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"PhI(OCOCF3)2-mediated Ruthenium catalyzed highly site-selective direct ortho-C-H monoarylation of 2-phenylpyridine and 1-phenyl-1H-pyrazole and its derivatives by arylboronic acids"

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$PhI(OCOCF_3)_2$-mediated Ruthenium catalyzed highly site-selective direct ortho-C-H monoarylation of 2-phenylpyridine and 1-phenyl-1H-pyrazole and its derivatives by arylboronic acids

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We report a concise, versatile, and practical method for $PhI(OCOCF_3)_2$ mediated direct ortho C-H monoarylation of 2-phenylpyridine and its derivatives and 1-phenyl-1H-pyrazole via Ru catalyzed reaction. The significant advantage of this transformation is the creation of highly site selective C-C bond by using arylboronic acids as arylating agent under mild reaction conditions.

Aromatic C-H bonds are ubiquitous, an attribute that make them attractive starting materials for the construction of complex molecules *via* direct C-H activation, and functionalization under transition-metal catalyzed conditions. However, this same characteristic is also a great obstacle to developing practical methods for highly site-selective C-H bond functionalization reactions. This is because to achieve useful yields of a single product, the aromatic C-H functionalization must occur with high degree of site-selectivity for one C-H bond over the others within a molecule. In recent years, however, the advances in the development of homogeneous catalysis using various Pd, Ru, and Rh complexes as catalysts has set the stage for such challenging C-H bond functionalization.[1-7] The key to this development is a good understanding of C-H bond cyclometallation step that occur with transition-metals *via* chelation effect of the substrate that contains at least one chelating atom in proximity to the C-H bond that needs to be functionalized selectively.[1-7,8a]

Substituted pyridines such as 2-phenylpyridine and its derivatives not only constitute important bioactive compounds but also form excellent substrates for cyclometallation with transition-metal catalysts.[8] Therefore, they are ideal substrates for facile site-selective ortho aromatic C-H bonds functionalization for important C-C cross-coupling reactions such as direct C-H monoarylation. Such site-selective reactions have been reported for substituted pyridines using Rh, Ru, and Pd catalysis.[7, 9] However, the available reports are often pertinent to either ortho-alkyl or meta-alkyl substituted 2-phenylpyridine derivatives.[10-11] In the former case, one of the two ortho-C-H bonds in the phenyl ring of 2-phenylpyridine is blocked by alkyl substitution which prevents the formation of non-selective biarylated products. In the latter, site-selective monoarylations bearing meta-alkyl-substituents are controlled by steric interactions. Unfortunately, similar reactions still remain challenging for 2-phenylpyridine and its derivatives that contain two ortho aromatic C-H bonds that can be directly monoarylated with preference of one over another with high degree of site-selectivity.[12,13] However, serendipitously, we have discovered that the $[Ru(p\text{-cymene})Cl_2]_2$ catalyst system in the presence of $PhI(OCOCF_3)_2$ (a hyper-valent iodine oxidant)[12] in catalytic amounts, without requiring any external base or inorganic additives, directly enables highly site-selective direct monoarylation of 2-phenylpyridine with arylboronic acids.[9f] This new finding and the scope of this protocol for a range of substrate combinations for site-selective direct ortho C-H monoarylation in 2-phenylpyridine and its derivatives forms the focus of this paper.

We began our preliminary investigation by studying the direct aromatic ortho C-H monoarylation of 2-phenylpyridine using three different Ru catalysts with phenylboronicacid as arylating agent with various additives in different solvents at 100ºC in a sealed tube. The screening of the reaction conditions are summarized in Table 1. As can be seen, a variety of parameters such as nature of Ru catalyst, additives, and solvent play crucial role not only on the efficacy but also on the efficiency of the reaction. Notably, in the absence of Ru catalyst, as well as when additives alone were evaluated as catalyst, the direct C-H arylation reaction did not proceed at all for the model reaction. Among three Ru catalysts, namely, $RuCl_3$, $Ru(PPh)_3Cl$, and $[Ru(p\text{-cymene})Cl_2]_2$ evaluated for the model reaction, only the latter catalyst gave promising yields for desired C-H monoarylated product with additives such as benzoic acid (25%), bis(acetoxy)iodobenzene (20%) and silver oxide (10%) in toluene. A dramatic increase in the yield of desired

