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Regioselective palladium-catalyzed phenylation of ethyl 4-oxazolecarboxylate

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Abstract—The efficient and regioselective palladium-catalyzed C-2 arylation of ethyl 4-oxazolecarboxylate **1** with phenyliodide is described. The different parameters (solvent, base, ligand and catalyst) for the optimal conditions of this arylation process have been screened.

Aryl-substituted oxazoles are common features of a wide range of biologically active marine natural products.[1] They are also of considerable interest in medicinal chemistry[2] and as organic materials owing to their properties to emit light under radiations.[3] Current arylating methods usually employed to build up this di(hetero)aromatic systems are based upon a preliminary halogenation or metalation reaction followed by a transition metal-catalyzed cross-coupling reaction with aryl(heteroaryl)metals or aryl(heteroaryl)halides, respectively.[4] In recent years, it has been shown that electron-rich heteroarenes including oxazole can be directly arylated with a variety of aryl halides under direct transition metal catalyzed C–H bond functionalization.[5,6] This method appears very appealing since it does not require the rather tricky preliminary preparation of the requisite organometallic or halogenated azoles. However, this straightforward approach is fraught with difficulties associated with the regiochemistry of the coupling process, particularly with unsubstituted oxazoles.[6i] In this context, we conjectured that oxazole **1** equipped with a carboxylate function at the C-4 position of the heterocyclic nucleus could represent an interesting alternative model for probing arylation experiments. The choice of this structurally simple model originated from the following premises: (i) ethyl 4-oxazole carboxylate **1** is readily accessible by a two-step procedure[7] from the commercially available ethylisocyanoacetate; (ii) the presence of an EWG group at the C-4 position should allow the tailored and selective direct C–H arylation at the C-2 and/or C-5 position of the heterocyclic unit by a proper choice of experimental conditions. Literature precedent on the regioselective arylation of carboxylated furan and thiophene[6j] gave support to this assumption; (iii) the ethyl carboxylate function may undergo further chemical transformations at various oxidation states and then give access to diversely C-4 functionalized aryloxazoles, which can be regarded as key intermediates for the synthesis of more complex natural products; (iv) finally, the ethyl carboxylate function could be also easily removed by a decarboxylation process and then be considered as a temporarily blocking and/or activating group.[8] We then embarked on a program aimed at the regioselective palladium-catalyzed phenylation of ethyl 4-oxazolecarboxylate **1**.

Initially, as a typical experiment,[9] ethyl 4-oxazolecarboxylate **1** was allowed to react with phenyliodide in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and Cs_2CO_3 (2 equiv) in refluxing dioxane for 18 h. Rather disappointingly this operation delivered a mixture of 2-phenyloxazole **2** (30%), 5-phenyloxazole **3** (12%) and 2,5-diphenyloxazole **4** (17%) (Scheme 1; Table 1, entry 1).[10] Noteworthy Cs_2CO_3 appeared the

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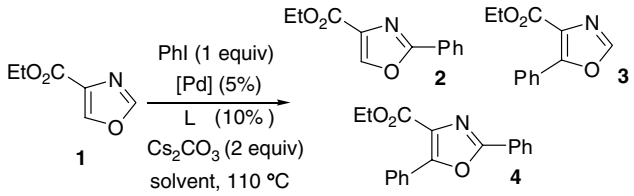


Scheme 1.

Table 1. Initial experiments of phenylation of **1**

Entry	[Pd]	L	Solv.	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]
1	$Pd(OAc)_2$	PPh_3	Dioxane	30	12	17
2	$Pd(OAc)_2$	PPh_3	DMF	40	0	0
3	$Pd(OAc)_2$	—	Dioxane	46	0	0
3	$Pd_2(dba)_3$	—	NMP	41	0	0
4	Pd/C	—	NMP	0	0	0
5	$Pd(PPh_3)_4$	—	Toluene	20	2	6
6	$Co(OAc)_2$	IMes	DMF	—	—	—

[a] Isolated product (two runs).

base of choice to secure the aryl–heteroaryl bond formation since performing the same reaction with K_2CO_3 or K_3PO_4 led only to recovered starting material.

