## Palladium-Catalyzed Direct C-2 Arylation of Indoles with Aryl Halides in Aqueous Medium

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**Abstract:** A newly developed, efficient catalytic system for direct C2-arylation of indoles with aryl halides in aqueous medium under mild conditions (80 °C) is reported. These procedures are free of toxic solvents, and exhibit improved yields and high chemo- and regioselectivity.

**Key words:** arylation, indole, aqueous medium, green chemistry, synthetic method

2-Arylindoles are a class of important synthetic intermediates of various biologically and medicinally active molecules.<sup>1</sup> Many traditional approaches to these compounds often require pre-functionalization of indoles including multistep synthesis processes, <sup>1e,2</sup> so recent work has mainly focused on the development of transition-metalcatalyzed methods for the direct C-H arylation of indoles.<sup>3</sup> Typically, such arylations involve a coupling between an aryl halide or pseudohalide and an indole derivative catalyzed by palladium complexes at high temperature (120–160 °C).<sup>4</sup> Although several attempts have been made to perform these reactions under thermally mild conditions (room temperature to 80 °C),<sup>5</sup> use of (potentially toxic) organic solvents is always the norm, which by definition fails to meet the 12 principles of green chemistry.6

To solve these problems, scattered reports have mentioned the direct arylation of (hetero)arenes in aqueous medium.<sup>7</sup> Recently, Joucla et al. have carried out the direct C–H arylation of indoles 'on water'.<sup>8</sup> However, high temperatures (110 °C) are required, and the yields and selectivity are also unsatisfactory. As a part of our interest in designing cross-coupling reactions in water, we describe here a novel and facile protocol for the direct C-2 arylation of indoles in aqueous medium under mild conditions (80 °C), with improved yields and high regioselectivity.

Silver(I) carboxylates, which can be generated in situ through a procedure from  $Ag_2O$  and the corresponding carboxylic acids, have proved to be efficient additives for the direct C-2 arylation of indoles, which could increase the rate of the palladation step (*path b*) and enhance the electrophilicity of a cationic palladium species (**IV**; Scheme 1).<sup>5b,9</sup> Furthermore, many Pd-catalyzed cross-

*SYNLETT* 2012, 23, 2992–2996 Advanced online publication: 28.11.2012 DOI: 10.1055/s-0032-1317702; Art ID: ST-2012-W0882-L © Georg Thieme Verlag Stuttgart · New York couplings in water could be promoted by adding appropriate surfactants.<sup>10</sup> Thus, we hypothesized that use of carboxylate salts formed in situ from bases and carboxylic acids (or carboxylic acid anhydrides) and surfactants could accelerate the direct arylation of indoles in water.



Scheme 1 Working hypothesis: an activated palladium(II) species for C–H arylation

As a starting point, we performed a test reaction of iodobenzene and indole in 2 wt.% PTS 600 aqueous micelles catalyzed by bis[di-tert-butyl(4-dimethylaminophenyl)phosphino]dichloropalladium(II) [Pd(Amphos)<sub>2</sub>Cl<sub>2</sub>, 2 mol%] using NaOH and o-nitrobenzoic acid (A) as the additives at 60 °C for 24 hours. A low yield (19%) of 2-phenyl-1*H*-indole (**2a**) was obtained (Table 1, entry 1). After screening several bases and carboxylic acids (or carboxylic acid anhydrides; entries 1-8), the combination of NaOH and tetrachlorophthalic anhydride (TCPA, B; Figure 1) was found to be the best selection for the reaction (entry 3). To further improve these modest results, different surfactants and catalysts were employed in the system (entries 3 and 9-16), but limited success was found. Surprisingly, the reaction in aqueous micelles was more sluggish than 'on water' (entry 12),<sup>11</sup> suggesting that the aqueous micelle system may inhibit the ion exchange between substrates and additives, and thereby decrease the reaction rate.<sup>12</sup>



