

# 2,3-Disubstituted Indoles through the Palladium-Catalyzed Reaction of Aryl Chlorides with *o*-Alkynyltrifluoroacetanilides

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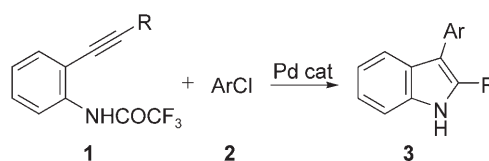
**Abstract:** 2,3-Disubstituted indoles can be prepared in moderate to excellent yields by reacting readily available *o*-alkynyltrifluoroacetanilides with aryl chlorides in MeCN at 120 °C in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and Xphos.

**Keywords:** alkynes; aminopalladation-reductive elimination; cyclization; indoles; palladium

## Introduction

The palladium-catalyzed reaction of *o*-alkynyltrifluoroacetanilides with organopalladium complexes generated *in situ* has been proved to be a remarkably efficient and versatile procedure for the *de novo* construction of the substituted pyrrole nucleus incorporated into the indole system.<sup>[1]</sup> A wide variety of precursors of organopalladium complexes, required to trigger the cyclization of *o*-alkynyltrifluoroacetanilides through the aminopalladation-reductive elimination mechanism, have been successfully employed in this chemistry, including aryl iodides, bromides, and triflates. Obviously, extension of the procedure to aryl chlorides would greatly widen its scope and generality because of the wider diversity of available compounds and their lower cost. Because of their reluctance to undergo oxidative addition to Pd(0) centers, aryl chlorides were known to be usually unreactive under the conditions used for aryl iodides, bromides and triflates. However, in the past seven years or so remarkable progress has been achieved in their utilization in palladium-catalyzed reactions and a vast array of C–C bond forming reactions (such as Suzuki, Stille, Negishi, Sonogashira cross-couplings and Heck reactions) as well as C–N and C–O bond forming reactions, usually referred to as Buchwald–Hartwig reactions, has been accomplished by using aryl chlorides

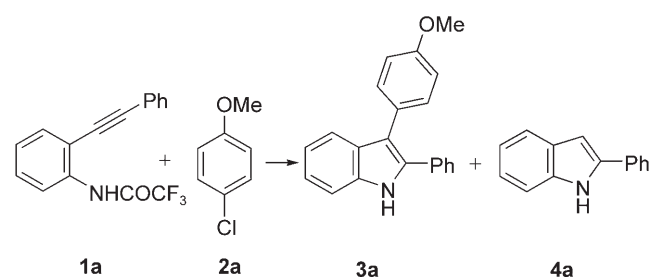
as coupling partners.<sup>[2]</sup> Therefore, as part of our continuing interest in the construction of the indole ring from acyclic alkynes, we decided to explore the feasibility of a process in which aryl chlorides could be used as partners in a cyclization process leading to N–H-free, 2-substituted 3-aryl/heteroarylindoles **3** from *o*-alkynyltrifluoroacetanilides **1** (Scheme 1). Herein we report the results of this study.



Scheme 1.

## Results and Discussion

The palladium-catalyzed reaction of *o*-(phenylethynyl)trifluoroacetanilide (**1a**) and *p*-chloroanisole (**2a**), expected to be one of the most reluctant aryl chlorides to enter the catalytic cycle producing the desired indole products, was chosen as the model system for our initial investigation of this cyclization process (Scheme 2). The preparation of the starting alkyne for this chemistry is quite simple and straightforward. In



Scheme 2.

general, the appropriate *o*-alkynyltrifluoroacetanilides are readily available, usually in high yields, in two steps from *o*-iodoaniline *via* Sonogashira cross-coupling with terminal alkynes followed by a trifluoroacetylation step.<sup>[3]</sup>

One of the major problems in realizing this indole synthesis with relatively unreactive precursors of organopalladium complexes is the competitive formation of simple 2-substituted indoles **4**, the formation of which does not involve the aryl halide partner. In some cases, 2-substituted indoles can even be the main reaction products.

