Pd-Catalyzed *ortho*-Arylation of *N*-Aryloxazolidinones with Simple Arenes Using Sodium Persulfate

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Dedicated to Prof. Xiyan Lu for his contributions to Pd catalysis.

Abstract: We report a Pd-catalyzed *ortho*-arylation of *N*-aryloxazolidinones under mild conditions. Our oxidative cross-coupling consumes sodium persulfate ($Na_2S_2O_8$), a green and environmentally benign reagent, as the terminal oxidant. Trifluoroacetic acid (TFA) is critical for reactivity.

Key words: palladium, arylation, biaryl, cross-coupling, metallacycle

N-Aryloxazolidinones have promising medicinal value as both antidepressant and antibacterial agents.[1] Two notable examples include DuP 721, linezolid, and toloxatone (Figure 1). As such, efforts toward their preparation have attracted attention from the synthetic community.[2] Developing methods for late-stage functionalization of *N*-aryloxazolidinone would aid the drug-discovery process by providing an efficient approach for pursuing structure–activity relationships (SAR). Despite recent developments in ligand-assisted C–H bond activation,[3] cyclometalation directed by the cyclic carbamate functionality is rare.[4] Sanford and co-workers demonstrated that hypervalent iodine reagents were suitable cross-coupling partners for direct arylation.[4a] Herein, we report an approach to *N*-biphenyloxazolidinones by Pd-catalyzed oxidative *ortho*-arylation with simple arenes and sodium persulfate ($Na_2S_2O_8$, Scheme 1).

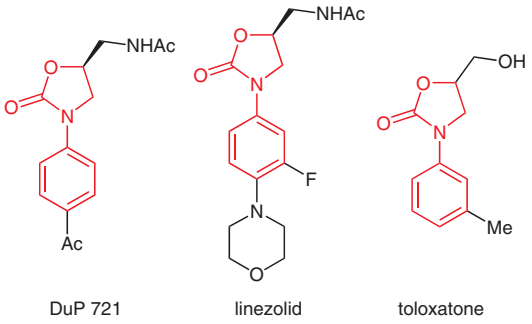
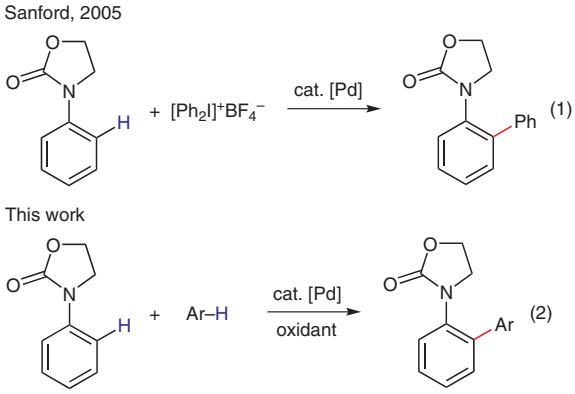


Figure 1 Examples of therapeutic *N*-aryloxazolidinones[1]

Biaryl C–C bonds are traditionally formed by transition-metal-catalyzed cross-coupling of an organohalide with a suitable organometallic reagent.[5] Cross-coupling of simple arenes involving concomitant oxidation of two C–H bonds is an attractive alternative.[3a,4c,6] By installing functionalities in the substrate capable of coordinating to palladium, regioselective functionalization is possible.[4c,6g–l] Our group reported an oxidative cross-coupling using $Na_2S_2O_8$ as the stoichiometric oxidant in the presence of trifluoroacetic acid (TFA).[4c,6i] We observed efficient *ortho*-arylation of *N*-aryloxazolidinones with electron-deficient arenes under similar conditions (Table 1). While strong oxidants (i.e., $Na_2S_2O_8$) were effective, weaker oxidants including copper and silver salts (Table 1, entries 5–11) led to decreased efficiencies. Removing either the palladium catalyst or TFA led to inhibition of the oxidative cross-coupling (Table 1, entries 1 and 2).



