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COMMUNICATION

Dioxazolones as Masked Ester Surrogates in the Pd(II)-Catalyzed Direct C-H Arylation of 6,5-Fused Heterocycles.

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A simple and effective Pd(II)-catalyzed regioselective C(2)-H arylation of 6,5-fused heterocycles with dioxazolones as masked ester surrogate under mild conditions is reported. The significance of the arylation is highlighted by the new reactivity demonstrated in dioxazolones *via* proximal C-H activation of the cyclic carbonate of hydroxamic acid functionality under protic conditions.

Over the past two decades, transition-metal-catalysed C–H bond functionalization has revolutionized organic synthesis in delivering straightforward approaches for the rapid construction of carbon-carbon and carbon-heteroatom bonds.[1] Heterobiaryl scaffolds widely exist in natural products and pharmaceuticals, while also serving as intermediates in organic synthesis. In this context, 2-aryl benzo[*b*]furans and their derivatives are of considerable interest as they possess remarkable biological activities (Figure 1).[2-3] Despite the great progress in C-H bond arylation,[4] methods for the construction of C-2 arylated benzo[*b*]furans are rather limited. Conventional methods focus on cross-coupling strategies which strongly rely on pre-functionalized substrates. In contrast to cross-coupling reactions, the direct C-H bond functionalization of heteroarenes with aryl (pseudo) halides and aryl boronic acids have been developed to enable C-H arylation.

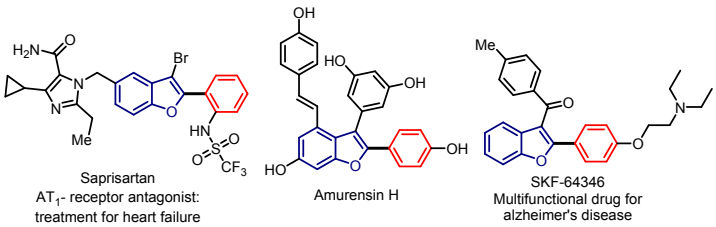
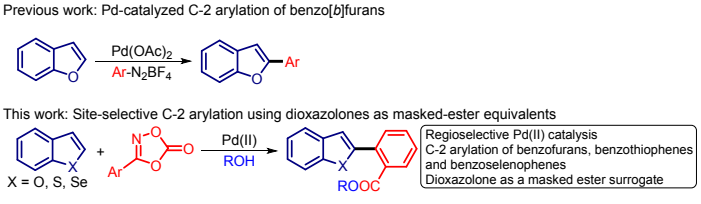


Figure 1: Selected bioactive molecules containing 2-Aryl benzo[*b*]furans.

However, some of these reported methods require the use of rather harsh conditions which limits their functional group compatibility. In spite of the advances in C-H arylation, the formation of 2-aryl benzo[*b*]furans have been relatively scarcely reported.[5-6] In 2014, Schnürch and co-workers reported the C-H bond arylation of benzo[*b*]furans using aryl bromides as the arylating agents.[6c] Recently, Noel and co-workers described a selective C-H arylation of benzo[*b*]furans using aryldiazonium salts.[7b] Although this is most selective protocol so far, there is still a demand for exploring simple and efficient methods for arylation employing highly reactive and atom-economical aryl donors.

Our continuous effort in C-H functionalization, to develop direct and site-selective C-C bond formation prompted us to investigate 1,4,2-dioxazol-5-ones as masked ester surrogates under protic conditions.[8] The limited exploration of esters as a directing group in C-H functionalizations can be attributed to the poor coordination ability of the ester functionality.[9] Meanwhile, as highly reactive precursors, dioxazolones have been intensively studied as a coupling partner for direct C-N bond forming reactions. It would therefore be intriguing to determine whether 1,4,2-dioxazol-5-ones can be employed as activated aryl targets, which to the best of our knowledge, has not been reported previously. Therefore, the challenge remains to explore the other reactivity pattern of dioxazolones unlike their efficiency for imido insertion. We describe herein a site-selective C-2 arylation of benzo[*b*]furans assisted *via* 1,4,2-dioxazol-5-ones as masked ester equivalents, under mild conditions (Scheme 1).



Scheme 1: Pd-catalyzed C-2 arylation of 6,5- fused heterocycles.