Figure 1 The chemical structures of A-C

Additionally, a series of organic solvents was selected as the co-solvents to improve the poor solubility of substrates in water,<sup>13</sup> and only EtOH–H<sub>2</sub>O (1:1) provided a trace of product (entries 18–20). Remarkably, the extent of reaction could be increased by reducing the ratio of EtOH to water (entries 20–23). Presumably, adding limited amounts of co-solvent to water sufficiently maintains the hydrophilicity and hydrogen bonding effects of water, which may accelerate formation of palladium intermediates **III** and **IV**, and raise the electrophilicity of cationic palladium species **IV**.<sup>14</sup>

 Table 1 Optimization of Reaction Conditions<sup>a</sup>



| Entry           | Solvent (v/v)                               | Acid | Base              | Catalyst                                                       | Yield (%) <sup>b</sup> |
|-----------------|---------------------------------------------|------|-------------------|----------------------------------------------------------------|------------------------|
| 1               | 2 wt% PTS 600°-H <sub>2</sub> O             | Α    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 19                     |
| 2               | 2 wt% PTS 600°-H <sub>2</sub> O             | AcOH | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 5                      |
| 3               | 2 wt% PTS 600°-H <sub>2</sub> O             | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 35                     |
| 4               | 2 wt% PTS 600°–H <sub>2</sub> O             | С    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 3                      |
| 5               | 2 wt% PTS 600°–H <sub>2</sub> O             | _    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 6               | 2 wt% PTS 600°–H <sub>2</sub> O             | В    | Ag <sub>2</sub> O | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 7               | 2 wt% PTS 600°–H <sub>2</sub> O             | В    | NaOt-Bu           | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 26                     |
| 8               | 2 wt% PTS 600°–H <sub>2</sub> O             | В    | DABCO             | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 10                     |
| 9               | 2 wt% SDS-H <sub>2</sub> O                  | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 10              | 2 wt% CTAB–H <sub>2</sub> O                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 11              | 2 wt% TX 100 <sup>d</sup> -H <sub>2</sub> O | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 9                      |
| 12              | H <sub>2</sub> O                            | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 48                     |
| 13              | H <sub>2</sub> O                            | В    | NaOH              | $Pd(OAc)_2$ (2 mol%)                                           | 14                     |
| 14              | H <sub>2</sub> O                            | В    | NaOH              | Pd(dppf)Cl <sub>2</sub> (2 mol%)                               | 22                     |
| 15              | H <sub>2</sub> O                            | В    | NaOH              | $Pd(PPh_3)_2Cl_2 (2 mol\%)$                                    | 7                      |
| 16              | H <sub>2</sub> O                            | В    | NaOH              | Pd(BF <sub>4</sub> ) <sub>2</sub> (MeCN) <sub>4</sub> (2 mol%) | 15                     |
| 17              | H <sub>2</sub> O <sup>e</sup>               | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 18              | PEG 200–H <sub>2</sub> O (1:1)              | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 19              | AcOH-H <sub>2</sub> O (1:1)                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | nr                     |
| 20              | EtOH-H <sub>2</sub> O (1:1)                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 4                      |
| 21              | H <sub>2</sub> O–EtOH (2:1)                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 24                     |
| 22              | H <sub>2</sub> O–EtOH (5:1)                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 63, 80 <sup>f,g</sup>  |
| 23              | H <sub>2</sub> O–EtOH (10:1)                | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 66, 76 <sup>f,g</sup>  |
| 24              | H <sub>2</sub> O–DMAc (5:1)                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 19                     |
| 25 <sup>h</sup> | H <sub>2</sub> O–EtOH (5:1)                 | В    | NaOH              | Pd(Amphos) <sub>2</sub> Cl <sub>2</sub> (20 mol%)              | 72 <sup>f,g</sup>      |





<sup>a</sup> Reaction conditions: iodobenzene (0.375 mmol), **1a** (0.250 mmol), catalyst, NaOH (0.375 mmol), acid (0.375 mmol), solvent (0.6 mL), 60 °C, 24 h.

<sup>b</sup> Yield was determined by GC–MS.

<sup>c</sup> PTS 600 = Polyoxyethanyl  $\alpha$ -tocopheryl sebacate 600.

<sup>d</sup> TX 100 = *t*-Octylphenoxypolyethoxyethanol.

e TBAB (20 mol%) was used.

<sup>f</sup> The reaction was carried out at 80 °C.

