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3-Aryl-2-oxazolidinones through the Palladium-Catalyzed *N*-Arylation of 2-Oxazolidinones

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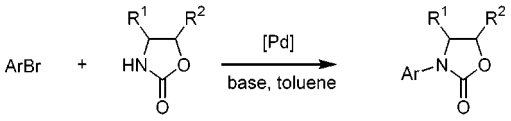
ABSTRACT



3-Aryl-2-oxazolidinones are obtained in good yields through the palladium-catalyzed *N*-arylation of 2-oxazolidinones with aryl bromides. The nature of aryl bromides, phosphine ligands, bases, and solvents strongly affects the reaction outcome.

Substituted 3-aryl-2-oxazolidinones have recently attracted much attention as pharmacologically active compounds. For example, 5-acetamidomethyl-3-aryl-2-oxazolidinones[1] have been shown to exhibit a potent antibacterial activity, and 5-(hydroxymethyl)-3-(3-methyl phenyl)-2-oxazolidinone is a drug used as an antidepressant.[2] For this reason, a variety of approaches to this class of compounds have been described,[1e,3] and some of them are based on palladium catalysis.[4] New and flexible synthetic protocols, however, are highly desirable, especially when they accommodate important functionalities and are broad in scope.

In our efforts aimed at the development of new syntheses of heterocycles, we were interested in the preparation of 3-aryl-2-oxazolidinones and envisaged the palladium-catalyzed carbon−nitrogen bond-forming reactions between aryl halides and amines or amides[5] as a viable route to this

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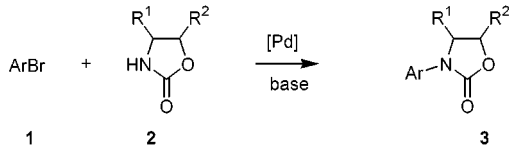
class of compounds. Particularly, we thought that the palladium-catalyzed *N*-arylation of the 2-oxazolidinone nucleus (Scheme 1) might provide a convenient and useful alternative to known methods.

Scheme 1 *N*-Arylation of 2-Oxazolidinones



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Here we report that such a process can be attained and that its success depends on the appropriate selection of some reaction parameters such as the nature of the catalyst system, the base, and the solvent.

Initial attempts were based on the use of the same catalyst system applied to the preparation of *N*-aryl lactams[6] [Pd(OAc)$_2$, dppf,[7a] NaOBu^t, toluene, 120 °C]. Under these conditions, good results were obtained with aryl bromides containing electron-withdrawing groups *para* to the bromo group (Table 1, entries 1−3),[8] though with *p*-bromobenzaldehyde only a moderate yield was attained most probably because of the instability of the aldehyde group under the reaction conditions (Table 1, entry 4). Electron−neutral and slightly electron-rich aryl bromides failed to give the desired products (Table 1, entries 6−8). Therefore, to extend the methodology to a wider range of aryl bromides, *m*-bromoanisole was selected as the model system and the influence of phosphine ligand, bases, and solvents on the reaction outcome was briefly investigated.

Table 1. Pd(OAc)$_2$/dppf-Catalyzed *N*-Arylation of 2-Oxazolidinone **1** (R^1 = R^2 = H)[a]

entry	aryl bromide **1**	time (h)	yield (%), **3**[b]
1	*p*-CN-C$_6$H$_4$-Br	24	75, **a**
2	*p*-NO$_2$-C$_6$H$_4$-Br	5	80, **b**
3	*p*-MeCO-C$_6$H$_4$-Br	3	71, **c**
4	*p*-CHO-C$_6$H$_4$-Br	5	45, **d**[c]
5	*p*-CHO-C$_6$H$_4$-Br	5	—[d]
6	PhBr	16	tr, **e**
7	*m*-MeO-C$_6$H$_4$-Br	16	9, **f**
8	*p*-Bu^t-C$_6$H$_4$-Br	16	tr, **g**

[a] Unless otherwise stated, reactions were performed in toluene at 120 °C using the following molar ratios: **1**:**2**:Pd(OAc)$_2$:dppf: NaOBu^t = 1:1.5:0.05:0.05:1.4. [b] Yields refer to single runs and are given for isolated products. The compounds are 95−99% pure as judged by NMR and HPLC analysis. [c] *p*-Bromobenzyl alcohol and *tert*-butyl *p*-bromobenzoate, very likely generated via a Cannizzaro-type reaction, were isolated in 19% and 3% yield, respectively. [d] In the presence of Cs$_2$CO$_3$. *p*-Bromobenzaldehyde was recovered in 51% yield.