We initiated our studies with benzo[*b*]furan (**1**) and 3-phenyl-1,4,2-dioxazol-5-one (**2**) as the model substrates for this C-2 arylation and after considerable optimization (Table 1),[10] the desired coupled product methyl 2-(benzofuran-2-yl)benzoate

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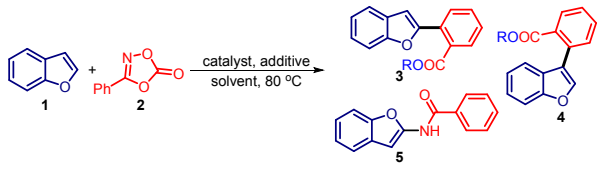
(**3aa**) was obtained in 55% yield using $Pd(OAc)_2$ (10 mol%), $Cu(OTf)_2$ (1.0 equiv.) and KF (1.5 equiv.) in MeOH at reflux temperature under inert conditions (Table 1, entry 2). Control experiments revealed that both $Pd(OAc)_2$ and the KF additive are indispensable in this transformation (Table 1, entries 3-4). Different oxidants were then investigated but $Cu(OTf)_2$ was found to perform much better than AgOTf and $Cu(OAc)_2$ (entry 7).[10] Besides $Pd(OAc)_2$, other transition metal catalysts (Rh and Ru) failed to catalyze this transformation. Among the other additives investigated, KF most-efficiently provided the C-2 arylated product **3**.

Table 1. Optimization of the reaction conditions[a]



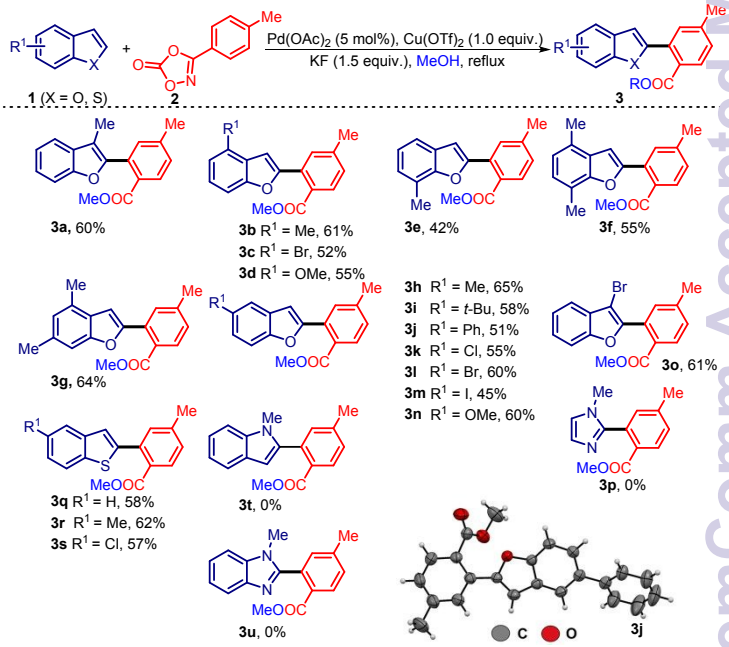
Entry	Catalyst/oxidant	Additive	Solvent	Yield[b] (%) of **3aa**
1	$Pd(OAc)_2$ / $Cu(OTf)_2$	KF	DCE	NR
2	$Pd(OAc)_2$ / $Cu(OTf)_2$	KF	MeOH	55
3	$Pd(OAc)_2$ / $Cu(OTf)_2$	-	MeOH	<10
4	$Cu(OTf)_2$	KF	MeOH	NR
5	$Pd(OAc)_2$	-	MeOH	NR
6	**$Pd(OAc)_2$ / $Cu(OTf)_2$**	**KF**	**MeOH**	**60[c]**
7	$Pd(OAc)_2$ / AgOTf	KF	MeOH	41
8	$Pd(TFA)_2$ / AgOTf	KF	MeOH	20
9	$Pd(OAc)_2$ / $Cu(OTf)_2$	KOAc	MeOH	NR
10	$Pd(OAc)_2$ / $Cu(OTf)_2$	KF	toluene	Complex mixture[d]
11	$Pd(OAc)_2$ / $Cu(OTf)_2$	KF	MeOH	NR[e]
12	$[RhCp^*Cl_2]_2$ / $AgSbF_6$	KOAc	DCE	NR
13	$[RhCp^*Cl_2]_2$ / $AgSbF_6$	KOAc	MeOH	NR
14	$[Ru(p\text{-cym})Cl_2]_2$/ $AgSbF_6$	KOAc	MeOH	NR

