Published in final edited form as:

Org Lett. 2010 May 21; 12(10): 2306–2309. doi:10.1021/ol100666v.

α -Arylation of 3-Aryloxindoles

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Abstract

A versatile method for the synthesis of 3,3-diaryloxindoles via Pd-catalyzed α -arylations or an S_NAr reaction is described. The reaction proceeds using mild base, is tolerant of a variety of functional groups, and is capable of preparing hindered all-carbon quaternary centers.

The efficient construction of quaternary carbon centers remains an important challenge for organic chemists,¹ and 3,3-disubstituted oxindoles represent a structural motif found in numerous biologically active natural products and a series of pharmaceutically active compounds.^{2, 3} Recently, several methods for the synthesis of 3, 3-disubstituted oxindoles have been described;⁴ however, reports on the preparation of 3,3-diaryloxindoles are rare. 3,3-Diaryloxindoles have been prepared and studied as mineralocorticoid receptor antagonists^{3a} and anti-cancer agents,^{3b} yet the structural diversity of these compounds was limited by the available methods for their synthesis (Scheme 1). Symmetrical 3,3-diaryloxindoles were first prepared in 1885 by Baeyer and Lazarus via the double electrophilic aromatic substitution of isatin using electron-rich arenes and sulfuric acid.⁵ In 1998, Olah and coworkers refined this method by using a superacid, triflic acid, to synthesize symmetrical 3,3-diaryloxindoles.⁶ Nicolaou used a related method to prepare unsymmetrical 3,3-diaryloxindoles by subjecting 3-hydroxyl-3-aryloxindoles to strong acids and *N*-protected tyrosine derivatives.^{11a,b} No other method for the synthesis of unsymmetrical diaryloxindole derivatives has been disclosed, and given that these are Friedel-Crafts alkylation reactions, harsh conditions and electron rich aromatic substrates are required. In addition, the regiochemical outcome is dictated by the substrate, providing *ortho*-, *para*- products, and thereby narrowing the scope of this method. These limitations as well as our interest in the preparation of 3,3-diaryloxindole substrates for the synthesis of natural products prompted us to pursue a milder and more versatile method.

The transition metal-catalyzed α -arylation of carbonyl compounds has emerged as a powerful and versatile method.⁷ In 2007, Willis reported the first Pd-catalyzed α -arylation of oxindoles.⁸ In 2008, Buchwald reported the Pd-catalyzed α -arylation of 3-alkyloxindoles⁹ and, more recently, the asymmetric version of this reaction.¹⁰ Herein, we describe a general approach to the preparation of 3,3-diaryloxindoles via α -arylation of 3-aryloxindoles under mild conditions with or without Pd catalysis.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. The material is available free of charge via the Internet at <http://pubs.acs.org>.

In the course of our studies on the synthesis of diazonamide A,¹¹ we wished to examine the two disconnections shown in Figure 1 (A and B) wherein the quaternary carbon is prepared by the α -arylation of an oxindole enolate. These disconnections require a method for the synthesis of 3,3-diaryloxindoles, and given the facility of Pd-catalyzed α -arylations, we expected this to be a viable method for this transformation. We began with the α -arylation of *N*-benzyl-3-phenyloxindole (**2**) with either bromobenzene or *ortho*-bromotoluene in order to study the viability and optimization of this reaction (Table 1). We found using bromobenzene that the best conditions were Pd(OAc)₂ (5 mol %), *t*-Bu₃PHBF₄¹² (10 mol %), and Cs₂CO₃ (3.0 equiv) in toluene at reflux (entry 1).¹³ These are related to the conditions of Hartwig, who has formed quaternary centers via the α -arylation of dialkyl esters.¹⁴ Using these conditions *ortho*-bromotoluene also reacts to provide the product in 80% yield (entry 7). Pd(dba)₂ can also be used and provides comparable yields (entry 2); however, in later studies, we found that the dibenzylideneacetone by-product at times co-elutes with our product, thereby complicating purification. Other ligands were less satisfactory; for example, XPhos (2-dicyclohexylphosphino-2',4',6'-tri-isopropylbiphenyl), provides recovered starting material (entry 3), while RuPhos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl) provides good yields, but is significantly slower (entry 4).¹⁵ Other carbonate bases, such as K₂CO₃, also provide high yields, but are slower (entry 5). A solvent survey was conducted, and toluene was found to be superior to other solvents, such as DMF, 1,4-dioxane, or *tert*-butanol (entries 6, 8, and 9).

With optimized conditions in hand, we studied the substrate scope using compound **2** (Table 2). We find that the reaction is compatible with a variety of substitution patterns and functional groups on the aryl bromide, including electron donating (methoxy, hydroxy, and amino groups) and electron withdrawing substituents (chloro, formyl, keto, and trifluoromethyl groups). All are good partners in this reaction and provide the products in excellent yields (entries 1-9). In addition, due to the enhanced acidity of the oxindole, no ketone arylation¹⁶ is observed with substrate **3** (entry 6). Further, the use of the mild, reversible carbonate base renders the reaction compatible with protic substituents, such as phenol (entry 7) and aniline (entry 8) groups. The reaction is also remarkably tolerant of steric hinderance in the aryl bromide component, in addition to *ortho*-bromotoluene (Table 1, entry 7) and *ortho*-bromoanisole (entry 3), the highly hindered di-*ortho*-substituted aryl bromide **4** also reacted cleanly to provide the product in 64% yield (entry 10). This is in contrast to other Pd-catalyzed enolate arylation reactions wherein low yields have been reported with *ortho*-substituted aryl halides.^{10,17}

We then studied the effects of sterics in the enolate component using the 3-*ortho*-substituted-phenyloxindole substrates **5** and **6** (Table 3). Both substrates were competent with *meta*- and *para*-substituted aryl bromides, providing the products in good yields (entries 1-3, 5-6), although long reaction times were required. No arylation products were observed in the case of *ortho*-bromoanisole due to the extreme steric hindrance of the product (entry 4).

