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Twofold C−H Functionalization: Palladium-Catalyzed *Ortho* Arylation of Anilides

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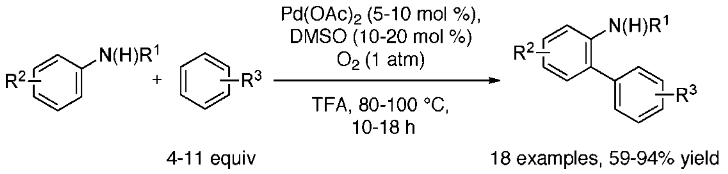
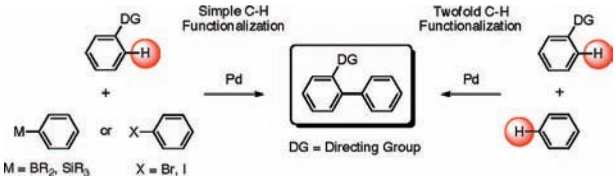
ABSTRACT



The *ortho* arylation of anilides to form biphenyls via a twofold C−H functionalization/C−C bond-forming process is described. The oxidative coupling takes place in the presence of 5−10 mol % of $Pd(OAc)_2$, 10−20 mol % of DMSO, and 4−11 equiv of the aryl substrate in TFA under an oxygen atmosphere. No metal-containing cocatalyst is required.

Organic chemists are faced with the challenges of accessing complex organic molecules efficiently, producing a minimum amount of waste and handling nonrenewable or natural resources as economically as possible. In that context, the growing number of reports of catalytic, direct functionalization of C−H bonds by transition metals represents a promising advance.[1,2] The application of C−H bond functionalization to the synthesis of biaryls, molecules with important applications in the polymer and pharmaceutical sciences, illustrates the potential utility of these protocols.[3]

Scheme 1. Palladium-Catalyzed Simple and twofold C−H Functionalization in the Presence of a Directing Group



As shown in Scheme 1, biaryl synthesis via C−H bond activation has been achieved via simple[4] and, most recently, via twofold[5] C−H functionalization approaches. High regioselectivities have generally been observed only when electron-rich arenes[5c−e] ordirecting groups (DG)[6] such as

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(1) For recent reviews of C−H functionalization, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

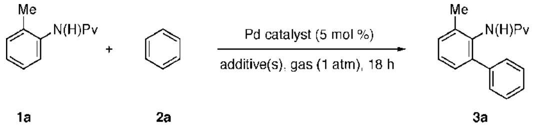
(2) For selected examples using palladium as a catalyst, see: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (c) Cai, G.; Fu, Y.; Le, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (d) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (e) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (f) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (g) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (h) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

(3) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: New York, 2001; Vol. 82, pp 1−293.

(4) (a) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (b) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (d) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

10.1021/ol800619c CCC: $40.75

Table 1. Screening Results of the Arylation of 2-Methylpivalanilide with Benzene



entry[a]	**2a** (equiv)	Pd catalyst	additive(s)	gas	*T* (°C)	convn[b] (%)	yield[b] (%)
1	11	$Pd(OAc)_2$		O_2	80	8	3
2	11	$Pd(OAc)_2$	5 equiv of HOAc	O_2	80	11	3
3[c]	11	$Pd(OAc)_2$	5 equiv of TFA	O_2	80	66	64
4	11	$Pd(OAc)_2$	5 equiv of TFA, 10 mol % of DMSO	O_2	80	91	87
5	11	$Pd(O_2CCF_3)_2$	5 equiv of TFA, 10 mol % of DMSO	O_2	80	20	16
6	11	$PdCl_2$	5 equiv of TFA, 10 mol % of DMSO	O_2	80	8	
7	11	$Pd(OAc)_2$	5 equiv of TFA, 10 mol % of DMSO	O_2	90	100	92[d]
8	4	$Pd(OAc)_2$	10 equiv of TFA, 10 mol % of DMSO	O_2	100	97	78
9[e]	11	$Pd(OAc)_2$	5 equiv of TFA, 10 mol % of DMSO	air	80	82	76