We then opted to test the regiocontrolled conditions successfully adopted by Sharp[6j] for the regioselective arylation of the structurally related models, that is, 3-furan and 3-thiophenecarboxylates. Results are presented in Table 1 (entries 2–5). Interestingly, the use of the high polar solvent dimethylformamide (DMF) delivered exclusively the C-2 monoarylated compound **2** albeit in moderate yield (entry 2). Rather similar results were observed for reactions carried out in the absence of ligand (46%, entry 3) as well as with $Pd_2(dba)_3$ in solvent NMP (41%, entry 4) but the use of Pd/C was completely inefficient (entry 5). In contrast to the Sharp's furan and thiophene models[6j] the use of a rich phosphine ligand catalyst $Pd(PPh_3)_4$ in toluene did not permit to reverse the regiochemical outcome of the reaction and the 2-phenyloxazole derivative **2** was still solely obtained with a poor yield (entry 6). Sames recently reported a regioselective cobalt-catalyzed phenylation at the C-5 position of an unsubstituted oxazole in a modest 36% yield[6i] but attempts to phenylate compound **1** under these conditions met with no success (entry 7).

At this stage, we then decided to keep the initial conditions defined for the optimal formation of arylated products **2**–**4** (59%, Table 1, entry 1) and we set out to screen different bulky electron-rich ligands. Results are summarized in Figure 1 where it can be seen that the arylation process was effective without ligand and that the use of bulky alkylphosphines gave invariably rise to a mixture of arylated products with a moderate 59% average yield. We were pleased to observe that the use of the highly bulky Buchwald's ligand, that is, the 2-(dicyclohexylphosphino)-biphenyl, allowed regiospecific arylation at C-2 position of the oxazole nucleus then leading to the 2-phenyloxazole derivative **2** with a fairly good 69% yield.

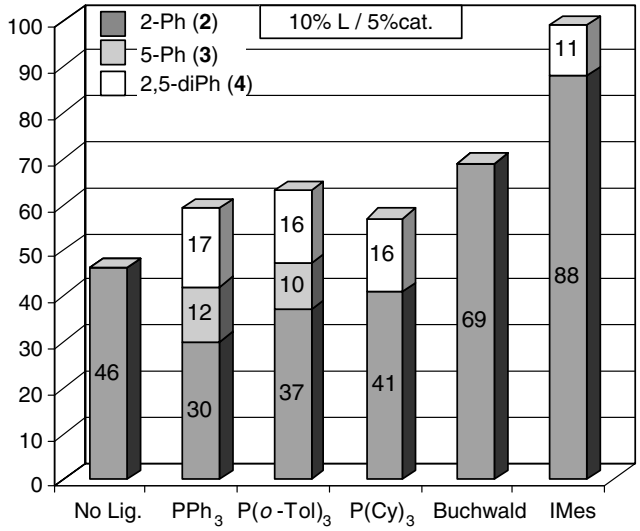


Figure 1. Screening of ligands. Reaction conditions: **1** (0.2 mmol), PhI (0.2 mmol), $Pd(OAc)_2$/L (5 mol %/10 mol %), Cs_2CO_3 (2 equiv), dioxane, 110 °C, 18 h.

But above all dramatically increased efficiency of the arylation process was observed by making use of 1,3-bis-(mesitylimidazolyl)carbene (IMes), which provided a 88% yield of the same regioisomer **2**. However, this was slightly detrimental to the selectivity of the reaction since **2** was accompanied with the diarylated compound **4** (11% yield).

At this stage, we switched our attention to a regiospecific arylation process at the C-2 position that would disfavor the contamination with the regioisomer **3** and the diarylated compound **4**.

To reach this goal, we kept specifically the two ligands giving the best percentage of the desired C-5 arylated isomer **3** in the first experiments, that is, PPh_3 and P(*o*-Tol)$_3$ (Fig. 1) and we investigated the influence of two parameters, the catalyst/ligand ratio and the nature of the solvent (dioxane, toluene or DMF). The results of the comparison with the first assays are presented in Figure 2. Increasing the catalyst amount had no significant influence on the production of the C-5 arylated isomer but the best selectivity for the C-2 position of the oxazole nucleus was obtained with PPh_3 as the ligand.

We then examined the influence of the solvent polarity on the survey of the regiochemistry (Fig. 3). In all cases, the 2-phenyloxazole derivative **2** was obtained as the major product and it should be pointed out that this regioisomer was obtained exclusively and in an excellent yield (86%) for the arylation reaction carried out in toluene using P(*o*-Tol)$_3$ as ligand. This latter result prompted us to investigate in this hydrocarbon solvent Buchwald's phosphine and the IMes carbene ligand, which proved to be efficient in the ethereal solvent dioxane (Fig. 1). Comparative results are presented in Figure 3. As expected, the 2-phenyloxazole derivative **2** was obtained as the major product. Buchwald's ligand gave excellent yield in all solvents but the IMes ligand revealed to be more efficient using dioxane as the solvent.

