ORGANIC LETTERS

2008
Vol. 10, No. 7
1413−1415

Palladium-Catalyzed α-Arylation of Oxindoles

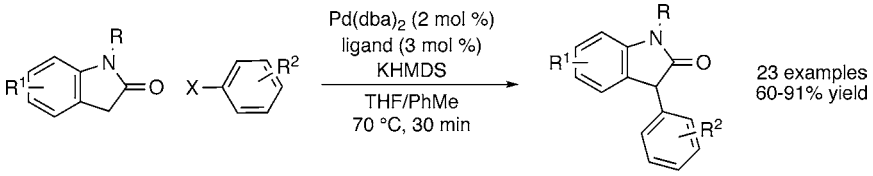
Matthew J. Durbin[†] and Michael C. Willis*[,‡]

Department of Chemistry, University of Bath, Bath, BA2 7AY, United Kingdom, and Department of Chemistry, University of Oxford, Chemical Research Laboratory, Mansfield Road, Oxford, OX1 3TA, United Kingdom

michael.willis@chem.ox.ac.uk

Received January 21, 2008

ABSTRACT



A catalyst generated from $Pd(dba)_2$ and the bulky electron-rich phosphine ligand 2-(dicyclohexylphosphino)-2′,4′, 6′-tri-*i*-propyl-1–1′-biphenyl is effective for the α-arylation of oxindoles. Generation of the potassium-enolates of a range of oxindoles allows coupling with aryl chlorides, bromides, and triflates. Significant variation of the substitution pattern on both the oxindole and aryl halide is possible.

Oxindoles, specifically those with C-3 functionalization, represent an important motif in a number of natural products[1] and pharmaceutical targets. They display biological activity against a variety of neurodegenerative disorders[2] and exhibit anti-tumor[3] and anti-HIV properties.[4] An important subclass are the C-3 aryl oxindoles, which maintain an important role in potassium channel modulation for the treatment of post-stroke patients.[5] Traditional methods for their preparation include reduction of a parent isatin[6] and palladium catalyzed asymmetric intramolecular cyclization.[7] However, such protocols are unsuitable if the oxindole core is already present in the substrate, and there remains a need for an efficient process for intermolecular arylation of the C-3 position.[8]

Palladium-catalyzed α-arylations of carbonyl and related compounds have been achieved with a range of nucleophiles including enolates of ketones,[9] aldehydes,[10] malonates,[9a] esters,[11] silyl enol ethers,[12] nitriles,[13] and amides.[7a,11b,14] The arylation of amide enolates represents one of the most challenging of this group of compounds due to the high pK_a

[†] University of Bath.
[‡] University of Oxford.

(1) (a) Bindra, J. S. In *Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, p 83. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(2) Berg, S.; Bhat, R.; Edwards, P.; Hellberg, S. *PCT Int. Appl.* **2003**, (WO 2003055877 A1 20030710 CAN 139:101026).

(3) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432.

(4) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105.

(5) (a) Gribkoff, V. K.; Starrett, J. E., Jr.; Dworetzky, S. I.; Hewawasam, P.; Boissard, C. G.; Cook, D. A.; Frantz, S. W.; Heman, K.; Hibbard, J. R.; Huston, K.; Johnson, G.; Krishnan, B. S.; Kinney, G. G.; Lombardo, L. A.; Meanwell, N. A.; Molinoff, P. B.; Myers, R. A.; Moon, S. L.; Ortiz, A.; Pajor, L.; Pieschl, R. L.; Post-Munson, D. J.; Signor, L. J.; Srinivas, N.; Taber, M. T.; Thalody, G.; Trojnacki, J. T.; Wiener, H.; Yeleswaram. K.; Yeola, S. W. *Nat. Med.* **2001**, *7*, 471. (b) Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Boissard, C. G.; Martinez, E.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E., Jr. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023. (c) Hewawasam, P.; Gribkoff, V. K.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487. (d) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353.

