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α-Arylation of 3-Aryloxindoles

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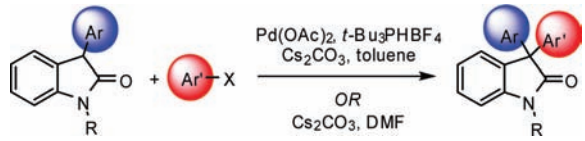
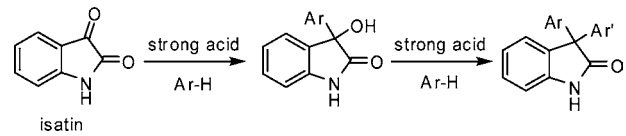
ABSTRACT



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 mineralocortocoid receptor antagonists[3a] and anticancer 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 co-workers 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

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



(1) *Quaternary Stereocenters-Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005.

(2) For current reviews of 3,3-disubstituted oxindole related natural products, see : (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219. (b) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 5262–5271. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758. (d) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170–8176.

(3) For biological active 3,3-diaryloxindoles, see: (a) Neel, D. A.; Brown, M. L.; Lander, P. A.; Grese, T. A.; Defauw, J. M.; Doti, R. A.; Fields, T.; Kelley, S. A.; Smith, S.; Zimmerman, K. M.; Steinberg, M. I.; Jadhav, P. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2553–2557. (b) Uddin, M. K.; Reignier, S. G.; Coulter, T.; Montalbetti, C.; Gråsäs, C.; Butcher, S.; Krog-Jensen, C.; Felding, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2854–2857.

(4) For selected recent examples of the synthesis of 3,3-disubstitued oxindoles, see : (a) Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484–8487. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548–14549. (c) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303–3306. (d) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583–3586. (e) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569–5572. (f) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162–16163. (g) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14–15. (h) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636–1639. (i) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825. (j) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037–8041. (k) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274–4276.

(5) Baeyer, A.; Lazarus, M. J. *Chem. Ber.* **1885**, *18*, 2637–2643.

(6) Klumpp, D. A.; Yeung, K.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1998**, *63*, 4481–4484.

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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-diarlyoxidnole 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-alkyloxindoles[9] 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.

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

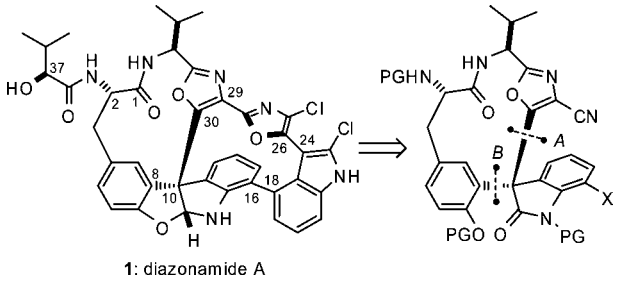
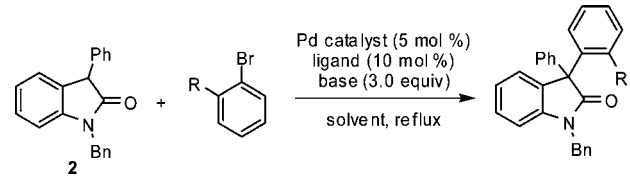


Figure 1. Structure of diazonamide A and key disconnections.

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 *o*-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*-Bu_3PHBF_4[12] (10 mol %), and Cs_2CO_3 (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 *o*-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 byproduct 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 K_2CO_3, also provide high yields but are slower (entry 5). A solvent survey was conducted, and toluene was found

Table 1. Reaction Optimization



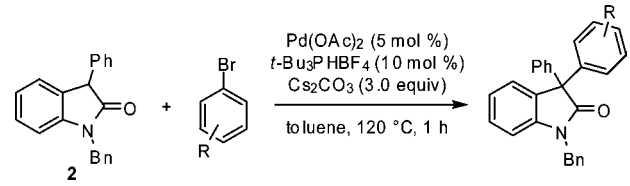
entry	conditions	R	yield (%)[a]
1	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 30 min	H	95
2	$Pd(dba)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 30 min	H	93
3	$Pd(dba)_2$, XPhos, Cs_2CO_3, toluene, 3 h	H	0
4	$Pd(dba)_2$, RuPhos, Cs_2CO_3, toluene, 3 h	H	93
5	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, K_2CO_3, toluene, 5 h	H	92
6	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, DMF, 120 °C, 3 h	H	0
7	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 3.5 h	Me	80
8	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, dioxane, 18 h	Me	10
9	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, *t*-BuOH, 12 h	Me	0

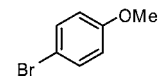
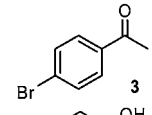
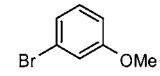
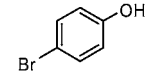
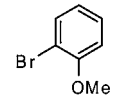
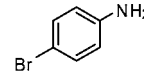
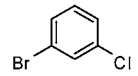
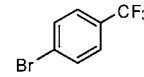
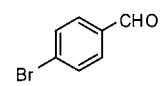
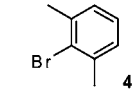
[a] Isolated yield after flash chromatography.