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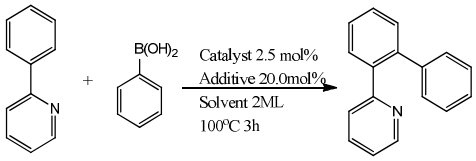
† Electronic Supplementary Information (ESI) available: Experimental Procedure, and NMR data available.

monoarylated product up to 85% was obtained when bis(trifluoroacetoxy)iodobenzene oxidant was used as additive with Ru(*p*-cymene)Cl_2 catalyst in toluene. This result is indeed very surprising because the use of structurally and functionally similar bis(acetoxy)iodobenzene oxidant gave only 20% yield for desired product. It should be noted that 1:1.2 loading of reactants are desirable because at higher loadings (1:2.4) the reaction gave non-selective biarylated product in low yields (20%) (Table 1; entry 13). Finally, it should be noted that in all the reactions screened using stoichiometric amounts of reagents, we have obtained only site-selective monoarylated products.

Table 1: Optimization of Ruthenium catalysed arylation of 2-phenyl pyridine with phenylboronicacid and various additives [a,b]

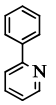
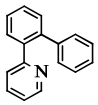
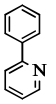
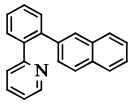
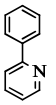
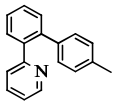
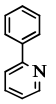
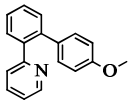
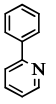
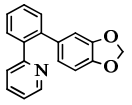
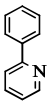
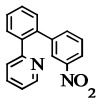
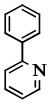
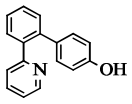
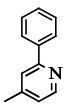
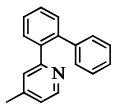
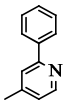
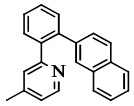


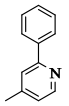
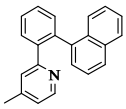
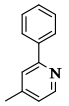
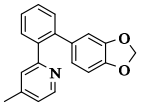
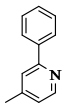
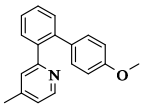
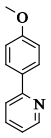
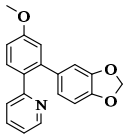
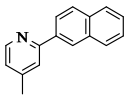
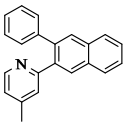
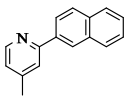
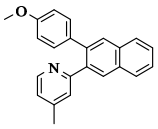
Entry	Catalyst	Additive	Solvent	Yield(%)
1	[Ru(*p*-cymene)Cl_2]$_2$	$Cu(OAC)_2$	Toluene	Trace
2	[Ru(*p*-cymene)Cl_2]$_2$	$AgSbF_6$	Toluene	Trace
3	[Ru(*p*-cymene)Cl_2]$_2$	Cu_2O	Toluene	Trace
4	[Ru(*p*cymene)Cl_2]$_2$	PhCOOH	Toluene	25
5	[Ru(*p*-cymene)Cl_2]$_2$	$PhI(OCOCH_3)_2$	Toluene	20
6	[Ru(*p*-cymene)Cl_2]$_2$	Ag_2O	Toluene	10
7	[Ru(*p*-cymene)Cl_2]$_2$	$PhI(OCOCF_3)_2$	Toluene	85
8	$RuCl_3$	$PhI(OCOCF_3)_2$	Toluene	Trace
9	[Ru(*p*-cymene)Cl_2]$_2$	$PhI(OCOCF_3)_2$	CH_3CN	10
10	[Ru(*p*-cymene)Cl_2]$_2$	$PhI(OCOCF_3)_2$	dioxane	20
11	[Ru(*p*-cymene)Cl_2]$_2$	$PhI(OCOCF_3)_2$	THF	40
12	[Ru(*p*-cymene)Cl_2]$_2$	$KO^tBu + PhI(OTf)_2$	Toluene	Trace[c]
13	[Ru(*p*-cymene)Cl_2]$_2$	$PhI(OCOCF_3)_2$	Toluene	20[d]
14	$Ru(PPh_3)_2Cl_2$	$PhI(OCOCF_3)_2$	Toluene	Trace
15	[Ru(*p*-cymene)Cl_2]$_2$	----	Toluene	Trace
16	----	$PhI(OCOCF_3)_2$	Toluene	<10%