<sup>g</sup> Isolated yield.

<sup>h</sup> Amount of NaOH (as the base) used was 3 equiv.

Although  $H_2O$ -EtOH (10:1) resulted in the highest yield at 60 °C (entry 23),  $H_2O$ -EtOH (5:1) emerged as the better choice along with an increase in reaction temperature to 80 °C (entry 22). A solvent switch to DMAc led to a much lower yield of the desired product (entry 24), and increasing the amount of NaOH also proved to be harmful for the reaction (entry 25). To compare and contrast these couplings with the previous work,<sup>8</sup> a direct comparison of the coupling between indole and iodobenzene was performed. As shown in Scheme 2, our protocol could afford higher yield and regioselectivity by using less catalyst under milder conditions (Scheme 2).



Scheme 2 The coupling of indole and iodobenzene

Encouraged by these preliminary results, various aryl halides were chosen to establish the scope and generality of the protocol (Scheme 3). Aryl iodides containing electronwithdrawing or electron-donating groups reacted well to yield the corresponding 2-arylindoles. However, aryl iodides with strong electron-withdrawing groups (such as



Scheme 3 The couplings of various aryl halides with indole in aqueous medium, with isolated yields of the 2-arylindole products. *Reagents and conditions*: aryl halide (0.375 mmol), **1a** (0.250 mmol), Pd(Amphos)<sub>2</sub>Cl<sub>2</sub> (0.050 mmol), NaOH (0.375 mmol), TCPA (0.375 mmol), H<sub>2</sub>O–EtOH (5:1; 0.6 mL), 80 °C, 24 h. <sup>a</sup> The yield of **2** and the ratio of **2**/3 were determined by GC–MS. <sup>b</sup> Values in brackets refer to the ratio of **2**/3.

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Scheme 4 The couplings of aryl iodides with various indoles in aqueous medium, with isolated yields of the 2-arylindole products. *Reagents and conditions*: aryl halide (0.375 mmol), 1 (0.250 mmol), Pd(Amphos)<sub>2</sub>Cl<sub>2</sub> (0.050 mmol), NaOH (0.375 mmol), TCPA (0.375 mmol), H<sub>2</sub>O-EtOH (5:1, 0.6 mL), 80 °C, 24 h. <sup>a</sup> The yield of **2u** was determined by GC–MS. <sup>b</sup> No reaction was observed.



Scheme 5 A potential application of direct C-2 arylation of indoles to total synthesis

4-nitro-1-iodobenzene) afforded only traces of the final product (2i). The coupling appeared to be unaffected by steric effects (2h). In all cases, only 2-arylindoles (2/3 >50:1) were formed when aryl iodides were employed. Initial attempts were also made to couple aryl bromides with indole under identical conditions. As expected, the reactions were more sluggish (2a, 2j and 2k), likely due to the rate of oxidative insertion. Moreover, the reaction regioselectivity was also unsatisfactory (2a and 2j).

Likewise, a variety of indoles could also be coupled with aryl iodides efficiently in an aqueous medium (Scheme 4). Unlike previous reports, <sup>4e,f,5b</sup> *N*-methylindole was found to be less active than indole itself under these conditions (**20–q**). Presumably, the free (NH)-indoles could form a more electron-rich intermediate in strong basic aqueous medium. Indoles bearing a strong electron-withdrawing group (e.g., 5-nitroindole) gave a poor yield of the product

(2u, 9%). Disappointingly, the use of 7-azaindole (2w) resulted in no arylation. It should be noted that the coupling of 3-methylindole with iodobenzene only afforded trace 2v, indicating that a C-3-to-C-2 migration (1,2-migration) of palladium may take place during the reaction,<sup>4b</sup> which would be inhibited due to a methyl group on the C-3 indole ring. Alternately, a steric effect in 3-methylindole may be operative.