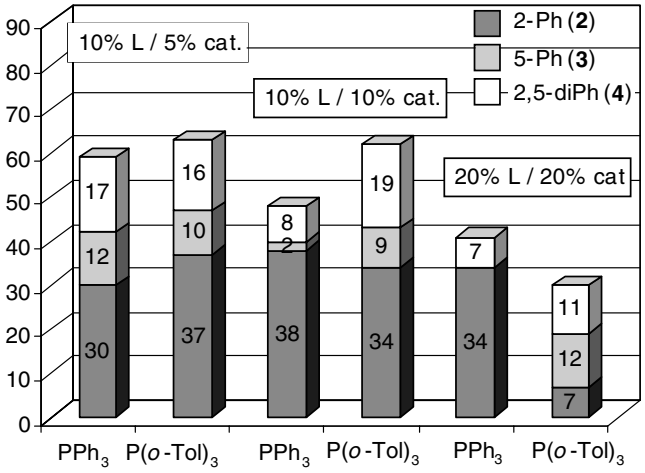
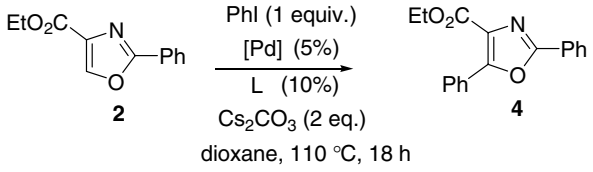


Figure 2. Screening of ligand/$Pd(OAc)_2$. Reaction conditions: **1** (0.2 mmol), PhI (0.2 mmol), L/cat (mol %), Cs_2CO_3 (2 equiv), dioxane, 110 °C, 18 h.

At this stage of our study it appears clearly that direct C–H arylation process applied to the model **1** highly favored the formation of the C-2 arylated regioisomer. It turns out clearly that all used ligands are able to selectively produce the 2-substituted product but the choice of the solvent is of central importance. In contrast, the efficiency of this process is undoubtedly associated with the bulkiness of the ligands and we can reasonably assume that the steric hindrance of these systems is the most significant factor operating for the regiocontrol of the oxazole nucleus arylation process.

The results of arylation reactions performed on ethyl 2-phenyl-4-oxazolecarboxylate **2** with a panel of ligands corroborate this hypothesis (Table 2). Thus, the bulky Buchwald's ligand and the IMes carbene ligand provided only poor yields of the diarylated compound **4** (entries 3 and 4) whereas the less hindered P(*o*-Tol)$_3$ ligand delivered almost quantitatively the diphenyloxazole derivative (entry 2). Noteworthy whereas P(*o*-Tol)$_3$ gives selectively the 2-substituted product **2** in toluene (Fig. 3), the 2,5-disubstituted model **4** is obtained in very good yield upon treatment of **2** under the same conditions. We can therefore assume that the second reaction is much slower than the first one.

Table 2. Phenylation of 2-phenyloxazole derivative **2**



Entry	L	**4** (%)[a]	**2** (S.M., %)[a]
1	PPh_3	47	46
2	P(*o*-Tol)$_3$	81 (96)[b]	8 (0)[b]
3	Buchwald	27	66
4	Imes	24	57

[a] Yield of isolated product.
[b] The reaction was performed in toluene as the solvent.

From the following observations: (i) the high selectivity of the arylation of ethyl 4-oxazolecarboxylate **1** at the C-2 position; (ii) the lack of influence of the solvent polarity and ligand/catalyst ratio on the C-2 regioselectivity; (iii) the strong evidence that steric hindrance is the main factor controlling the regioselectivity, one can tentatively envisage two mechanisms,[5,6b,h,j,m] depicted in Scheme 2, which involve either a cross-coupling reaction (pathway A) or an electrophilic substitution process (pathway B).

It has been reported that arylation at acidic sites of heterocycles could be promoted by addition of CuI salt.[6e,i,j,m] In order to test the viability of pathway