Optimized reaction conditions: [a] 1.0 mmol 2-phenylpyridine, 1.2 mmol phenylboronic acid, 2.5 mol% Ru-catalyst, 20.0 mol% additive, and 2 ml of solvent for 3h. [b] Isolated yields. [c] Reaction with 20 mol% each of KO^tBu and $PhI(OTf)_2$ [d] biarylated product formed when reaction was performed with 2.4 mmol of phenylboronic acid.

Using optimized reaction conditions in hand, the scope of the reaction was evaluated for various substrates, and the results from this study are presented in Table 2. As was the case with phenylboronic acid (1a), we have obtained excellent yields as high as high as 89% for monoarylated product (2a) in 2-phenylpyridine when 2-naphthylboronic acid was used as arylating agent. Similarly, arylboronic acids containing electron-donating groups in the phenyl ring such as *p*-methyl (3a), *p*-methoxy (4a), methylenedioxy (5a) also gave excellent yields for desired monoarylated products (87%-91%) with 2-phenylpyridine. Interestingly, the arylboronicacids that contain electron-withdrawing groups such as *m*-NO_2, (6a) and *p*-OH (7a) in the aromatic ring gave desired products only in moderate yields, such as 65% and 72%, respectively.

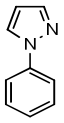
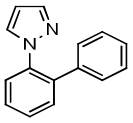
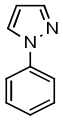
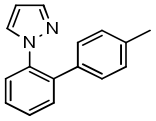
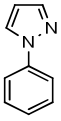
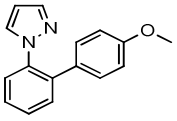
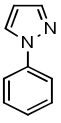
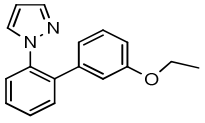
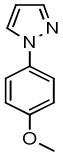
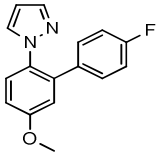
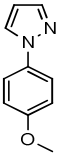
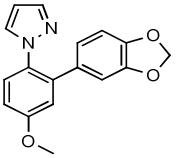
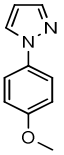
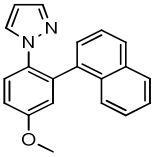
Table 2: Direct ortho C-H monoarylation reactions of diverse arylboronicacids with 2-phenylpyridine and its derivatives.

Entry	Substrate	Product	Code	Yield(%)
1			1a	85
2			2a	89
3			3a	87
4			4a	92
5			5a	90
6			6a	65
7			7a	72
8			8a	78
9			9a	83

Entry	substrate	Product	Code	Yield(%)
10			10a	85
11			11a	75
12			12a	89
13			13a	91
14			14a	76
15			15a	76