(6) (a) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (b) Hewawasam, P.; Erway, M. *Tetrahedron Lett.* **1998**, *39*, 3981.

(7) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (b) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1743. (c) Kündig, E. P.; Seidel, T. M.; Jia, Y.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484.

(8) During the preparation of this manuscript a report detailing the α-vinylation of an oxindole derivative appeared: Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343.

(9) (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (c) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (d) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581.

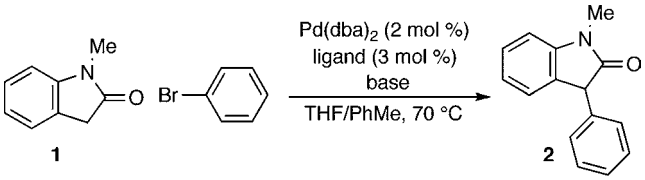
(10) (a) Martín, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236. (b) Terao, Y.; Fukuoka, Y.; Satoh, T.; Nomura, M.; Miura, M. *Tetrahedron Lett.* **2002**, *43*, 101.

10.1021/ol800141t CCC: $40.75
Published on Web 03/06/2008

of the substrates, necessitating the use of strong bases which can limit the substrate scope. Elegant work utilizing transmetallation of lithium to the corresponding zinc enolates has broadened the scope of the process;[15] however, examples of the direct arylation of cyclic amides remain rare,[14a] and efficient catalyst systems are dependent on the individual amide. Hartwig has demonstrated a tandem intra-intermolecular palladium-catalyzed process for the preparation of C-3 aryl oxindoles, in which the first arylation constructs the oxindole core and the second installs the C-3 substituent.[7a] As far as we are aware, no procedure for the palladium-catalyzed arylation of an isolated intact oxindole has been described; in this communication, we report an efficent procedure for this transformation.[16]

We selected the coupling of *N*-methyloxindole **1** and bromobenzene as our test system; our optimization study is summarized in Table 1. Initial experiments were based on those used by Hartwig in his two-step process for the preparation of 3-aryl oxindoles. Unfortunately, the use of a catalyst generated from PCy_3 and $Pd(OAc)_2$, employing NaO^tBu as base, failed to deliver any of the arylated product (entry 1). Our attention then turned to systems that had been used successfully for the arylation of amides and, importantly, were centered on the use of KHMDS as base; employing the ligands BINAP, P^tBu_3, PCy_3, or dppf in combination with KHMDS was unsuccessful (entries 2−5). The use of the electron-rich biphenyl-based phosphine ligands **3**[17] and **4** was more profitable;[18] a reaction employing ligand **3** delivered the expected arylated product in 20% yield; however, a significant improvement was achieved when the more sterically demanding ligand **4** was employed, and the product was isolated in 91% yield (entries 6 and 7). We also established that the equivalents of base employed could be reduced from 2.0 to 1.1 with only minimal effect on reaction efficiency (entry 8). Given the increased acidity of oxindole derivatives relative to simple amides,[19] we explored the use of weaker bases. However, a variety of alternatives (Cs_2CO_3, K_3PO_4, NEt_3, DBU) were all unsuccessful and delivered only trace amounts of the product at best. These observations suggested that the formation of a formal alkali metal enolate was necessary for efficient reaction. In addition to potassium, sodium enolates could also be employed, although these resulted in lower yielding reactions (entries 10 and 11). Finally, we established that the reaction time could be reduced from the initial 3 h to only 30 min, with the product still being isolated in an impressive 95% yield (entries 12 and 13).