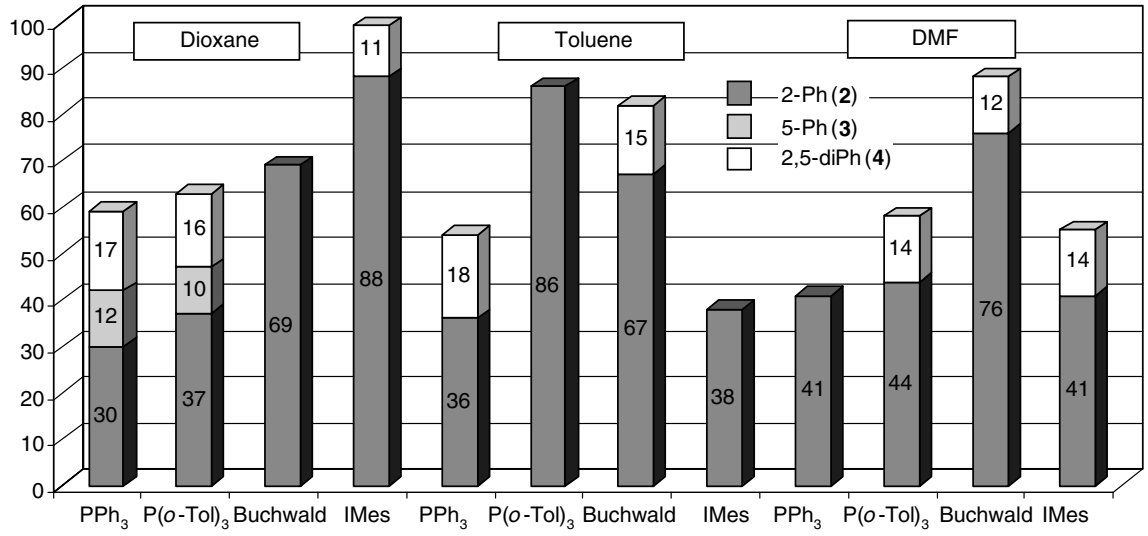
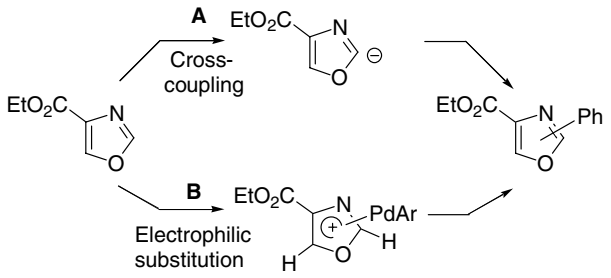


Figure 3. Screening of solvents. Reaction conditions: **1** (0.2 mmol), PhI (0.2 mmol), $Pd(OAc)_2$/L (5 mol %/10 mol %), Cs_2CO_3 (2 equiv), solvent, 110 °C, 18 h.



Scheme 2. The two mechanistic hypothesis for the arylation of ethyl 4-oxazolecarboxylate **1**.

A, we then attempted to perform the arylation of **1** using CuI as co-catalyst but the reaction failed. Consequently, the electrophilic aromatic substitution initially proposed by Miura[6m] appears to be the likeliest mechanism for the arylation of such an electron-rich heteroarene.[5] According to this mechanistic pathway, arylation should occur at the most electron-rich site. Ab initio calculations (Cerius^2/6-31G*) on model **1** have revealed that the HOMO indicating the most rich-electron site resides on C-2 and C-5 carbons. Arylation should then occur at these two positions. We were pleased to observe that all experimental observations gave support to this electrophilic substitution mechanism. The preferred formation of the C-2 arylated compound may tentatively be assigned to a less hindered C-2 position.

In conclusion, a straightforward and efficient regioselective C-2 phenylation of ethyl 4-oxazolecarboxylate **1** has been disclosed. The screening of the different parameters (base, solvent, catalyst/ligand ratio) has revealed that the arylation process is more efficient with the bulky electron-rich ligands 2-(dicyclohexylphosphino)biphenyl in dioxane and the electron-poor ligand P(*o*-Tol)$_3$ in toluene, which both allow excellent yield and selectivity. Furthermore, it has been established that the solvent and the ligand/catalyst ratio have no significant influence on the preferential C-2 versus C-5 arylation of the parent model thus supporting an electrophilic substitution pathway for the C-2 and C-5 arylation as well. We believe that this work demonstrates a general methodology for arylation of oxazole derivatives, which could be applied to 2,4- and 2,4,5-polysubstituted and functionalized models. Further work in this direction is now in progress.

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9. The phenylation reactions were carried out in a tube sealed under Ar. A solution of ethyl 4-oxazolecarboxylate (**1**, 50 mg, 0.35 mmol) was allowed to react with phenyl iodide (71.5 mg, 0.35 mmol) in the appropriate solvent (1 mL) with the different catalysts and ligands at 110 °C under stirring for 18 h. The reaction mixture was filtered

on Celite® and purified by flash column chromatography on silica gel using AcOEt–hexanes (20:80) as eluent.
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