[a] Reactions carried out on a 1.0 mmol scale. [b] Corrected GC data with dodecane as internal standard. [c] Reaction was carried out multiple times with significantly varying results. [d] Isolated yield: 90% (average of two runs). [e] Reaction carried out on a 0.2 mmol scale.

anilides or pyridine are used as one of the coupling partners. Despite substantial practical advances, however, important limitations such as the need for Cu or Ag salts as cooxidants (oftentimes in stoichiometric amounts)[5a,4d] and the requirement of up to a 100 equivalent excess of arene coupling partner limit the synthetic utility of these methods. Fewer examples have been reported of palladium-catalyzed C−H functionalization using molecular oxygen as the only oxidant.[7] In one elegant example, Stoltz and co-workers described the oxidative annulation of indoles using a catalytic system of Pd(II)/ligand/O_2 (1 atm).[8]

During our investigations in C−H activation-type reactions, we found that a twofold C−H functionalization occurs between anilides and arenes to form substituted biaryls using 5−10 mol % of $Pd(OAc)_2$ and 4−11 equiv of the aryl coupling partner in the presence of oxygen as the terminal oxidant.

Initially, we studied the coupling of 2-methylpivalanilide (**1a**) with benzene (**2a**) in the presence of $Pd(OAc)_2$ and oxygen (1 atm) to afford **3a** (Table 1).[9] The effects of different palladium sources, additives, and temperature were systematically examined. Low conversion of **1a** to **3a** was observed in the presence of 5 mol % of $Pd(OAc)_2$ and 11 equiv (1 mL) of benzene (**2a**) under an oxygen atmosphere at 80 °C (entry 1). Similar results were obtained when 5 equiv of acetic acid (AcOH) were added (entry 2). The substitution of trifluoroacetic acid (TFA) for AcOH resulted in better yields, but these results were not fully reproducible. After some experimentation we found that loss of active catalyst through palladium black formation could be slowed by the addition of DMSO (10 mol %), thus affording the expected biaryl in excellent yield (entry 4). The best results were finally obtained at 90 °C, at which temperature **3a** was isolated in 92% yield (entry 7).

The reaction could also be carried out with only 4 equiv of **2a** by increasing the amount of TFA to 10 equiv, although the corresponding yield was lower. During the course of our work, an elegant related paper by Shi appeared.[5a] In this disclosure, a single example of twofold C−H functionalization using 6 equiv of arene coupling partner was reported.[10] As shown in entry 9, oxygen could be replaced effectively by air, but lower conversions were generally achieved under these conditions. Poor results were obtained if $Pd(OAc)_2$ was substituted by other palladium salts such as $Pd(O_2CCF_3)_2$ or $PdCl_2$ (entries 5 and 6).

Using these optimized conditions, we next explored the scope and generality of this process using benzene (**2a**) as an arylating reagent. As shown in Table 2 (entry 1), acetanilides, as well as pivalanilides, can be efficiently arylated using our protocol. Nonetheless, due to their greater stability and selectivity at higher temperatures, we decided to focus our attention on pivalanilides.

Neutral or electron-rich substituents on the anilide afforded arylated products in good yields of up to 91% (entries 2−5). In the case of the slightly electron-deficient fluorinated compound **1g** the temperature had to be raised to 100 °C to obtain a satisfactory yield of 68% (entry 6). However, even

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(5) (a) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (e) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

(6) (a) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382.

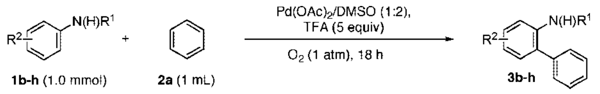
(7) (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (b) Stahl, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (c) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. (d) Hagelin, H.; Oslob, J. D.; Åkermark, B. *Chem. Eur. J.* **1999**, *5*, 2413. (e) Shue, R. S. *J. Chem. Soc. Chem. Commun.* **1971**, 1510.