Scheme 1 Catalytic arylation of *N*-aryloxazolidinones[4]

With our optimized conditions, a number of *N*-aryloxazolindinones were subjected to *ortho*-arylation (Table 2). Electron-deficient arenes (e.g., *o*-dichlorobenzene, *o*-difluorobenzene) were optimal arene coupling partners. In *ortho*-disubstituted arenes, arylation favors functionalization of the C4–H bond selectively; however, using *o*-difluorobenzene, a minor regioisomer resulting from coupling of the C3–H bond was also observed (Table 2, entries 2, 5, 7, 8, 10, 12–13).

Characterization of the regioisomers was confirmed by X-ray crystallography (Figure 2). This observation contrasts our related work on oxidative *ortho*-arylation of *O*-phenylcarbamates where we observed highly regioselective coupling with a wide array of simple arenes.[4c] When we used 1-chloro-2-fluorobenzene as the cross-coupling partner (Table 2, entries 3 and 6), arylation occurred at both

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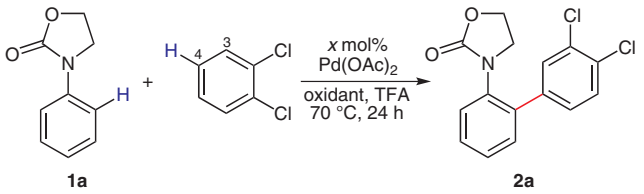
Table 1 Reaction Optimization[a]



1a 2a

Entry	x (mol%)	Oxidant (equiv)	TFA (equiv)	Yield (%)[b]
1	0	$Na_2S_2O_8$ (3)	5	0
2	10	$Na_2S_2O_8$ (3)	0	0
3	10	$Na_2S_2O_8$ (3)	5	91 (74[c])
4	10	Oxone (2)	5	0
5	10	AgOAc (3)	5	0
6	10	Ag_2CO_3 (3)	5	1
7	10	$Cu(OAc)_2$ (3)	5	4
8	10	benzoquinone (3)	5	2
9	10	$Ce(SO_4)_2{\cdot}4H_2O$ (3)	5	2
10	10	$Mn(OAc)_3{\cdot}2H_2O$ (3)	5	0
11	10	O_2 (1 atm)	5	8

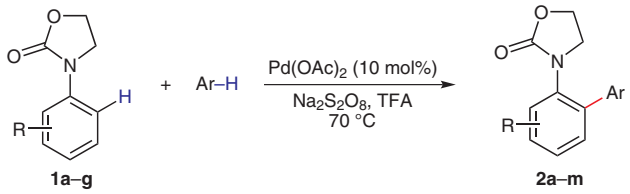
[a] Conditions: substrate (0.2 mmol), *o*-dichlorobenzene (1 mL).
[b] Conversion determined by GC analysis.
[c] Isolated yield after 43 h.

C4 and C5, suggesting that steric factors predominantly dictate the regioselectivity of C–C bond formation. This reaction tolerates electron-neutral (Table 2, entries 1–12) and electron-rich (Table 2, entry 13) *N*-aryloxazolidinones.

Oxidative *ortho*-arylation with electron-neutral and electron-rich arenes, however, was unproductive (Table 3). This is likely due to competing homodimerization of either the substrate or unactivated arene coupling partner if either of these components is significantly more electron rich than the other. Moreover, more electron-rich simple arenes undergo higher levels of homocoupling than their electron-poor congeners.[4c,6i] This reactivity complements that of *N*-phenylpyrrolidinones[6i] (Table 3, entries 4–6). On the other hand, diphenylimidazolidinones were inefficient in directed oxidative coupling with *o*-dimethoxybenzene, benzene, and *o*-dichlorobenzene (Table 3, entries 7–9).

In analogy to our earlier work,[4c,6i] we propose the mechanism of this oxidative coupling involves initial ligand-assisted cyclopalladation followed by an arene C–H bond-activation step. The details of this mechanism, however, warrant further studies. In summary, we have disclosed an efficient oxidative arene cross-coupling approach for the direct functionalization of *N*-aryloxazolidinones. Our strategy employs unactivated arenes as the coupling partners using $Na_2S_2O_8$, an environmentally benign and easy to handle stoichiometric oxidant.

