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Palladium-Catalyzed Intermolecular α-Arylation of *N*-Protected 2-Piperidinones

Janine Cossy,* Arnault de Filippis, and Domingo Gomez Pardo

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

janine.cossy@espci.fr

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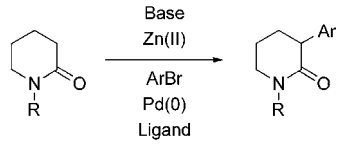
ABSTRACT



The α-arylation of the zinc enolate of *N*-protected 2-piperidinones with aryl bromides in the presence of a palladium catalyst is described as a general method.

The addition of nucleophiles to aryl halides can occur by three pathways: addition−elimination (via a Meisenheimer complex), elimination−addition (benzyne), or electron transfer (radical, anion−radical).[1] More recently, palladium-catalyzed coupling reactions of aryl halides or pseudohalides with nucleophiles have been developed.[2] It has been shown that the palladium-catalyzed intermolecular coupling of halides and keto enolates or ester enolates is a useful method for synthesizing α-aryl ketones[3] and α-aryl esters.[4] Arylation of other carboxylic acid derivatives such as amides are less common.[5] Intermolecular arylation of the lithium enolate of *N*,*N*-dimethylamides with aryl halides in the presence of a palladium catalyst occurs in moderate yields and is not general.[5a] Intramolecular arylation of *N*-(2-halophenyl)amides was also reported and led to α-phenylpyrrolidinones.[5]

To our knowledge, only one example of palladium-catalyzed intermolecular coupling of aryl halides with a cyclic amide, the *N*-methylpyrrolidinone, has been reported.[5a] Here, we would like to report a general method for the α-arylation of piperidinone enolates (Scheme 1).

(1) (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1952**, *49*, 273−412. (b) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139−147. (c) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.1 and references therein. (d) Norris, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.2 and references therein. (e) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.3 and references therein.

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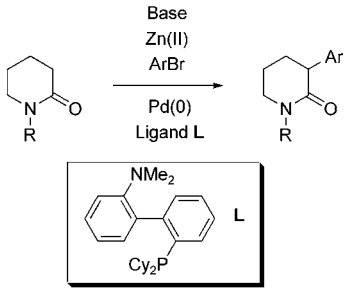
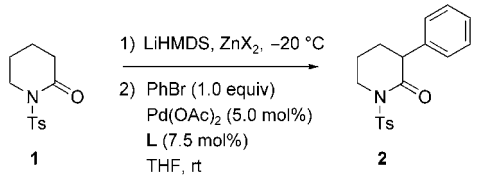
Scheme 1



When *N*-tosylpiperidinone **1** (2.3 equiv) was treated, under the conditions used for the α-arylation of esters,[4a] with LiHMDS (2.5 equiv) in the presence of bromobenzene (1.0 equiv), $Pd(OAc)_2$ (3.0 mol %), and the bulky electron-rich 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl **L** (6.3 mol %), in toluene at room temperature or at 80 °C, no arylation occurred. To increase the reactivity of the enolate, the zinc enolate of **1** was prepared. After treatment of the *N*-tosylpiperidinone **1** (1.0 equiv) with LiHMDS (0.95 equiv), $ZnCl_2$ (1.1 equiv) was added to the lithium enolate. The addition of the zinc enolate to a combination of $Pd(OAc)_2$ (5 mol %), ligand **L** (7.5 mol %), and bromobenzene (1.0 equiv) led to the α-aryl tosylpiperidinone **2** in 48% yield after 8 h at room temperature (Table 1, entry 1).[6] It is worth noting that the yield was calculated from bromobenzene. The moderate yield in **2** could result from the abstraction of the C3 proton of the α-arylpiperidinone **2** by the enolate of **1**, as the C3 proton in **2** is more acidic than the C3 protons in **1**.[4c] However, the yield in **2** was not increased when bromobenzene was treated with 2 equiv of the zinc enolate of **1** (Table 1, entry 2).

Table 1.