Indeed, when the reaction of **1a** with **2a** was attempted under the reaction conditions that were successfully employed with aryl bromides<sup>[4]</sup> [Pd(PPh<sub>3</sub>)<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, MeCN] for 24 h, but increasing the temperature to 120 °C, indole **3a** was obtained in trace amounts along with a 20% yield of **4a**. The starting alkyne was recovered in 53% yield and *o*-(phenylethynyl)aniline, derived from the hydrolysis of **1a**, was isolated in 9% yield. No significantly better results were obtained by using Pd<sub>2</sub>(dba)<sub>3</sub> as the Pd(0) source in the presence of Cs<sub>2</sub>CO<sub>3</sub> and the air-stable HP-(*t*-Bu)<sub>3</sub>BF<sub>4</sub> (which is converted into the corresponding bulky phosphine ligand by simple deprotonation under the reaction conditions)<sup>[5]</sup> or 1,3-bis-(2,4,6-trimethylphenyl)imidazolium chloride (shown to generate *in situ*, in the presence of Cs<sub>2</sub>CO<sub>3</sub> as the base, the corresponding carbene ligand)<sup>[6]</sup> in MeCN at 120 °C for 24 h. The efficacy of both these ligand precursors in palladium-catalyzed reactions of aryl chlorides were originally demonstrated *via* their successful utilization in Suzuki and Stille cross-couplings and Heck reactions. However, when used with our model system they led to the formation of **3a** in 5 and 10% yield, respectively, with 2-phenylindole (**4a**) being isolated in 60 and 45% yield.

Control experiments revealed that both palladium catalysis and base are required for the competitive cyclization of **1a** to **4a** (Scheme 3). Indeed, compound **4a** was isolated only in 4% yield together with an 8% yield of *o*-(phenylethynyl)aniline upon treatment of **1a** with Cs<sub>2</sub>CO<sub>3</sub> in MeCN at 120 °C for 24 h while omitting the palladium catalyst. The starting alkyne **1a** was recovered in 82% yield. In the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and omitting the base, **4a** was formed in

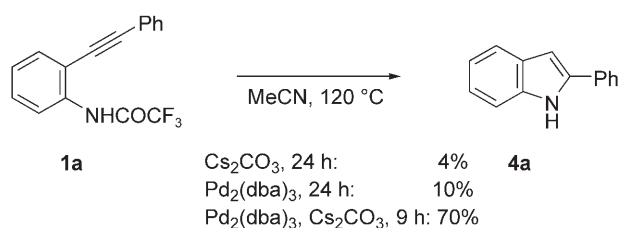
10% yield and the starting alkyne **1a** was recovered in 78% yield. When **1a** was subjected to the palladium catalyst in the presence of Cs<sub>2</sub>CO<sub>3</sub>, compound **4a** was isolated in 70% yield.

The acidity of the N–H bond, which plays an important role in the aminopalladation-reductive elimination reaction (*vide infra*), was found to play an important role in the formation of **4a** as well. In fact, whereas **1a** was converted in high yield into **4a** in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub> (Scheme 3), *o*-(phenylethynyl)aniline containing a less acidic N–H bond was recovered in almost quantitative yield when it was subjected to the same conditions.

Since the palladium-catalyzed cyclization of **1a** to **4a** does not necessarily require the presence of phosphine ligands – as suggested by the isolation of **4a** in high yield with Pd<sub>2</sub>(dba)<sub>3</sub> (Scheme 3) – whereas the formation of  $\sigma$ -arylpalladium complexes from aryl halides is strongly dependent on the nature of phosphine ligands,<sup>[1]</sup> we decided to explore the role of phosphine ligands in controlling the **3** vs. **4** pathway. In particular, we turned our attention to the utilization of biarylmonophosphines, a class of phosphine ligands introduced by Buchwald et al.<sup>[7]</sup> which were shown to produce catalyst systems with a greater degree of activity in the oxidative addition of aryl chlorides to Pd(0) species than other commonly used ligands. For example, they were reported to give excellent results in palladium-catalyzed C–N bond forming reactions<sup>[7b]</sup> and Suzuki–Miyaura cross-coupling reactions<sup>[7c]</sup> involving aryl chlorides. Some results from that study are summarized in Table 1.