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

Table 2. Arylation of *N*-Benzyl-3-phenyloxindole (**2**)



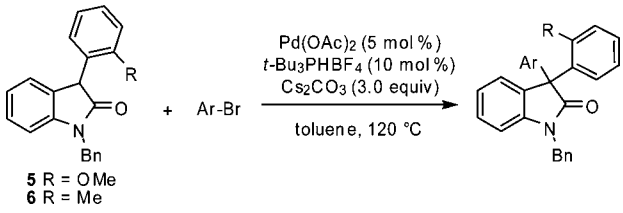
entry	Ar-Br	yield (%)[a]	entry	Ar-Br	yield (%)[a]
1		91	6	 **3**	88
2		94	7		81[c]
3		75[b]	8		85
4		78	9		85
5		79	10	 **4**	64[d]

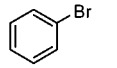
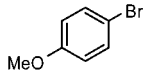
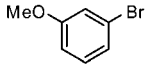
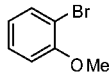
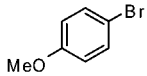
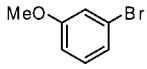
[a] Isolated yield after flash chromatography. [b] After 2 h. [c] $Pd(dba)_2$ was used instead of $Pd(OAc)_2$, which provided lower yield (53%). [d] After 20 h.

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 arylation[16] 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 hindrance in the aryl bromide component; in addition to *o*-bromotoluene (Table 1, entry 7) and *o*-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 arylations 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*-substitued phenyloxindole substrates **5** and **6** (Table 3). Both substrates were competent

Table 3. Arylation of 3-*ortho*-Substitued Pheyloxindoles (**5** and **6**)



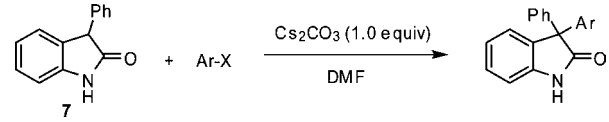
entry	oxindole	Ar-Br	time (d)	yield (%)[a]
1	**5**		1	92
2	**5**		2	90
3	**5**		2	81
4	**5**		1	0
5	**6**		2	82[b,c]
6	**6**		2	86[b,d]

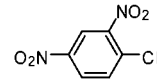
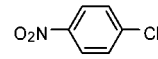
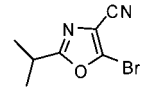
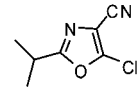
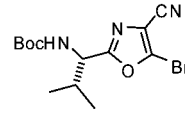
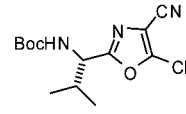
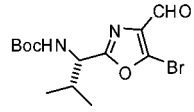
[a] Isolated yield after flash chromatography. [b] $Pd(dba)_2$ (10 mol %), *t*-Bu_3PHBF_4 (20 mol %), Cs_2CO_3 (3.0 equiv), toluene, sealed tube, 120 °C, 2 d. [c] 52% yield after 3 d when the title conditions were used. [d] 50% yield after 3 d when the title conditions were used.

with *meta*- and *para*-substituted aryl bromides, providing the products in good yields (entries 1−3, 5, and 6), although long reaction times were required. No arylation products were observed in the case of *o*-bromoanisole due to the extreme steric hindrance at the transition state (entry 4).

For highly electron-deficient aryl halides, arylations can proceed without Pd catalysts via an S_NAr mechanism (Table 4). Common S_NAr substrates, such as 2,4-dinitrochloroben-

Table 4. Arylations without Pd-Catalyst



entry	Ar-X	temp (°C)	time (h)	yield (%)[a]
1		rt	1	96
2		120	3	93
3		65	7	75
4		65	5	58
5		65	5	76[b]
6		65	5	68[b]
7		65	5	70[b]

[a] Isolated yield after flash chromatography. [b] Obtained as an approximately 1:1 mixture of diastereomers.

zene (entry 1) and *p*-nitrochlorobenzene (entry 2) react with 3-phenyloxindole (**7**)[18] to cleanly provide the α-arylation

(7) For recent reviews of α-arylations, see: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707.

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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-halooxazoles[21] 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.

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

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(13) The use of chlorobenzene in place of bromobenzene in our optimized conditions provided the desired product in less than 5% yield. The use of LHMDS in place of Cs_2CO_3 was not beneficial, even after 5 h. In both these reactions, Pd black was observed, suggesting that no active catalyst remained in solution.

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