To further demonstrate the potential of this methodology, 2-arylindole 2x, a crucial intermediate en route to 8-desbromohinckdentine A<sup>1</sup>, was smoothly generated by the coupling of indole with 2-bromo-1-iodobenzene in this aqueous medium (Scheme 5), avoiding the harsh reaction conditions described in a previous report.<sup>1a</sup>

In conclusion, the direct C-2 arylation of indoles can be performed in aqueous media under mild conditions (80

°C).<sup>15</sup> This novel procedure is environmentally friendly in that no toxic solvent is required in the coupling step. Limited amounts of water–ethanol (5:1) are invested, and workup entails only an in-flask extraction with a minimal amount of a single, recoverable organic solvent. The protocol also exhibits improved yields and high chemo-/ regioselectivity, thereby offering considerable potential for applications to complex targets in organic synthesis.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## **References and Notes**

- (a) Liu, Y.; McWhorter, W. W. J. Am. Chem. Soc. 2003, 125, 4240. (b) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. Org. Lett. 2008, 11, 197. (c) Rohini, R.; Muralidhar Reddy, P.; Shanker, K.; Hu, A.; Ravinder, V. Eur. J. Med. Chem. 2010, 45, 1200.
   (d) Nahed, F. A. E.; Mona, M. K.; Mona, K. S.; Azza, R. M.; Galal, S. H.; Sara, A. N. J. Chem. Pharm. Res. 2011, 3, 248.
   (e) Cacchi, S.; Fabrizi, G. Chem. Rev. 2005, 105, 2873.
   (f) Rohini, R.; Shanker, K.; Reddy, P. M.; Sekhar, V. C.; Ravinder, V. Arch. Pharm. 2009, 342, 533.
- (2) (a) Chauder, B.; Larkin, A.; Snieckus, V. Org. Lett. 2002, 4, 815. (b) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. Org. Lett. 2003, 5, 1899. (c) Dandu, R.; Tao, M.; Josef, K. A.; Bacon, E. R.; Hudkins, R. L. J. Heterocycl. Chem. 2007, 44, 437. (d) Hughes, T. V.; Emanuel, S. L.; O'Grady, H. R.; Connolly, P. J.; Rugg, C.; Fuentes-Pesquera, A. R.; Karnachi, P.; Alexander, R.; Middleton, S. A. Bioorg. Med. Chem. Lett. 2008, 18, 5130.
- (3) (a) Joucla, L.; Djakovitch, L. Adv. Synth. Catal. 2009, 351, 673. (b) Lebrasseur, N.; Larrosa, I. Adv. Heterocycl. Chem. 2012, 105, 309. (c) Boorman, T. C.; Larrosa, I. In Progress in Heterocyclic Chemistry; Vol. 22; Gribble, G.; Joule, J., Eds.; Elsevier: Amsterdam, 2011, 1.
- (4) (a) Sezen, B.; Sames, D. J. Am. Chem. Soc. 2006, 128, 8364.
  (b) Lane, B. S.; Brown, M. A.; Sames, D. J. Am. Chem. Soc. 2005, 127, 8050. (c) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. Tetrahedron 2007, 63, 1970. (d) Wang, X.; Gribkov, D. V.; Sames, D. J. Org. Chem. 2007, 72, 1476.
  (e) Huang, Y.; Lin, Z.; Cao, R. Chem.-Eur. J. 2011, 17, 12706. (f) Wang, L.; Yi, W.-B.; Cai, C. Chem. Commun. 2011, 47, 806. (g) Lane, B. S.; Sames, D. Org. Lett. 2004, 6, 2897. (h) Nikulin, M.; Lebedev, A.; Voskoboinikov, A.; Beletskaya, I. Dokl. Chem. (Engl. Transl.) 2008, 423, 326. (i) Nadres, E. T.; Lazareva, A.; Daugulis, O. J. Org. Chem. 2010, 76, 471.
- (5) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. J. Am. Chem. Soc. 2006, 128, 4972. (b) Lebrasseur, N.; Larrosa, I. J. Am. Chem. Soc. 2008, 130, 2926. (c) Jiao, L.; Bach, T. J. Am. Chem. Soc. 2011, 133, 12990.
- (6) (a) Anastas, P. T.; Warner, J. C. In *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

(b) Anastas, P. T.; Williamson, T. In *Green Chemistry, Frontiers in Benign Chemical Synthesis and Process*; Oxford University of Press: Oxford, **1998**. (c) Capello, C.; Fischer, U.; Hungerbuhler, K. *Green Chem.* **2007**, *9*, 927.