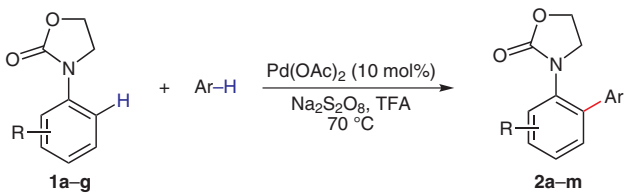
Table 2 Oxidative *ortho*-Arylation of *N*-Aryloxazolidinones[a]

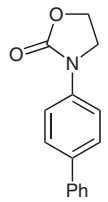
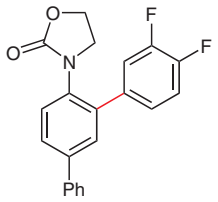
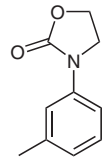
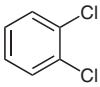
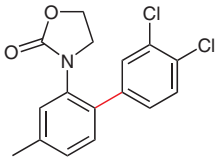
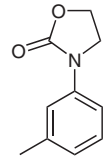
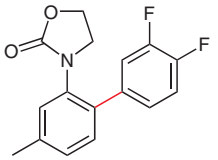
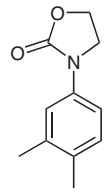
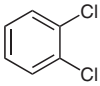
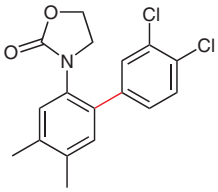
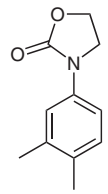
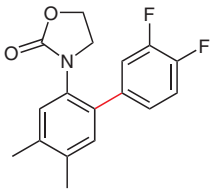
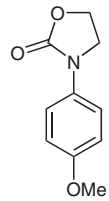
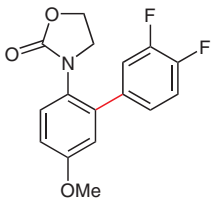


1a–g 2a–m

Entry	Substrate	Arene	Product	Yield (%)[b]
1	**1a**		**2a**	74
2	**1a**		**2b**	73 (93:7)[c]
3	**1a**		**2c**	72 (54:41:5)[c]
4	**1b**		**2d**	99
5	**1b**		**2e**	92 (90:10)[c]
6	**1b**		**2f**	97 (56:40:4)[c]
7	**1c**		**2g**	66 (91:9)[c]

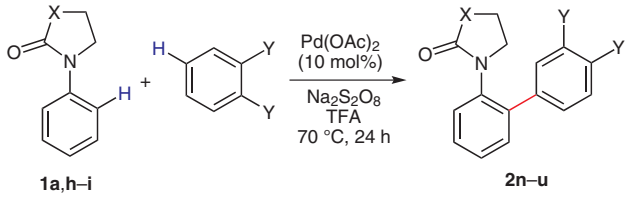
Table 2 Oxidative *ortho*-Arylation of *N*-Aryloxazolidinones[a] (continued)



Entry	Substrate	Arene	Product	Yield (%)[b]
8	 **1d**		 **2h**	38 (94:6)[c]
9	 **1e**		 **2i**	99 (84:16)[c]
10	 **1e**		 **2j**	98 (91:9)[c]
11	 **1f**		 **2k**	99[d]
12	 **1f**		 **2l**	99 (84:16)[c]
13	 **1g**		 **2m**	90 (90:10)[c]

[a] Conditions: Substrate (0.2 mmol), arene (1 mL), $Pd(OAc)_2$ (10 mol%), $Na_2S_2O_8$ (3 equiv), TFA (5 equiv), 35.5–47.5 h.
[b] Isolated yields.
[c] Isolated as a mixture of isomeric products. See Supporting Information for details.
[d] $K_2S_2O_8$ (3 equiv) was used.

