields were calculated after flash chromatography.
[*] 32% of Michael addition product was also isolated.

yield of the arylated product. We found maximum yield 82% for 1,3-DMU (Table 2, entry 1) and lowest yield 56% for 1-benzyl-3-ethyluracil (Table 2, entry 9). It seems that the steric factor might have played some role in the formation of desired 6-arylated product. We also tested 3-methyl-2′,3′,5′-triacetyluridine (Table 2, entry 12), but it remained unchanged, i.e., no arylated product was found. 1-Methyl-3-ethyl and 1,3-diethyluracils also gave good yields of the products, in 75% and 70%, respectively (Table 2, entry 6, 7). For simple uracil (Table 2, entry 11) no arylated product was isolated and total recovery of stating material was observed. On the other hand, 1-benzyl-3-ethyluracil afforded moderate yield (56%) of 6-arylated product along with the Michael addition product **4** in 32% yield.

Furthermore, we studied the oxidative Heck reaction of 1,3-DMU with different types of arylboronic acids. The substituted arylboronic acids containing methyl or methoxy group also underwent the reaction smoothly under the same condition to give the corresponding 6-arylated product in good to high yield. For 2-methyl phenylboronic acid (Table 2, entry 2) the yield was somewhat lower indicating again that steric effect might have some influence on the fate of the reaction. The chloro group was also well tolerated in this reaction condition and offered 69% yield of **3j** (Table 2, entry 10). We also explored the reactivity of boronic ester and hetero arylboronic acids in this oxidative Heck process. When dimethyl phenyl boronate was treated with compound **1a,** the compound **3a** was obtained in comparatively lower yield of 40%. On the other hand when we tried heteroaromatic boronic acids (5-methoxypyridin-2-ylboronic acid, thiophen-2-ylboronic acid) the starting precursor remained unchanged.

A possible mechanistic pathway for the oxidative Heck reaction of arylboronic acid (**2**) with uracil (**1**) is shown in Scheme 1. Palladium phenanthroline complex[15] (**A**) takes part in a metal insertion step to form the complex **B** which subsequently adds to C–C double bond of uracil in *syn* fashion.[16] This palladated uracil (**C**) in turn, may afford the target compound **3** in two possible pathways; (i) base-catalyzed *β*-elimination via an E2-like mechanism or by (ii) *syn*-elimination via palladotropic shift.[17] Our failure to obtain the desired product in the base catalyzed condition (Table 1, entry 2) indicates that the reaction is most probably not going through *anti*-elimination mode.[12b] So this eliminates the possibility of pathway (i). We hypothesize that a palladotropic shift helps **C** to remain in equilibrium with **E** via the intermediacy of **D.** Now **E** would likely afford the desired product **3** via *syn*-elimination. In this reaction molecular oxygen plays an important role to complete the catalytic cycle by reoxidizing Pd(0) to Pd(II). When *N*-1 position is substituted by the benzyl group, it gets very difficult for the eliminating groups to come in *syn*-periplanar position, required for the elimination, due to steric reason with the phenyl ring at C-6 position. As a result, we obtained the product **4** in substantial amount along with the product **3i**.[12b] These findings rule out the base



Scheme 1. Proposed mechanism for the oxidative Heck reaction.

assisted β-elimination and give strong indications toward a ligand-assisted *syn*-elimination for this oxidative Heck[12b] type reaction. Thus, the function of phenanthroline, we conclude, in this reaction is as a ligand, not as a base.

In conclusion, we have developed an efficient, regioselective, and atom economical ligand assisted and base-free protocol for the synthesis of 6-aryl uracils via palladium-catalyzed oxidative Heck reaction of *N*-substituted uracils and arylboronic acids. This methodology provides a clear-cut route to biologically appealing 6-aryl uracils via regioselective direct arylation without prefunctionalization.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013 . 12 .092.

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