Only minor amounts of **3f** were formed by using a variety of catalyst systems such as Pd(OAc)$_2$/P(Cy)$_3$[7b] or Pd(OAc)$_2$/P(Bu^t)$_3$ at 120 °C in the presence of lithium, sodium, potassium carbonate, and bicarbonate bases, or NaOBu^t in toluene, or Pd$_2$(dba)$_3$/dppf in the presence of NaOBu^t in toluene. Even the use of Pd$_2$(dba)$_3$ with the chelating ligand Xantphos[7c,9] and Cs$_2$CO$_3$ in dioxane (conditions reported to give excellent results with amides and carbamates)[10] led to the formation of **3f** in trace amounts. Use of the same catalyst system and base [Pd$_2$(dba)$_3$, Xantphos, Cs$_2$CO$_3$] but switching to toluene as the solvent produced a significant improvement, still unsatisfactory, however, from a synthetic point of view: **3f** was isolated in 38% yield.

Eventually, we were pleased to find that subjecting *m*-bromoanisole to 2-oxazolidinone in the presence of Pd(OAc)$_2$, Xantphos, and NaOBu^t, in toluene, at 120 °C for 16 h afforded **3f** in 73% yield (15% at 100 °C). Substitution of Pd(OAc)$_2$ with Pd$_2$(dba)$_3$, keeping all other parameters the same, produced a similar result (**3f** was isolated in 71% yield). When the procedure[11] was extended to include other aryl bromides (Table 2), Pd(OAc)$_2$ and Pd$_2$(dba)$_3$ gave similar results in some cases (Table 2, entries 5 and 6), but in general, the latter was found to give higher yields (Table 2, entries 3 and 4, 9 and 10, 13 and 14). Consequently, Pd$_2$(dba)$_3$ was used as catalyst precursor.

Under these conditions [Pd$_2$(dba)$_3$, Xantphos, NaOBu^t, toluene, 120 °C], a variety of neutral, slightly electron-rich, and slightly electron-poor aryl bromides reacted satisfactorily. Depending on the nature of the aryl bromide, minor amounts of *N*-phenyl derivatives, most probably generated via phenyl transfer from the ligand to the nitrogen atom,[12] were isolated (see, for example, Table 2, caption to entry 17). The presence of substituents close to the carbon−bromo bond was found to hamper the reaction (Table 2, compare entry 11 with entries 12 and 13, and entry 4 with 15).

With aryl bromides containing electron-withdrawing groups *para* to the bromo group, the Pd(OAc)$_2$/dppf combination

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(7) (a) dppf = 1, 1′-bis(diphenylphosphino)ferrocene. (b) Cy = cyclohexyl. (c) 9,9-Dimethyl-4,6-bis(diphenylphosphino)xanthene.

(8) **Representative Procedure.** A solution of dppf (25.0 mg, 0.045 mmol) and Pd(OAc)$_2$(8.4 mg, 0.019 mmol) in toluene (1 mL) was stirred under argon at room temperature for 20 min. Then, *p*-bromoacetophenone (150 mg, 0.75 mmol), 2-oxazolidinone (82 mg, 1.13 mmol), NaOBu^t (101.4 mg, 1.056 mmol), and toluene (2 mL) were added. The reaction mixture was refluxed at 120 °C for 2 h. After this time, the mixture was cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried (Na$_2$SO$_4$) and concentrated under vacuum. The residue was purified by chromatography on silica gel eluting with a *n*-hexane/ethyl acetate 60/40 (v/v) mixture to give **3c** (109 mg, 71% yield).

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(11) **Representative Procedure.** A solution of Xantphos (21.7 mg, 0.037 mmol) and Pd$_2$(dba)$_3$ (17 mg, 0.19 mmol) in toluene (1 mL) was stirred under argon at room temperature for 20 min. Then, *m*-bromoanisole (95 μL, 0.75 mmol), 2-oxazolidinone (71.3 mg, 1.1 mmol), NaOBu^t (100.9 mg, 1.4 mmol), and toluene (1 mL) were added. The reaction mixture was refluxed at 120 °C for 16 h. After this time, the mixture was cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried (Na$_2$SO$_4$) and concentrated under vacuum. The residue was purified by chromatography on silica gel eluting with a *n*-hexane/ethyl acetate 70/30 (v/v) mixture to give **3f** (103 mg, 71% yield).