Table 3 Electronic Effects of Oxidative *ortho*-Arylation[a]



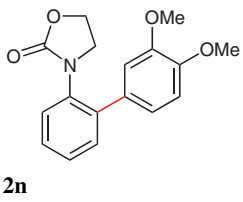
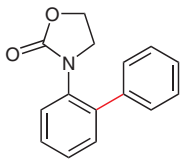
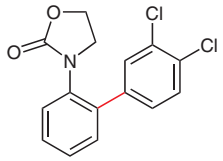
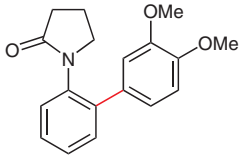
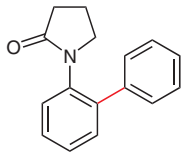
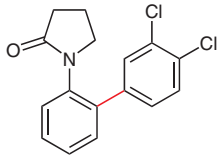
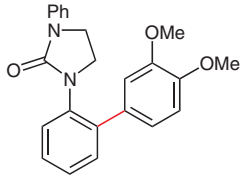
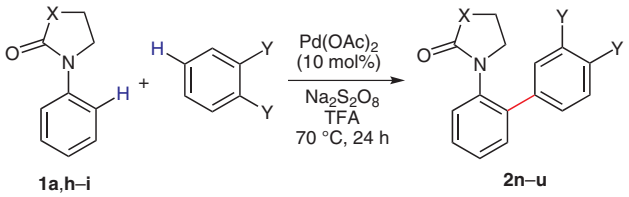
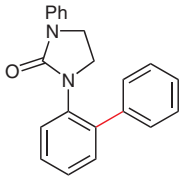
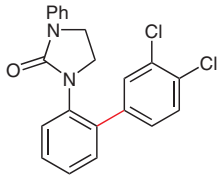
Entry	X	Y	Product	Yield (%)[b]
1	O	OMe	 **2n**	0
2	O	H	 **2o**	14
3	O	Cl	 **2a**	91 (74[c])
4	CH_2	OMe	 **2p**	12 (73[d])
5	CH_2	H	 **2q**	74 (83[e])
6	CH_2	Cl	 **2r**	3
7	NPh	OMe	 **2s**	0

Table 3 Electronic Effects of Oxidative *ortho*-Arylation[a]



1a,h–i 2n–u

Entry	X	Y	Product	Yield (%)[b]
8	NPh	H	 **2t**	0
9	NPh	Cl	 **2u**	0

[a] Conditions: substrate (0.2 mmol), arene (1 mL), $Pd(OAc)_2$ (10 mol%), $Na_2S_2O_8$ (3 equiv), TFA (5 equiv).
[b] Conversion determined by GC analysis.
[c] Isolated yield after 43 h.
[d] Isolated yield in 0.5 mL *o*-dimethoxybenzene at 90 °C after 54 h.
[e] Isolated yield after 23 h.

General Procedure for the Pd-Catalyzed Oxidative *ortho*-Arylation

In a one-dram vial equipped with a Teflon cap was added the substrate (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), $Na_2S_2O_8$ (0.6 mmol), and the unactivated arene (1 mL). TFA (1 mmol) was added to the resulting suspension. The vial was stirred on a heating block at 70 °C for the indicated length of time. The reaction mixture was cooled to r.t., diluted in EtOAc, and washed with sat. $NaHCO_3$. Subsequently, the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography or preparative TLC (eluent: hexanes–EtOAc) to afford the pure arylation products. See Supporting Information for more details.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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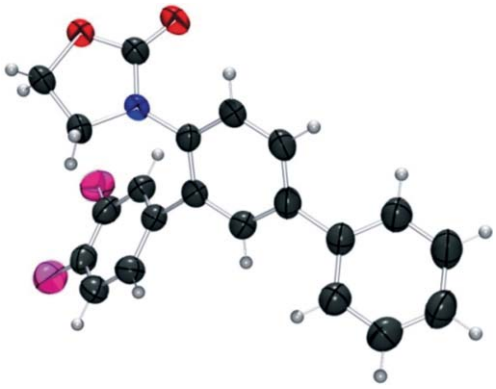

Figure 2 ORTEP plot of the major isomer of arylation product **2h**; anisotropic displacement ellipsoids are shown at the 50% probability level

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