(8) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, doi:10.1016/j.tet.2008.01.052.

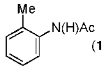
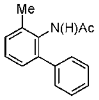
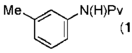
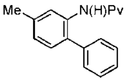
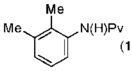
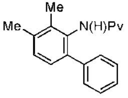
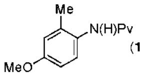
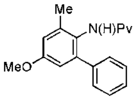
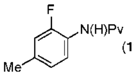
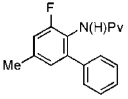
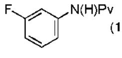
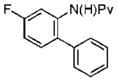
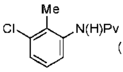
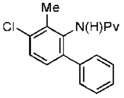
(9) Unsubstituted pivalanilide gave rise to a variable mixture of mono- and bis-ortho arylated products. Similar results were observed by Daugulis et al. See ref 4d for details.

(10) According to the Supporting Information of ref 5a, most of the examples use 28−37 equiv of arene counterpart.

Table 2. Arylation of Anilides with Benzene

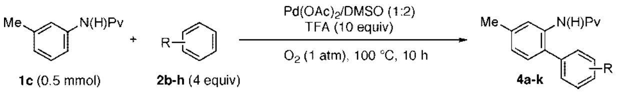


1b-h (1.0 mmol) + **2a** (1 mL) → **3b-h**

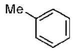
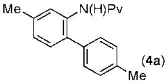
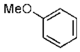
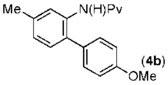
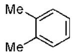
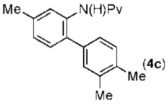
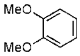
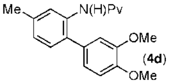
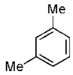
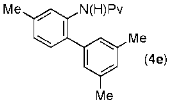
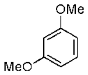
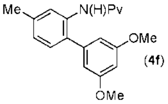
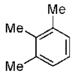
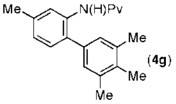
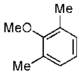
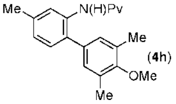
entry	anilide	Pd(OAc)$_2$	temp	biphenyl	yield^a
1	 (**1b**)	5 mol %	80 °C		70% (**3b**)
2	 (**1c**)	5 mol %	90 °C		91% (**3c**)
3	 (**1d**)	10 mol %	90 °C		84% (**3d**)
4	 (**1e**)	7.5 mol %	80 °C		87% (**3e**)
5	 (**1f**)	10 mol %	90 °C		86% (**3f**)
6	 (**1g**)	10 mol %	100 °C		68%^{b} (**3g**)
7	 (**1h**)	10 mol %	55 °C		59%^{b,c} (**3h**)

[a] Isolated yield, average of two runs. [b] Incomplete conversion of the starting material. [c] Reaction run for 96 h.

Table 3. Arylation of Anilides with Different Aryls



1c (0.5 mmol) + **2b-h** (4 equiv) → **4a-k**

entry	arene	product	Pd(OAc)$_2$	selectivity^a	yield^b
1		 (**4a**)	7.5 mol %	*o*:*m*:*p* 1:16:16	82%^{c}
2		 (**4b**)	7.5 mol %	*o*:*m*:*p* 1:2:12	77%
3		 (**4c**)	7.5 mol %	1,2,3:1,2,4 1:40	92%
4		 (**4d**)	7.5 mol %	–	94%
5		 (**4e**)	10 mol %	1,2,4:1,3,5 1:4.1	62%^{d}
6		 (**4f**)	10 mol %	1,2,4:1,3,5 1:11	79%^{d}
7		 (**4g**)	10 mol %	1,2,3,4:1,2,3,5 1:10	88%^{c}
8		 (**4h**)	10 mol %	1,2,3,4:1,2,3,5 1:20	66%^{d}