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Table 2. $Pd_2(dba)_3$- or $Pd(OAc)_2$/Xantphos-Catalyzed *N*-Arylation of 2-Oxazolidinone **2** ($R^1 = R^2 = H$)[a]

entry	aryl bromide **1**	[Pd]	yield (%), **3**[b]
1	*m*-MeO-C_6H_4-Br	$Pd(OAc)_2$	73, **f**
2	*m*-MeO-C_6H_4-Br	$Pd_2(dba)_3$	71, **f**
3	PhBr	$Pd(OAc)_2$	55, **e**
4	PhBr	$Pd_2(dba)_3$	63, **e**
5	*m*-CF_3-C_6H_4-Br	$Pd(OAc)_2$	85, **h**[c,d]
6	*m*-CF_3-C_6H_4-Br	$Pd_2(dba)_3$	88, **h**[c,e]
7	*p*-F-C_6H_4-Br	$Pd_2(dba)_3$	53, **i**[c,f]
8	*m*-F-C_6H_4-Br	$Pd_2(dba)_3$	60, **j**
9	*m*-CN-C_6H_4-Br	$Pd(OAc)_2$	16, **k**
10	*m*-CN-C_6H_4-Br	$Pd_2(dba)_3$	45, **k**
11	2-bromo-naphthalene	$Pd_2(dba)_3$	66, **l**
12	1-bromo-naphthalene	$Pd_2(dba)_3$	50, **m**
13	9-bromo-anthracene	$Pd(OAc)_2$	2, **n**
14	9-bromo-anthracene	$Pd_2(dba)_3$	31, **n**
15	*o*-Me-C_6H_4-Br	$Pd_2(dba)_3$	tr, **o**
16	*p*-Me-C_6H_4-Br	$Pd_2(dba)_3$	48, **p**
17	*p*-Bu^t-C_6H_4-Br	$Pd_2(dba)_3$	49, **g**[g]
18	*p*-C_6H_4-C_6H_4-Br	$Pd_2(dba)_3$	64, **q**
19	*m*-MeCO-C_6H_4-Br	$Pd_2(dba)_3$	25, **r**[h]
20	*m*-MeCO-C_6H_4-Br	$Pd_2(dba)_3$	60, **r**[c,i]
21	*p*-MeCO-C_6H_4-Br	$Pd_2(dba)_3$	30, **c**[l]
22	*p*-MeCO-C_6H_4-Br	$Pd_2(dba)_3$	40, **c**[c,m]
23	*p*-NO_2-C_6H_4-Br	$Pd_2(dba)_3$	50, **b**
24	*p*-CHO-C_6H_4-Br	$Pd_2(dba)_3$	18, **d**[n]
25	*p*-CHO-C_6H_4-Br	$Pd_2(dba)_3$	79, **d**[o,p]
26	*p*-CHO-C_6H_4-Br	$Pd_2(dba)_3$	7, **d**[o]

[a] Unless otherwise stated, reactions were performed in toluene at 120 °C for 16 h using the following molar ratios: **1**:**2**:[Pd]:Xantphos:$NaOBu^t$ = 1:1.1:0.05:0.05:1.4. [b] Yields refer to single runs and are given for isolated products. The compounds are 95−99% pure as judged by NMR and HPLC analysis. [c] A **1**:**2** = 1:2 molar ratio was used. [d] Under standard conditions, **3h** was isolated in 38% yield. [e] Under standard conditions, **3h** was isolated in 63% yield. [f] Under standard conditions, **3i** was isolated in 17% yield. [g] 3-Phenyl-2-oxazolidinone was isolated in 11% yield. [h] Oxazolidinone derivatives with dimeric and trimeric *N*-aryl substituents were isolated in 24% and 6% yield, respectively. [i] The oxazolildinone derivative containing a dimeric *N*-aryl substituent was isolated in 21% yield. [l] The oxazolildinone derivative containing a dimeric *N*-aryl substituent was isolated in 19% yield. [m] The oxazolidinone derivative containing a dimeric *N*-aryl substituent was isolated in 8% yield. [n] For 1 h. [o] At 100 °C for 1 h. [p] In the presence of Cs_2CO_3.