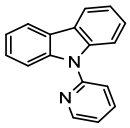
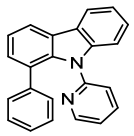
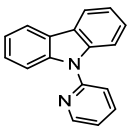
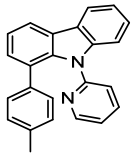
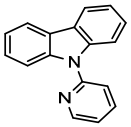
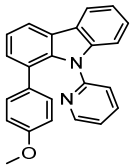
We also have evaluated the feasibility of similar site-selective monoarylation reactions involving meta-alkyl substitututed 2-phenylpyridine derivatives using our optimized reaction conditions. These studies are needed because we would like to know whether steric effects would also work favourable under our optimized reaction conditions. As a first step, we have reacted 2-([1,1'-biphenyl]-2-yl)-4-methylpyridine with phenylboronic acid, and this reaction gave desired monoarylated product (8a) in 78% yield. When the same pyridine substrate was reacted with 2-naphthylboronic acid, about 83% yields for the desired product (9a) was obtained. When 1-naphthylboronic acid was used, we have obtained site selectivity as high as 85% for monoarylated product (10a). Interestingly, when 3,4-methylenedioxyboronic acid is used as arylating agent, the ortho monoarylated product (11a) was obtained only in 75% yield. In contrast, when *p*-methoxyphenylboronic acid was reacted with 2-([1,1'-biphenyl]-2-yl)-4-methylpyridine, a much higher yield (89%) for (12a) was obtained. This result is consistent with our earlier observation that electron-donating *p*-methoxy functional bearing phenylboronic acid gave highest site-selectivity (92%) for mono-arylated product (4a) in reaction with 2-phenylpyridine. To better understand the role of *p*-OMe functional group, we synthesized 2-(-4-methoxyphenyl)-pyridine wherein *p*-OMe group is located in the phenyl ring of the 2-phenylpyridine instead of at the phenyl ring of boronic acid. This pyridyl substrate when reacted with 3,4-methylenedioxyboronic acid gave excellent yield (91%) for desired product (13a). Notably, our optimized monoarylation protocol are also applicable to *p*-methyl substituted 2-naphthylpyridine substrate. For example, the reaction of 4-methyl-2-(naphthalene-2-yl)pyridine with phenylboronic acid, we have obtained monoarylated product in 76% yield (14a). We have also performed the same reaction using *p*-methoxyphenylboronic acid so as to obtain desired product in 76% yield (15a). As was the case with direct arylation with 2-phenylpyridine (1a-6a), we did not observe formation of non-selective biarylated products.

Table 3: Direct ortho C-H monoarylation reactions of different arylboronicacids with 1-phenyl-1H-pyrazole and its derivative.

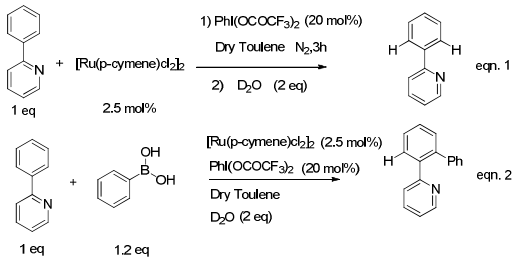
Entry	Substrate	Product	Code	Yield(%)
1			1a	78
2			2a	73
3			3a	85
4			4a	64
5			5a	71
6			6a	75
7			7a	68

We envisioned expanding the scope of this reaction to include other useful nitrogen-containing directing groups. As shown in Table 3, 1-Phenyl-1H-pyrazole (4a) and a variety of aryl boronic acids were subjected to the optimized reaction conditions, leading to the corresponding monoarylated products in good yields (64-85%). As was the case with direct arylation with 2-phenylpyridine (1a-6a) and its derivatives, we did not observe formation of non-selective biarylated products with1-Phenyl-1H-pyrazole (4a) substrate. However, our optimized reaction conditions when applied to 9-(pyridin-2-yl)-9H-carbazole substrate, as enumerated in Table 4, the monoarylation reaction did not proceed at all. It is unclear at this time why the negative result we have obtained with different substituted boronic acid with 9-(pyridin-2-yl)-9H-carbazole under our optimized reaction conditions (Table 4).

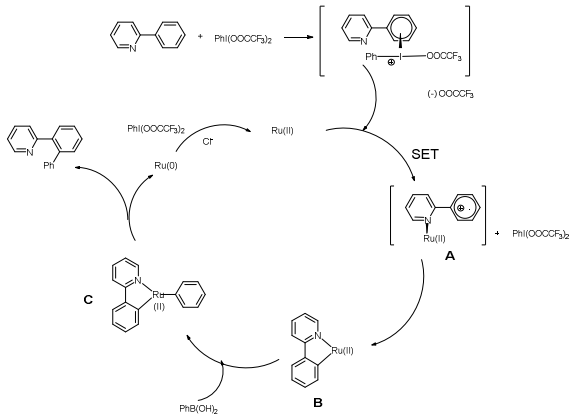
Table 4: Direct ortho C-H monoarylation reactions arylboronic-acids with 9-(pyridin-2-yl)-9H-carbazole.