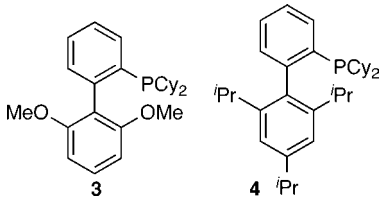
Table 1. Reaction Development for the Coupling of *N*-Methyloxindole and Bromobenzene[a]



1 2

entry	base (equiv)	ligand	time (h)	yield (%)[b]
1[c]	NaO^tBu	PCy_3	3	0
2	KHMDS (2.0)	BINAP	3	0
3	KHMDS (2.0)	$P^tBu_3.HBF_4$	3	<2
4	KHMDS (2.0)	PCy_3	3	0
5	KHMDS (2.0)	dppf	3	0
6	KHMDS (2.0)	**3**	3	20
7	KHMDS (2.0)	**4**	3	91
8	KHMDS (1.1)	**4**	3	90
9[d]	KHMDS (1.1)	**4**	3	0
10	NaHMDS (1.1)	**4**	3	81
11	NaH (1.1)	**4**	3	44
12	KHMDS (1.1)	**4**	1	90
13	KHMDS (1.1)	**4**	0.5	95

[a] Conditions; oxindole **1** (1.0 equiv), bromobenzene (1.1 equiv), 70 °C. [b] Isolated yields. [c] $Pd(OAc)_2$ and dioxane used. [d] Reaction performed at 25 °C.



3 4

We next explored variations in both the oxindole and aryl halide coupling partners (Table 2). *N*-Benzyl oxindole was used as the standard oxindole substrate: Entries 1−3 demonstrate that in addition to aryl bromides, both aryl chlorides and aryl triflates are also effective substrates. The reactions also tolerate significant functionalization of the aryl halide; both electron-donating and electron-withdrawing groups can be accommodated, and substituents *ortho*, *meta*, or *para* to the halide group can all be included (entries 4−13). When both bromo- and chloro-substituents were present in the arene, selective reaction at the bromo-substituent was always observed (entries 14 and 15). It is notable that this selectivity was preserved when 1-Br-2-MeO-5-Cl-benzene, which features a hindered Br-substituent, was employed as a substrate, allowing the efficient introduction of the 2-MeO-5-Cl-arene unit found in a number potassium channel openers (entry 16).[5b,d] Competition between a triflate

(11) (a) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (b) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (c) Bentz, E.; Moloney, M. G.; Westaway, S. M. *Tetrahedron Lett.* **2004**, *45*, 7395.

(12) (a) Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725. (b) Su, W.; Raders, S.; Verkade, J. G.; Liao, X.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852.

(13) (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(14) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (b) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

(15) (a) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (b) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (c) Pardo, D. G.; de Filippis, A.; Cossy, J. *Tetrahedron* **2004**, *60*, 9757.

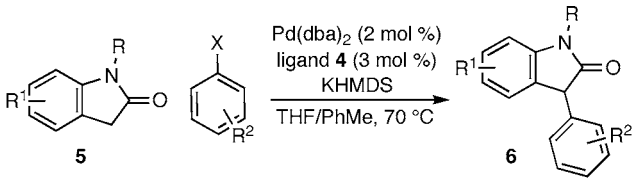
(16) For an application of Hartwig's tandem intra- intermolecular method for the synthesis of C-3 aryloxindoles, see; Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308.

(17) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

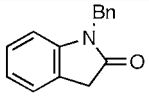
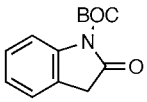
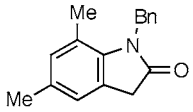
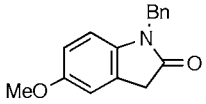
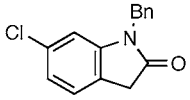
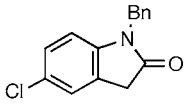
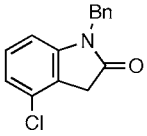
(18) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapers, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(19) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.