provides a better catalyst system (compare Table 1, entries 2−4 with Table 2, entries 21−24). Employing $Pd_2(dba)_3$ and Xantphos did not produce comparable yields, even by increasing the oxazolidinone to aryl bromide ratio (compare Table 2, entries 21 and 22 with Table 1, entry 3). With *p*-bromoacetophenone, as well as with *m*-bromoacetophenone, ketone arylation processes[13] were observed in the presence of the $Pd_2(dba)_3$/Xantphos catalyst system and oxazolidinone derivatives bearing *N*-aryl substituents arylated at the carbon α to the carbonyl group were isolated in significant yield (Table 2, captions to entries 19−22). *p*-Bromobenzaldehyde gave the best result using $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 as the base (Table 2, entry 25). Interestingly, no oxazolidinone derivative was isolated when the same reaction was carried out in the presence of $Pd(OAc)_2$, dppf, and Cs_2CO_3 (Table 1, entry 5).

Incidentally, it may be noted that subjection of *p*-bromobenzaldehyde and [1,3]-oxazinan-2-one, the six-membered ring analogue of 2-oxazolidinone, to these conditions gave the corresponding *N*-aryl derivative in 87% yield.

We next turned our attention to the *N*-arylation of 4- and 5-substituted 2-oxazolidinones. Good results were usually obtained both with substituents at C-4 (close to the nitrogen nucleophile) and with substituents at C-5 (Table 3).

Table 3. $Pd_2(dba)_3$/Xantphos-Catalyzed *N*-Arylation of 4- or 5-Substituted 2-Oxazolidinones **2**[a]

		substituted 2-oxazolidinone **2**		
entry	aryl bromide **1**	R^1	R^2	yield (%), **3**[b]
1	*p*-CHO-C_6H_4-Br	$PhCH_2$	H	87, **aa**[c]
2	*m*-MeO-C_6H_4-Br	$PhCH_2$	H	55, **ab**
3	*p*-Ph-C_6H_4-Br	$PhCH_2$	H	89, **ac**
4	*p*-CHO-C_6H_4-Br	$^iPrCH_2$	H	94, **ba**[c]
5	*m*-MeO-C_6H_4-Br	$^iPrCH_2$	H	42, **bb**
6	*p*-Ph-C_6H_4-Br	$^iPrCH_2$	H	64, **bc**
7	*p*-CHO-C_6H_4-Br	Me	H	95, **ca**[c]
8	*m*-MeO-C_6H_4-Br	Me	H	57, **cb**
9	*p*-Ph-C_6H_4-Br	Me	H	50, **cc**
10	*p*-CHO-C_6H_4-Br	H	Me	90, **da**[c]
11	*m*-MeO-C_6H_4-Br	H	Me	64, **db**
12	*p*-Ph-C_6H_4-Br	H	Me	62, **dc**

[a] Unless otherwise stated, reactions were performed in toluene at 120 °C for 16 h using the following molar ratios: **1**:**2**:$Pd_2(dba)_3$:Xantphos:$NaOBu^t$ = 1:1.1:0.025:0.05:1.4. [b] Yields refer to single runs and are given for isolated products. The compounds are 95−99% pure as judged by NMR and HPLC analysis. [c] At 100 °C for 1 h in the presence of Cs_2CO_3.

In summary, we have developed a convenient and straightforward procedure for the preparation of 3-aryl-2-oxazolidinones. With aryl bromides containing a *para* electron-withdrawing substituent, good results were obtained in the presence of $Pd(OAc)_2$, dppf, and $NaOBt^t$ in toluene, whereas neutral, slightly electron-rich, and slightly electron-poor aryl bromides reacted satisfactorily by using $Pd_2(dba)_3$, Xantphos, and $NaOBu^t$ in toluene. With *p*-bromobenzaldehyde the best result was obtained by using $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3.

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Supporting Information Available: Characterization data for 3-aryl-2-oxazolidinones **3a**−**n**, **p**−**r**, **aa**−**dc** and 4-(2-oxo-[1,3]oxazinan-3-yl)-benzaldehyde. This material is available free of charge via the Internet at http://pubs.acs.org.

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