Entry	Substrate	Product	Code	Yield(%)
1			1a	<10
2			2a	<10
3			3a	<10

As discussed earlier, Wan and Pfeffer et al. reported C–H bond electrophilic activation between $[Ru(benzene)Cl_2]_2$ and 2-phenylpyridine with k_H/k_D values of 1.5.[7a, 9f] Recently, several groups reported C–H activation by cooperative action of Ru(II) catalyst and base (concerted metallation deprotonation pathway).[14] Notably, only very poor yield was observed in our transformation in the presence of base (Table 1, entry 12). We have also obtained very low yield of the desired product when the reaction was performed using only $PhI(OOCCF_3)_2$ additive in the absence of Ru(II) (Table 1; entry16). On addition of 2 equiv. of D_2O to the reaction system containing 2-phenylpyridine in the absence of boronic acid, deuterium was not incorporated into the starting materials (eqn (1)). In the presence of boronic acid, however, the reaction gave, a large amount of non D-incorporated monoarylated product (eqn. 2) This demonstrates that preferential formations of non deuterated mono-substituted products were observed even when excess D_2O is used for the reaction (eqn. 2). Notably, these results are not surprising because, as described earlier, we have obtained highly site-selective formation of monoarylated products for as high as seven important substrates with arylboronic acids for 23 substrate combinations. On the basis of these results, we reasoned that both concerted metallation deprotonation pathway as well as initial electrophilic C-H bond cleavage and subsequent transmetallation with boronic acid were not determinant factor in the rate determining step of catalytic cycle even though cyclometallated species could be involved in reaction mechanism.



Scheme 1: Plausible mechanism for Ru catalyzed direct ortho C-H monoarylation of 2-phenylpyridine with arylboronic acid**.**



As an attempt to rationalize high site-selectivity observed for monoarylation, a plausible mechanism for the Ru(II)-catalyzed direct arylation of 2-phenylpyridine through aromatic C-H activation is presented in Scheme 1. First, the reaction of 2-phenylpyridine with bis(trifluoroacetoxy)iodobenzene affords formation of charge-transfer complexes. Such charge-transfer complexes are well known in the literature between arenes and $PhI(OOCCF_3)_2$ reagent.[15] This species, then reacts with Ru(II) precursor and in a single electron transfer (SET) pathway to form cationic radical species labelled A. This species in turn undergo cyclometallation reaction to form species labelled B reagent.[15] This species, then reacts with Ru(II) precursor and in a single electron transfer (SET) pathway to form cationic radical species labelled **A**. This species in turn undergo cyclometallation reaction to form species labelled **B**. This species in turn reacts with arylboronic acid to form corresponding monoarylated Ru(II) intermediate labelled **C**. Then, the reductive elimination of this species produce desired monoarylated product and Ru(0) species. Then the catalytic cycle continues with reactions with $PhI(OOCCF_3)_2$ and Cl^- ion to regenerate active Ru(II) species.

In summary, we developed a novel direct C-H arylation protocol using Ru-catalyzed oxidative coupling of arylboronic acids with arenes bearing 2-pyridyl and 2-pyrazole functionality. The outstanding site-selectivity of the ruthenium catalyst was reflected by the fact that lack of formation of undesired biarylated product originating from high nucleophilic reactivity of arylboronic acids. This operationally simple C-H functionalization was accomplished, in particular, through the use of hyper-valent based iodine based $PhI(OCOCF_3)_2$ reagent as oxidant in catalytic amounts under fairly mild conditions. The proposed charge transfer complex formation step in the proposed mechanism may partly explain observed high site-selectivity for monoarylated products for as many as 23 substrate combinations.

Acknowledgements

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