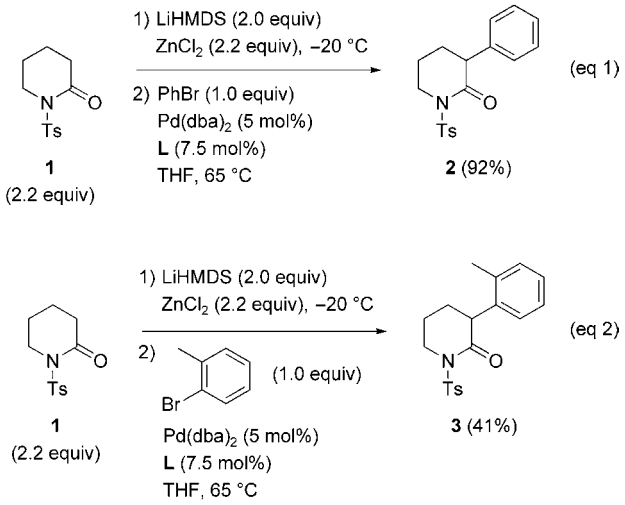


entry	**1** (equiv)	LiHMDS (equiv)	ZnX_2 (equiv)	yield (%)
1	1.0	0.95	$ZnCl_2$ (1.1)	48
2	2.2	2.0	$ZnCl_2$ (2.2)	48
3	2.2	2.0		22
4	2.2	2.0	$ZnBr_2$ (2.2)	0

It is noteworthy that better yields were obtained with the zinc enolate of **1** than with its lithium enolate (48% versus 22%, Table 1, entries 1 and 3) and that the preparation of the zinc enolate with $ZnCl_2$ is crucial, as the arylated product **2** was not obtained when the zinc enolate was prepared with $ZnBr_2$ (Table 1, entry 4).

The influence of the palladium catalyst was also studied by treating 2 equiv of the zinc enolate of **1** with 1 equiv of bromobenzene in the presence of $Pd(dba)_2$ (5.0 mol %) and **L** (7.5 mol %) in refluxing THF. The yield in **2** was increased to 92% by this method (Scheme 2, eq 1).[7] This reaction seems to be sensitive to the steric hindrance of the aromatic ring, as the arylation of **1** with 2-bromotoluene led to **3** in only 41% yield (Scheme 2, eq 2).

Scheme 2

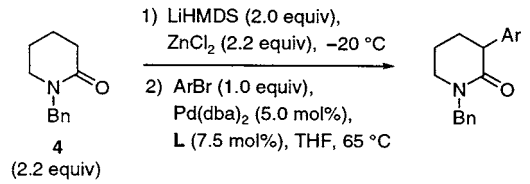


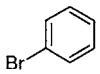
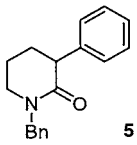
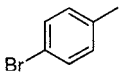
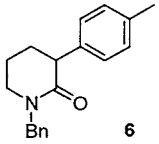
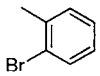
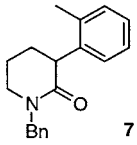
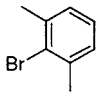
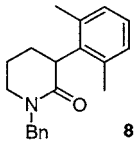
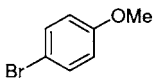
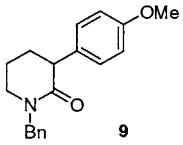
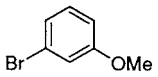
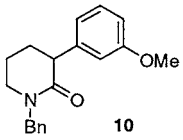
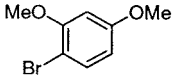
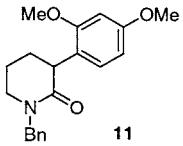
Since a benzyl protecting group is more easily removed than a tosyl group, *N*-benzylpiperidinone **4** was used to examine the arylation of its zinc enolate in the presence of $Pd(dba)_2$ and ligand **L** at 65 °C in THF. The results are reported in Table 2. Under these conditions, the yields of α-arylated *N*-benzylpiperidinones were always superior to 45% except in the case of bromo-2,6-dimethylbenzene, for which the α-arylation of **4** was not observed, probably due to steric hindrance (Table 2, entry 4). It is noteworthy that electron-donating groups in the *ortho* and/or *para* position increase the yield (Table 2, entries 5 and 7) and that the presence of an electron-donating group in the *meta* position decreases the yield (Table 2, entry 6). Under our conditions (LiHMDS, $ZnCl_2$, $Pd(dba)_2$, **L**, THF, 65 °C), the α-arylation

(6) Yield of the arylation of piperidinones is increased by a stoichiometric amount of zinc salt, which is in contrast with the arylation of lactones in the presence of $Ni(COD)_2$ and $ZnBr_2$. See: Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500−3501.