- (7) (a) René, O.; Fagnou, K. Org. Lett. 2010, 12, 2116.
  (b) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. Angew. Chem. Int. Ed. 2010, 49, 781. (c) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. Angew. Chem. Int. Ed. 2010, 49, 6629. (d) Turner, G. L.; Morris, J. A.; Greaney, M. F. Angew. Chem. Int. Ed. 2007, 46, 7996.
- (8) Joucla, L.; Batail, N.; Djakovitch, L. Adv. Synth. Catal. 2010, 352, 2929.
- (9) (a) Liston, D. J.; Lee, Y. J.; Scheidt, W. R.; Reed, C. A. J. Am. Chem. Soc. 1989, 111, 6643. (b) Albano, V. G.; Di Serio, M.; Monari, M.; Orabona, I.; Panunzi, A.; Ruffo, F. Inorg. Chem. 2002, 41, 2672. (c) Lafrance, M.; Fagnou, K. J. Am. Chem. Soc. 2006, 128, 16496.
- (10) (a) Lipshutz, B. H.; Ghorai, S. Aldrichimica Acta 2008, 41, 59. (b) Lipshutz, B. H.; Ghorai, S. Aldrichimica Acta 2012, 45, 3. (c) Lu, G.-P.; Cai, C. Colloid. Surface. Physicochem. Eng. Aspect. 2010, 355, 193. (d) Lin, L.; Li, Y.; Zhang, S.; Li, S. Synlett 2011, 1779. (e) Shinde, M. M.; Bhagwat, S. S. Colloid. Surface. Physicochem. Eng. Aspect. 2011, 380, 201. (f) Park, K.; Bae, G.; Park, A.; Kim, Y.; Choe, J.; Song, K. H.; Lee, S. Tetrahedron Lett. 2011, 52, 576. (g) Lessi, M.; Masini, T.; Nucara, L.; Bellina, F.; Rossi, R. Adv. Synth. Catal. 2011, 353, 501. (h) Duplais, C.; Krasovskiy, A.; Wattenberg, A.; Lipshutz, B. H. Chem. Commun. 2010, 46, 562.
- (11) (a) Chanda, A.; Fokin, V. V. Chem. Rev. 2009, 109, 725.
  (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. Angew. Chem. Int. Ed. 2005, 44, 3275. (c) Zhang, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. Eur. J. Org. Chem. 2006, 869. (d) Torihata, A.; Kuroda, C. Synlett 2011, 2035.
- (12) (a) Dwars, T.; Paetzold, E.; Oehme, G. Angew. Chem. Int. Ed. 2005, 44, 7174. (b) Morawetzm, H. In Catalysis and Inhibition in Solutions of Synthetic Polymers and in Micellar Solutions; Vol. 20; Eley, H. P. D. D.; Paul, B. W., Eds.; Academic Press: San Diego, 1969, 341.
- (13) (a) Lindström, U. M. Chem. Rev. 2002, 102, 2751. (b) Lu, G.-P.; Zeng, L.-Y.; Cai, C. Green Chem. 2011, 13, 998.
  (c) Lu, G.-P.; Cai, C. J. Chem. Res. 2011, 35, 547.
- (14) Butler, R. N.; Coyne, A. G. Chem. Rev. 2010, 110, 6302.
- (15) General Procedure for Direct C-2 Arylation of Indoles in Aqueous Medium: Pd(Amphos)<sub>2</sub>Cl<sub>2</sub> (0.005 mmol), NaOH (0.375 mmol), tetrachlorophthalic anhydride (TCPA; 0.375 mmol) and indole 1 (0.250 mmol) were weighed into a microwave vial at r.t. Aryl halide (0.375 mmol), EtOH (0.10 mL) and H<sub>2</sub>O (0.50 mL) were then added by syringe. The resulting solution was allowed to stir at 80 °C for 24 h. Upon completion, the reaction mixture was diluted with EtOAc (4.0 mL), filtered through a bed of silica gel layered over Celite, The volatiles were removed in vacuo to afford the crude product. The extent of conversion was determined by GC–MS. Further column chromatography on silica gel afforded the pure desired product 2.

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