Table 2. Scope of the Pd-Catalyzed α-Arylation of Oxindoles[a]



5 6

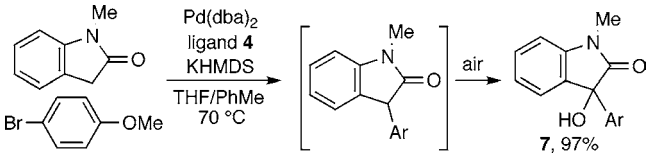
entry	oxindole	arene	yield (%)[b]
1		Br-C_6H_5	91
2		Cl-C_6H_5	70
3		TfO-C_6H_5	85
4		1-Br-4-^{t}Bu-C_6H_4	79
5		1-Br-4-MeO-C_6H_4	85
6		1-Cl-4-MeO-C_6H_4	70
7		1-Br-4-F_3C-C_6H_4	80
8		1-Cl-4-F_3C-C_6H_4	66
9		1-Br-3-Me-C_6H_4	77
10		1-Br-3-MeO-C_6H_4	85
11		1-Br-2-Me-C_6H_4	74
12		1-Cl-2-Me-C_6H_4	60
13		1-naphthyl	80
14		1-Br-4-Cl-C_6H_4	70[c]
15		1-Br-3-Cl-C_6H_4	73[c]
16		1-Br-2-MeO-5-Cl-C_6H_3	77[c]
17		1-Cl-4-TfO-C_6H_4	70[d]
18		Br-C_6H_5	60
19		1-Br-3-MeO-C_6H_4	67
20		1-Br-3-MeO-C_6H_4	76
21[e]		1-Br-3-MeO-C_6H_4	66
22[f]		1-Br-3-MeO-C_6H_4	70
23[f]		1-Br-3-MeO-C_6H_4	61

[a] Conditions; oxindole (1.0 equiv), arene (1.1 equiv), KHMDS (1.1 equiv), THF, 70 °C, 30 min. [b] Isolated yields. [c] Product from coupling at Br-substituent. [d] Product from coupling at TfO-substituent. [e] Reaction time 1 h. [f] Reaction time 2.5 h.

and a chloro group resulted in selective functionalization of the triflate substituent (entry 17). Variation of the oxindole *N*-substituent to an electron-withdrawing group was also possible, with the *N*-BOC derivative performing well (entry 18). The final five entries show that the introduction of substituents around the benzene ring of the oxindole is also viable under the present reaction conditions, with the last three entries showing that it is possible to retain a synthetically useful aryl chloride group on the oxindole during the coupling process (entries 19−23). Although reactions were routinely performed on a 0.25 mmol scale, it was possible to perform larger scale couplings. For example, the coupling of *N*-Me oxindole and bromobenzene on a 20 mmol scale (∼3 g of *N*-Me-oxindole) delivered the expected product in 85% yield.

When originally exploring the conditions needed to achieve smooth α-arylation reactions, we observed small amounts of products resulting from α-oxidation of the arylated compounds.[20] This was conveniently remedied by the use of degassed solvents. Conversely, if the C-3 oxidized compounds were the desired products they could be isolated in excellent yield by simply conducting the arylation as normal, followed by opening the reaction flask to air for an additonal 5 min (Scheme 1).[21]

Scheme 1. Tandem Arylation-Oxidation



In conclusion, we have shown that potassium enolates of a variety of oxindole derivatives undergo efficient C-3 arylation under the action of palladium catalysis. Significant variation of the aryl coupling partner is possible, with both electron-rich and electron-poor substituents tolerated well. Aryl bromides, chlorides and triflates are all viable substrates. Finally, access to C-3 aryl/C-3-hydroxy-oxindoles is possible via in-situ air oxidation of the C-3 arylated products.

Acknowledgment. This work was supported by the EPSRC.

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

OL800141T

(20) The susceptibility of oxindole enolates to oxidation is known, see, for example, ref 5c.

(21) Detailed studies of this process are beyond the scope of this Letter. However, we have established that simply stirring isolated 3-aryl oxindoles in a THF/PhMe mix open to air is not sufficient to produce the oxidized products.