Treatment of **1a** with 5 equivs. of *p*-chloroanisole in the presence of 0.025 equivs. of Pd<sub>2</sub>(dba)<sub>3</sub>, 0.1 equiv. phosphine ligand **a–e** and 1.5 equivs. of Cs<sub>2</sub>CO<sub>3</sub> in MeCN at 120 °C produced **4a** as the main product (Table 1, entries 1–5). Acceptable results were instead obtained with monophosphine **f**, Xphos, under the same conditions (Table 1, entry 6). Decreasing the excess of *p*-chloroanisole to 3 equivs. gave similar results (Table 1, entry 7) and with 1.5 equivs. of *p*-chloroanisole **4a** was isolated as the main product (Table 1, entry 8). We examined the effect of different amounts of Xphos and found that the best results were obtained when 0.1 equiv. of the phosphine were used. Increasing the amount of phosphine to 0.2 equivs. did not afford better results (Table 1, entry 9) whereas lower amounts of phosphine (0.05 equivs.) gave a lower yield and a lower **3a** to **4a** ratio (Table 1, entry 10). A further decrease to 0.025 equivs. led to the formation of **4a** as the main product (Table 1, entry 11). Even a decrease in the reaction temperature to 90 °C favored the formation of **4a** (Table 1, entry 12).

A more polar solvent such as DMF (Table 1, entry 15) afforded a higher **3a** to **4a** ratio, although the yield of **3a** was almost the same. The use of a less



Scheme 3.

**Table 1.** Biarylmonophosphine ligands in the palladium-catalyzed reaction of *o*-(phenylethynyl)trifluoroacetanilide (**1a**) with *p*-chloroanisole.<sup>[a]</sup>

| Entry | Phosphine ligand |          | Equivs. of phosphine | Equivs. of <i>p</i> -chloroanisole | <i>t</i> [h] | Yield of <b>3a</b> [%] <sup>[b]</sup> | Yield of <b>4a</b> [%] <sup>[b]</sup> |
|-------|------------------|----------|----------------------|------------------------------------|--------------|---------------------------------------|---------------------------------------|
| 1     |                  | <b>a</b> | 0.1                  | 5                                  | 7            | 4                                     | 94                                    |
| 2     |                  | <b>b</b> | 0.1                  | 5                                  | 24           | 15                                    | 59                                    |
| 3     |                  | <b>c</b> | 0.1                  | 5                                  | 24           | 27                                    | 48                                    |
| 4     |                  | <b>d</b> | 0.1                  | 5                                  | 8            | 36                                    | 42                                    |
| 5     |                  | <b>e</b> | 0.1                  | 5                                  | 7            | 23                                    | 75                                    |
| 6     |                  | <b>f</b> | 0.1                  | 5                                  | 8            | 57                                    | 26                                    |
| 7     |                  | <b>f</b> | 0.1                  | 3                                  | 8            | 55                                    | 25                                    |
| 8     |                  | <b>f</b> | 0.1                  | 1.5                                | 24           | 33                                    | 41                                    |
| 9     |                  | <b>f</b> | 0.2                  | 3                                  | 8            | 58                                    | 26                                    |
| 10    |                  | <b>f</b> | 0.05                 | 3                                  | 11           | 50                                    | 38                                    |
| 11    |                  | <b>f</b> | 0.025                | 3                                  | 9            | 37                                    | 40                                    |
| 12    |                  | <b>f</b> | 0.1                  | 3                                  | 6            | 10                                    | 58 <sup>[c]</sup>                     |
| 13    |                  | <b>f</b> | 0.1                  | 3                                  | 2            | 50                                    | 30 <sup>[d]</sup>                     |
| 14    |                  | <b>f</b> | 0.1                  | 3                                  | 1            | 58                                    | 13 <sup>[e]</sup>                     |
| 15    |                  | <b>f</b> | 0.1                  | 3                                  | 2            | 58                                    | 5 <sup>[f]</sup>                      |

<sup>[a]</sup> Unless otherwise stated, reactions were run in MeCN under an argon atmosphere in the presence of 0.025 equivs. of Pd<sub>2</sub>(dba)<sub>3</sub> and 1.5 equivs. of Cs<sub>2</sub>CO<sub>3</sub> at 120 °C.

<sup>[b]</sup> Yields are given for isolated products.