[a]Unless otherwise noted, all reactions were carried out using **1** (0.15 mmol), **2** (0.22 mmol), catalyst (10 mol %), oxidant (1.0 equiv.) in the presence of additive (1.5 equiv.) in a solvent (1.0 mL) at 80 °C for 12 h under N_2. [b]Isolated yields. [c]$Pd(OAc)_2$ (5 mol%), $Cu(OTf)_2$ (1.0 equiv.), KF (1.5 equiv.). [d]The reaction temperature is 110 °C. [e]Reaction under oxygen atmosphere.

Nature of the solvent had a noteworthy influence on this reaction, as the use of protic solvents such as MeOH, EtOH and ^{i}PrOH resulted in the desired product **(3)**. Non-alcoholic solvents such as DCE, acetonitrile, THF, DMF, DCM and toluene did not give desirable results (Table 1, entries 1, 10).[10] Decreasing the catalyst loading, and the amount of KF additive, as well as the oxidant, resulted in better product yield (Table 1, entry 6).[10] No product **3** was detected when the reaction was performed under an oxygen atmosphere (Table 1, entry 11).[10] Finally, the optimal conditions were found to be $Pd(OAc)_2$ (5 mol%), $Cu(OTf)_2$ (1.0 equiv.) and KF (1.5 equiv.) in MeOH at reflux temperature and **3** was obtained in 60% yield (Table 1, entry 6). It should be noted that in all the above reactions, exclusively C-2 arylated product **3** was obtained, neither the C-3 arylated product **4** or the amidation product **5** was detected in any of the cases.[10]

With the optimized conditions in hand, we investigated the scope of the reaction with respect to substituted benzo[*b*]furans and 1,4,2-dioxazol-5-ones as the coupling partner (Table 2). Good to moderate yields were obtained with substituents at various positions of benzo[*b*]furans and the C-2 selectivity was confirmed by X-ray crystallography of **3j** (CCDC 1897155). C-3 substituted benzo[*b*]furans gave desired products (Table 2, **3a, 3o**) in moderate yields under different protic solvents (MeOH, ^{i}PrOH). Diverse substituents at the C-4 and C-5 positions of benzo[*b*]furans (**1**) were well-tolerated with good yields (Table 2, **3b-3d, 3h-3n**). It was found that benzo[*b*]furans bearing electron-donating, electron-withdrawing substituents as well as halogens reacted smoothly with dioxazolones to afford C-2 arylated products in moderate yields. Disubstituted benzo[*b*]furans were also successfully reacted to afford C-2 arylated product (Table 2, **3f, 3g**) in decent yields. C-7 substituted benzo[*b*]furan was also found to be compatible and furnished the corresponding product **3e** with slightly decreased yield. To our delight, the methodology could also be successfully applied to synthesis C-2 selective arylated benzothiophenes (Table 2, **3q-3s**). However, much to our disappointment, *N*-Me indole, *N*-Me imidazole as well as the electron-poor pentafluorobenzene when subjected to the reaction conditions did not provide the desired arylation product (Table 2, **3t, 3u**).

Table 2. Substrate Scope of benzo[*b*]furans[a,b]

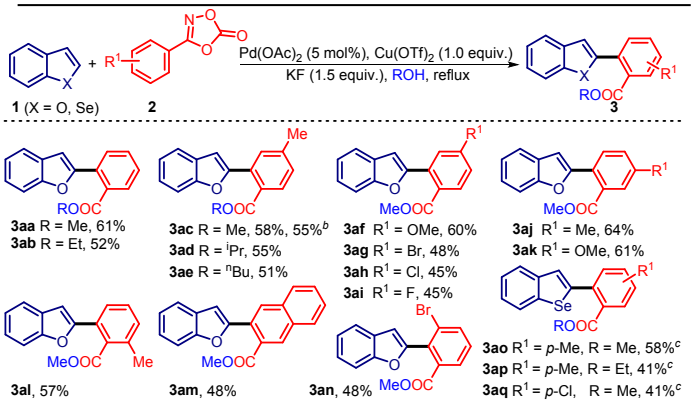


[a]Unless otherwise specified, all reactions were carried out using **1** (0.17 mmol), **2** (0.22 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OTf)_2$ (1.0 equiv.), KF (1.5 equiv.) at reflux temperature for 6 h-10 h under N_2. [b]Isolated yields after column chromatography purification.