(7) **Reaction Procedure for α-Arylation of *N*-Protected 2-Piperidinones.** To a stirred solution (or suspension) of the *N*-protected 2-piperidone (1.1 mmol, 2.2 equiv) in THF (2 mL) at −20 °C was added a solution of LiHMDS (1.0 mL, 2.0 equiv). After 20 min at −20 °C, a solution of $ZnCl_2$ (0.150 g, 1.1 mmol, 2.2 equiv) in THF (1 mL) was added. After another 20 min at −20 °C, the solution of zinc enolate was cannulated into a solution of 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethyl-amino)biphenyl **L** (0.015 g, 37.5 μmol, 7.5 mol %), $Pd(dba)_2$ (0.014 g, 25.0 μmol, 5.0 mol %), and aryl bromide (0.5 mmol, 1.0 equiv) in THF (1 mL). The solution was then heated in an oil bath at 65 °C for 8 h, cooled to room temperature, quenched with aqueous NH_4Cl, and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel using 80/20 or 70/30 cyclohexane/ethyl acetate.

Table 2.



entry	ArBr	product	% yield, ( )[a]
1		 **5**	98 (86)
2		 **6**	52 (35)
3		 **7**	46 (-)
4		 **8**	0 (-)
5		 **9**	77 (-)
6		 **10**	50 (-)
7		 **11**	84 (16)

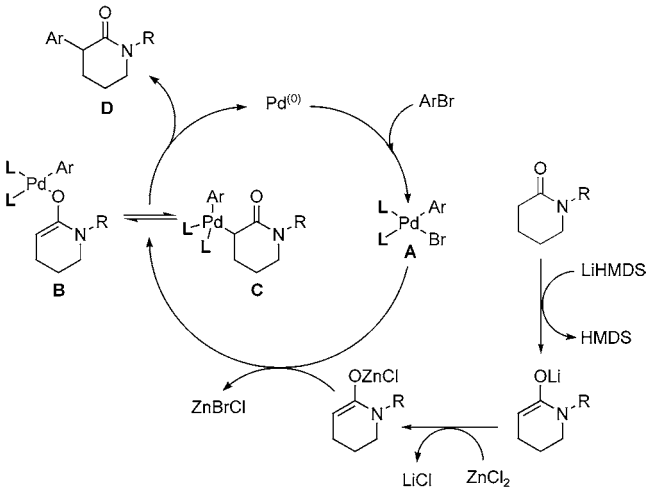
[a] % yield with LiHMDS (2.5 equiv), $Pd(OAc)_2$ (3.0 mol %), **L** (6.3 mol %), and ArBr (1.0 equiv) in toluene at 80 °C.[4a]

of *N*-substituted piperidinones does not depend on the substituent on the nitrogen, and the yields are better than those obtained without $ZnCl_2$ in the presence of $Pd(OAc)_2$ in toluene at 80 °C (Table 2).[4a]

The α-arylation of 2-piperidinones can be explained by a mechanism similar to the one previously proposed for the α-arylation of ketones,[3a,b] except that the lithium enolate is replaced by a zinc enolate.

Oxidative addition of Pd(0)Ln to the arylbromide provides the Pd(II) organometallic intermediate **A** (Scheme 3). Ligand

Scheme 3



substitution of the bromide by the zinc enolate leads to the Pd(II) organometallic intermediate **B** or **C**. Reductive elimination from intermediate **B** or **C** gives the α-arylpiperidinone **D** and regenerates the Pd(0)Ln catalyst. Under our conditions for the α-arylation of piperidinones, a *β*-hydride elimination pathway, which would produce an α,*β*-unsaturated piperidinone, was never observed. This observation points out the ability of the ligand **L** to render the palladium complexes L_4-coordinate.

In summary, we have developed a general method for the direct α-arylation of *N*-tosyl and *N*-benzylpiperidinones. Efforts to extend this reaction to other *N*-substituted piperidinones and mechanistic studies are currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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