<sup>[c]</sup> At 90 °C.

<sup>[d]</sup> In toluene.

<sup>[e]</sup> In toluene at 140 °C.

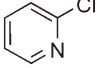
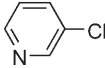
<sup>[f]</sup> In DMF.

polar solvent such as toluene gave a slightly lower yield at 120 °C (Table 1, entry 13), but **4a** was isolated in 58 % yield at 140 °C (Table 1, entry 14).

The influence of the nature of the *ortho* nitrogen in this chemistry was also briefly investigated. Apparently, the acidity of the N–H bond plays a key role for the success of the cyclization leading to 2,3-disubsti-

tuted indoles. No indole derivative was observed when *o*-(phenylethynyl)aniline was subjected to *p*-chloroanisole in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Xphos in MeCN at 120 °C after 24 h, the starting alkyne being recovered in 94 % yield. Switching to *o*-(phenylethynyl)acetanilide as the starting alkyne afforded a 12 % yield of **3a** and a 52 % yield of **4a**

**Table 2.** Synthesis of 2,3-disubstituted indoles **3** via the palladium-catalyzed reaction of *o*-(phenylethynyl)trifluoroacetanilide (**1a**) with aryl chlorides **2**.<sup>[a]</sup>

| Entry | Aryl chloride <b>2</b>                                                            | <b>2</b>  | <i>t</i> [h] | <b>3</b>  | Yield [%] <sup>[b]</sup> |
|-------|-----------------------------------------------------------------------------------|-----------|--------------|-----------|--------------------------|
| 1     | <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -Cl                                   | <b>2a</b> | overnight    | <b>3a</b> | 55                       |
| 2     | <i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub> -Cl                                   | <b>2b</b> | 3            | <b>3b</b> | 88                       |
| 3     | <i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> -Cl                                    | <b>2c</b> | 5.5          | <b>3c</b> | 48                       |
| 4     | <i>o</i> -Me-C <sub>6</sub> H <sub>4</sub> -Cl                                    | <b>2d</b> | 5.5          | <b>3d</b> | 40                       |
| 5     | PhCl                                                                              | <b>2e</b> | 3.5          | <b>3e</b> | 90                       |
| 6     | <i>p</i> -Me-CO-C <sub>6</sub> H <sub>4</sub> -Cl                                 | <b>2f</b> | 2            | <b>3f</b> | 94                       |
| 7     | <i>m</i> -MeO-CO-C <sub>6</sub> H <sub>4</sub> -Cl                                | <b>2g</b> | 3            | <b>3g</b> | 84                       |
| 8     | <i>m</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> Cl                       | <b>2h</b> | 1.5          | <b>3h</b> | 85                       |
| 9     |  | <b>2i</b> | 3            | <b>3i</b> | 83                       |
| 10    |  | <b>2j</b> | 2            | <b>3j</b> | 80                       |

<sup>[a]</sup> Reactions were run in MeCN under an argon atmosphere in the presence of 0.025 equivs. of Pd<sub>2</sub>(dba)<sub>3</sub>, 0.1 equiv. of Xphos, and 1.5 equivs. of Cs<sub>2</sub>CO<sub>3</sub> at 120 °C.

<sup>[b]</sup> Yields are given for isolated products.

(24 h) and using *o*-(phenylethynyl)trifluoroacetanilide (**1a**) gave **3a** and **4a** in 55 and 25 % yields, respectively (Table 1, entry 7).

On the basis of our screening study, we decided to choose MeCN as the most convenient solvent when the reaction was extended to other *o*-alkynyltrifluoroacetanilides and aryl chlorides. As shown in Table 2, under the conditions used in Table 1, entry 7 [Pd<sub>2</sub>(dba)<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Xphos, MeCN, 120 °C] excellent results were obtained with neutral (entry 5), electron-poor (entries 2, 6–8) aryl chlorides and heteroaryl chlorides (entries 9 and 10) whereas moderate to good yields were observed with electron-rich aryl chlorides (entries 1, 3, and 4).