Next, the reactivity of various substituted 1,4,2-dioxazol-5-ones were tested with benzo[*b*]furan **1** as the coupling partner. Dioxazolones bearing both electron-donating as well as electron-withdrawing aryl substitutents were found to react efficiently to give the corresponding arylated product **3** in good yields (Table 3, **3ac-3ai**). Notably, the methyl group at various positions of 3-phenyl-1,4,2-dioxazol-5-ones gave the C-2 selective product (Table 3, **3aj, 3al**). Interestingly, this protocol was also applicable to benzoselenophene (**3ao-3aq**), affording the corresponding products with moderate yields. To

test the practicality of this protocol, the reaction of **1a** with **2** was carried out in 1 mmol scale which worked smoothly (Table 3, **3ac** (55%)).

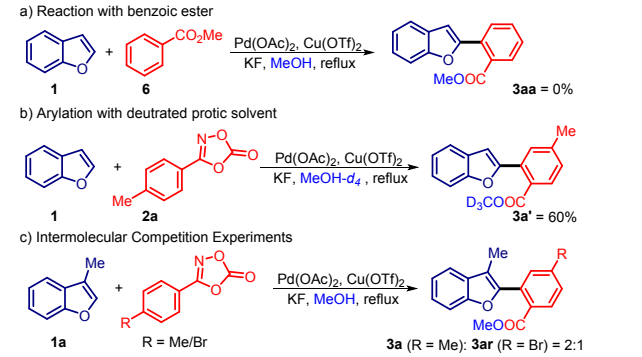
Table 3. Substrate Scope of 1,4,2-dioxazol-5-ones[a]



[a]Isolated yields after column chromatography purification. [b]Reaction carried at 1 mmol scale. [c]Reaction time 24 h.

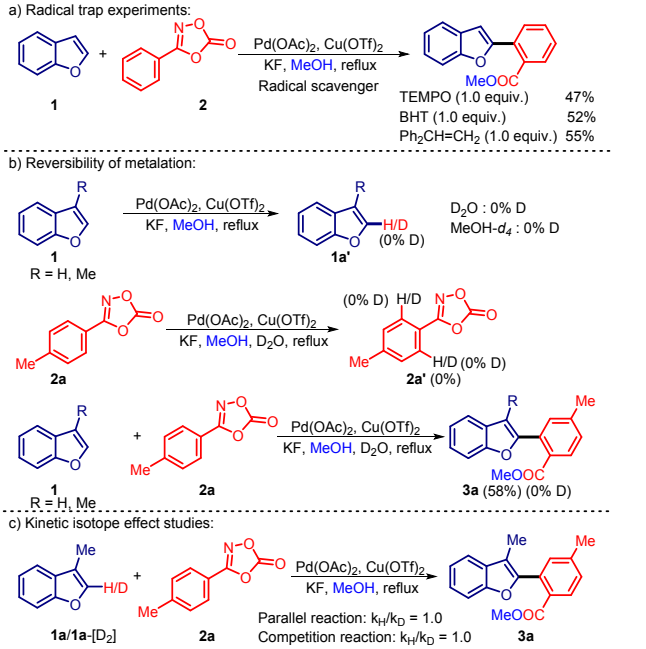
In attempts to gain an insight into the reaction mechanism, control experiments were performed as described in Scheme 2. Initially to understand the role of dioxazolone, C-2 arylation was conducted with benzoate ester and it did not afford any of the desired product **3aa** (Scheme 2a). This result excludes the possibility of the ester being involved in the reaction mechanism.