For highly electron-deficient aryl halides, arylation can proceed without Pd catalysts via an S_NAr mechanism (Table 4). Common S_NAr substrates, such as 2,4-dinitro-chlorobenzene (entry 1) and *p*-nitrochlorobenzene (entry 2) react with 3-phenyloxindole (**7**)¹⁸ to cleanly provide the α -arylation products in excellent yields. Protection of the oxindole nitrogen is not required for this reaction,¹⁹ and no *N*-arylation is observed.²⁰ More relevant to the synthesis of natural products, such as diazonamide A, electron deficient 5-halooxazoles²¹ also provide the desired products in good yields under these conditions (entries 3-7).

In conclusion, we have developed a versatile method to prepare 3,3-diaryloxindoles via Pd-catalyzed α -arylation of 3-aryloxindoles or via nucleophilic aromatic substitution with electron deficient aryl halides. The reaction proceeds using mild base, is tolerant of a variety of functional groups, and is capable of preparing hindered all-carbon quaternary centers. The

broad substrate scope and ability to form highly hindered carbon-carbon bonds should render this method applicable to the synthesis of natural products and other biologically active compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a generous grant from the National Institutes of Health (GM 48498).

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19. This reaction also proceeds with protected oxindoles. For an example, see reference 11 g.
20. The Pd-catalyzed arylation of **7**, the unprotected variant of **2**, was studied using bromobenzene (1.2 equiv) under our standard conditions ($\text{Pd}(\text{OAc})_2$, 5 mol %; *t*-Bu₃PHBF₄, 10 mol %; Cs_2CO_3 , 3.0 equiv; toluene at reflux for 24 h); however, no product was observed and only recovered **7** was isolated. On the other hand, by using LHMDs I (3.2 equiv) in place of Cs_2CO_3 we were able to obtain the desired product in 61% yield along with 31% recovered **7** after 12 h at reflux.
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Figure 1.
Structure of diazonamide A and key disconnections.

Scheme 1.
Friedel-Crafts Approach to 3,3-Diaryloxindoles

Table 1

Reaction Optimization

entry	conditions	R	yield (%) ^a
1	Pd(OAc) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , Cs ₂ CO ₃ , toluene, 30 min	H	95
2	Pd(dba) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , Cs ₂ CO ₃ , toluene, 30 min	H	93
3	Pd(dba) ₂ , XPhos, Cs ₂ CO ₃ , toluene, 3 h	H	0
4	Pd(dba) ₂ , RuPhos, Cs ₂ CO ₃ , toluene, 3 h	H	93
5	Pd(OAc) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , K ₂ CO ₃ , toluene, 5 h	H	92
6	Pd(OAc) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , Cs ₂ CO ₃ , DMF, 120 °C, 3 h	H	0
7	Pd(OAc) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , Cs ₂ CO ₃ , toluene, 3.5 h	Me	80
8	Pd(OAc) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , Cs ₂ CO ₃ , dioxane, 18 h	Me	10
9	Pd(OAc) ₂ , <i>t</i> -Bu ₃ PHBF ₄ , Cs ₂ CO ₃ , <i>t</i> -BuOH, 12 h	Me	0

^a Isolated yield after flash chromatography.

Table 2

Arylation of *N*-Benzyl-3-Phenyloxindole (**2**)

entry

Ar-Br

1

2

entry

Ar-Br

3

entry	Ar-Br
4
5
6
7
8

entry

Ar-Br

9

entry

Ar-Br

10

^a Isolated yield after flash chromatography.

^b After 2 h.

^c Pd(dba)₂ was used instead of Pd(OAc)₂, which provided lower yield (53%).

^d After 20 h.

Table 3Arylation of 3-*ortho*-Substituted-Pheylloxindoles (**5** & **6**)

entry oxindole

Ar-Br

B

1

5

entry	oxindole	Ar-Br
2	5	
3	5	
4	5

entry oxindole

Ar-Br

5

6

MeO

6

6

^a Isolated yield after flash chromatography.^b Pd(dba)_2 (10 mol %), $t\text{-Bu}_3\text{PHBF}_4$ (20 mol %), Cs_2CO_3 (3.0 equiv), toluene, sealed tube, 120 °C, 2 d.^c 52% yield after 3 d when the title condition was used.^d 50% yield after 3 d when the title condition was used.

Table 4

Arylations Without Pd-Catalyst

entry	Ar-X

1

2

entry

Ar-X

3

4

5

6

entry	Ar-X
7	

^a Isolated yield after flash chromatography.

^b About 1:1 mixture of diastereomers.