We next extended the procedure to *o*-alkynyltrifluoroacetanilides bearing electron-donating, electron-withdrawing, and alkyl substituents on one of the acetylenic carbons. Their reaction with a variety of aryl chlorides produced the corresponding 2,3-disubstituted indoles in moderate to high yields. The results obtained are summarized in Table 3 and confirm the tendency of electron-poor and almost neutral aryl chlorides to give better results than electron-rich aryl chlorides. *o*-Alkynyltrifluoroacetanilide **1c**, bearing an alkyl substituent, gave lower yields than *o*-alkynyltrifluoroacetanilides bearing aryl substituents (compare entry 4 with entries 3 and 8).

As to the mechanism, we believe that the formation of 2,3-disubstituted indoles proceeds through the aminopalladation-reductive elimination path<sup>[1]</sup> which involves the following basic steps: (a) formation of a  $\pi$ -alkyne- $\sigma$ -arylpalladium complex *via* coordination of **1** to a  $\sigma$ -arylpalladium intermediate generated *in situ* *via* oxidative addition of the aryl chloride to Pd(0), (b) intramolecular nucleophilic attack of the nitrogen across the activated carbon-carbon triple bond, (c) reductive elimination of the resultant  $\sigma$ -pyrrolyl- $\sigma$ -arylpalladium intermediate which affords the indole product **3** and regenerates the active palladium catalyst.

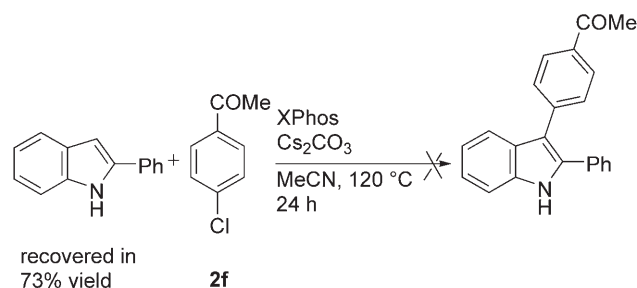
Formation of 2,3-disubstituted indoles **3** *via* direct palladium-catalyzed C-3 arylation of 2-substituted indoles **4** – derived from the cyclization of **1** (Scheme 3) – was ruled out by the following experiment. 2-Phenylindole was subjected to the reaction conditions producing 2,3-disubstituted indoles in the presence of *p*-chloroacetophenone (**2f**), one of the aryl chlorides which gave the highest yields (Table 2, entry 6; Table 3, entries 2 and 7). 2-Phenylindole was recovered in 73 % yield and no evidence was attained for the formation of 2-phenyl-3-(*p*-acetylphenyl)indole (Scheme 4).

**Table 3.** Synthesis of 2,3-disubstituted indoles **3** *via* the palladium-catalyzed reaction of *o*-alkynyltrifluoroacetanilides **1** with aryl chlorides **2**.<sup>[a]</sup>

| Entry | <i>o</i> -Alkynyltrifluoroacetanilide R ( <b>1</b> ) | <b>1</b>  | Aryl chloride ( <b>2</b> )                         | <b>2</b>  | <i>t</i> [h] | <b>3</b>  | Yield [%] <sup>[b]</sup> |
|-------|------------------------------------------------------|-----------|----------------------------------------------------|-----------|--------------|-----------|--------------------------|
| 1     | <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>          | <b>1b</b> | <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -Cl    | <b>2a</b> | 5            | <b>3k</b> | 40                       |
| 2     | <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>          | <b>1b</b> | <i>p</i> -Me-CO-C <sub>6</sub> H <sub>4</sub> -Cl  | <b>2f</b> | 5            | <b>3l</b> | 73                       |
| 3     | <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>          | <b>1b</b> | PhCl                                               | <b>2e</b> | 3            | <b>3m</b> | 60                       |
| 4     | <i>n</i> -C <sub>5</sub> H <sub>11</sub>             | <b>1c</b> | PhCl                                               | <b>2e</b> | 1.5          | <b>3n</b> | 40                       |
| 5     | <i>n</i> -C <sub>5</sub> H <sub>11</sub>             | <b>1c</b> | <i>m</i> -MeO-CO-C <sub>6</sub> H <sub>4</sub> -Cl | <b>2g</b> | 1.5          | <b>3o</b> | 54                       |
| 6     | <i>p</i> -Me-CO-C <sub>6</sub> H <sub>4</sub>        | <b>1d</b> | <i>m</i> -MeO-C <sub>6</sub> H <sub>4</sub> -Cl    | <b>2b</b> | 2.5          | <b>3p</b> | 56                       |
| 7     | <i>p</i> -Me-CO-C <sub>6</sub> H <sub>4</sub>        | <b>1d</b> | <i>p</i> -Me-CO-C <sub>6</sub> H <sub>4</sub> -Cl  | <b>2f</b> | 1            | <b>3q</b> | 87                       |
| 8     | <i>p</i> -Me-CO-C <sub>6</sub> H <sub>4</sub>        | <b>1d</b> | PhCl                                               | <b>2e</b> | 5.5          | <b>3r</b> | 50                       |