With the unprecedented mode of action of dioxazolone in the C-2 arylation reaction, we tried to delineate the role of the protic solvent in the reaction. For this we employed CD_3OD as the solvent under standard arylation conditions, which exclusively gave **3a'** with deuterium incorporation in the ester functionality of the C-2 aryl ring (Scheme 2b). To rationalize the mechanism, intermolecular competition experiments were carried out between differently substituted dioxazolones with 3-methyl benzofuran **1a** (Scheme 2c). This indicated electron-rich dioxazolones to be intrinsically reactive substrates. To further investigate the catalytic mechanism, several experiments were conducted. Radical trap experiments were undertaken with different radical scavengers, and the corresponding C-2 arylation product was obtained with only minor loss in the yield (Scheme 3a). This clearly excludes the possibility of a single electron transfer process being involved in the reaction pathway. Subsequently, the H/D exchange experiments were conducted in the presence of D_2O and CD_3OD as the co-solvent without arylation source, and these did not lead to deutration. This observation is indicative of an irreversible C–H metalation under optimized reaction conditions (Scheme 3b). Similarly, to examine the reversibility of C-H activation step, deuterium-labelling experiment was also performed on dioxazolone with D_2O as the co-solvent but no deuterium incorporation was observed on the starting material (Scheme 3b). Furthermore, when the benzofuran and dioxazolone was subjected to the standard conditions under D_2O as the co-solvent, no deuterium incorporation was observed, and the corresponding product was obtained with 58% yield (Scheme 3b). To further understand this C-H activation process, kinetic isotope effect on the benzofuran was measured. In the parallel reaction as well as in the intramolecular competition experiment, performed using **1a** and **1a**-[D_2] with the coupling partner **2a**, a value of k_H/k_D = 1.0 (Scheme 3c) was obtained.



Scheme 2: Control Experiments

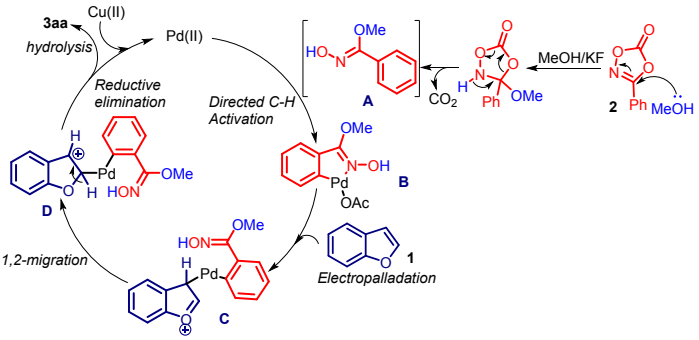
This suggested that the cleavage of C(2)-H bond of the benzofuran is not involved in the rate-determining step and that a concerted metalation deprotonation may not be involved. Unfortunately for us, despite our best efforts, we were unable to synthesize the C-2 deuterated dioxazolone.



Scheme 3: Mechanistic Studies

Based on the mechanistic studies conducted and the literature reports,[12] we propose a plausible catalytic cycle as depicted in Scheme 4. Initially the reaction pathway may involve formation of **A** where the dioxazolone **2** undergoes ring opening with CO_2 extrusion in presence of the protic solvent and the fluoride. C-H activation occurs to form the 5-membered palladacycle **B** *via* chelation-assistance of imine nitrogen atom on *N*-hydroxybenzimidate. Next, **1** directly coordinates with palladacycle **B** and *via* an electrophilic palladation leads to **C**. Subsequent 1,2-migration results in the intermediate **D**, followed by deprotonation.[12b,c] Finally,

reductive elimination and hydrolysis yields the desired product **3aa** and Cu(II) regenerates the catalyst.



Scheme 4: Proposed Reaction Mechanism

In summary, we have developed a palladium-catalyzed, site-selective C-2 arylation of 6,5-fused heterocycles with dioxazolones as the arylating agents. This methodology unveils a completely different mode of action of dioxazolones as a masked ester surrogate. This transformation proceeds smoothly with wide range of substrates and typically works with excellent levels of site-selectivity (C-2 arylation of benzofurans, benzothiophenes as well as benzoselenophenes) with good functional group tolerance. Thus, the method illustrates a convenient strategy for synthesis of 2-arylated-6, 5-fused heterocycle derivatives.

Conflicts of interest

There are no conflicts to declare.

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