[a] The ratio of the regioisomers was detemined by GC. [b] Isolated yield for the mixture of all regioisomers, average of two runs. [c] The ratio of the regioisomers was calculated by ^{1}H NMR. [d] Incomplete conversion. [e] 5 equiv of TFA were used.

with 10 mol % of Pd(OAc)$_2$, this reaction could not be driven to completion. Furthermore, the arylated product **3h** could be isolated in only 59% yield after 96 h at 55 °C (entry 7). In the case of the chlorinated example **1h**, the reaction had to be carried out at a lower temperature to prevent reduction of the aryl chloride and the immediate formation of palladium black. Electron-deficient substrates such as those substituted by CF$_3$, CO$_2$Me, or NO$_2$ groups underwent either no or only trace amounts of arylation.

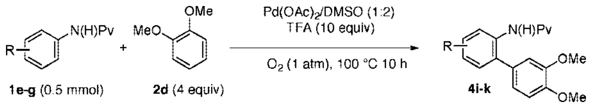
Prompted by these results, we next examined the arylation of anilides with arenes other than benzene (Table 3). Either electron-neutral or electron-rich arenes were equally effective using 7.5−10 mol % of Pd(OAc)$_2$. The use of toluene as coupling partner, however, afforded a mixture of *ortho*, *meta*, and *para* regioisomers (Table 3, entry 1). The regioselectivity was improved by employing anisole or arenes with several substituents. In particular, the use of veratrole as the arene coupling partner exclusively afforded the arylation product **4d** in excellent yield as the only regioisomer.

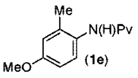
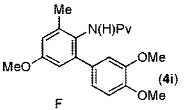
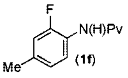
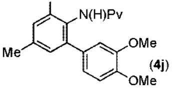
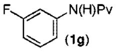
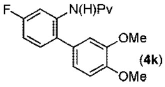
Although the electronic effects of the substituents on the arene are considerable in determining the substitution pattern of the product (Table 3, entries 1, 3, 5, 7 vs 2, 4, 6, 8), steric hindrance appears to play a more important role. For example, when 1,3-dimethoxybenzene was used as the arene coupling partner (entry 6), the 1,2,3-regioisomer arising from coupling of the most electron-rich carbon, was not observed. Indeed, with all substrates tested, arylation at less hindered positions was observed almost exclusively. In line with these results, the arylation of 1,4-dimethoxybenzene was consistently sluggish. These results are in accord with the results recently described by Sanford and co-workers.[5b]

Because of the excellent regioselectivity observed using veratrole **2d** as the arene coupling partner, we next turned our attention to the reaction of this substrate with pivalanilides with different substituents (Table 4). As expected, a single regioisomer was observed in all cases, yielding the corresponding biaryls in good yield.

It is worth mentioning that reactions employing fluorobenzene derivatives, such as 1,3-difluorobenzene or pentafluorobenzene, as the arene coupling partner resulted in notably low conversions under these conditions. The significant acidity of the *ortho* proton to the fluorine atom make these substrates particularly reactive in a proton abstraction-type mechanism. Thereby, our results suggest that another mechanism may be operative under our reaction conditions.[5b,11]

Table 4. Arylation of Anilides with Veratrole **2d**



entry	amide	product	Pd(OAc)$_2$	yield[a]
1	 (**1e**)	 (**4i**)	7.5 mol %	70%
2	 (**1f**)	 (**4j**)	10 mol %	70%[b]
3	 (**1g**)	 (**4k**)	10 mol %	73%[b]

[a] Isolated yield, average of two runs. [b] Incomplete conversion.

In summary, we have developed a practical and mild method for the synthesis of biaryl compounds from simple and readily accessible anilides and arenes via twofold C−H functionalization using molecular oxygen at atmospheric pressure as the only oxidant. Further mechanistic studies are currently underway.

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

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(11) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.