<sup>[a]</sup> Reactions were run in MeCN in the presence of 0.025 equivs. of Pd<sub>2</sub>(dba)<sub>3</sub>, 0.1 equiv of Xphos, and 1.5 equivs. of Cs<sub>2</sub>CO<sub>3</sub> at 120 °C.

<sup>[b]</sup> Yields are given for isolated products.



Scheme 4.

## Conclusions

In conclusion, we have developed a convenient straightforward approach for the construction of the functionalized pyrrole ring incorporated into the indole system from readily available *o*-alkynyltrifluoroacetanilides and aryl chlorides, thus widening significantly the scope of our indole synthesis. 2,3-Disubstituted indoles are isolated in moderate to excellent yields. The reaction tolerates a variety of important functional groups.

## Experimental Section

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. *o*-Alkynyltrifluoroacetanilides **1** were prepared according to the procedure described in the literature.<sup>[8]</sup> All of the reagents and the catalysts are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns, packed with SiO<sub>2</sub> 25–40 µm (Macherey&Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100.6 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. IR spectra were recorded with a Jasco FT-IR 430 spectrometer.

### Typical Procedure for the Preparation of 2,3-Disubstituted Indoles (**3**) from *o*-Alkynyltrifluoroacetanilides (**1**) and Aryl/Heteroaryl Chlorides (**2**)

To a 50 mL Carousel Tube Reactor (Radleys Discovery Technology) containing a magnetic stirring bar were added 2.0 mL of MeCN, **1a** (100 mg, 0.346 mmol), **2g** (144 µL, 1.039 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (7.9 mg, 0.0087 mmol), Xphos

(16.5 mg, 0.0346 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (169 mg, 0.519 mmol). The mixture was stirred for 3 h at 120 °C under argon. After this time, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The organic extract was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc, 85/15 v/v) to give **3g**; yield: 94.9 mg (84%); mp: 187–188 °C; IR (KBr):  $\nu$  = 3326, 1702, 1455 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 8.46 (bs, 1H), 8.28–8.25 (m, 1H), 8.03–7.99 (m, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.60–7.56 (m, 1H), 7.49–7.27 (m, 8H), 7.21 (t, *J* = 7.21 Hz, 1H), 3.93 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 167.4, 135.9, 134.9, 132.4, 131.2, 130.6, 128.8, 128.7, 128.6, 128.2, 127.9, 127.5, 122.9, 120.7, 119.4, 114.0, 111.1, 52.1; MS: *m/z* (relative intensity) = 327 (M<sup>+</sup>, 95), 133 (100); calcd. for C<sub>22</sub>H<sub>17</sub>NO<sub>2</sub>: 327.38.

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## References

- [1] a) For reviews, see: G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem.* **2002**, 2671; b) S. Cacchi, F. Fabrizi, *Chem. Rev.* **2005**, 105, 2873; see also: c) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. M. Parisi, *J. Org. Chem.* **2005**, 70, 6213.
- [2] For a recent review on palladium-catalyzed reactions of aryl chlorides, see: A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, 41, 4176.
- [3] S. Cacchi, G. Fabrizi, P. Pace, *J. Org. Chem.* **1998**, 63, 1001.
- [4] S. Cacchi, G. Fabrizi, D. Lamba, F. Marinelli, L. M. Parisi, *Synthesis* **2003**, 728.
- [5] M. Netherton, G. C. Fu, *Org. Lett.* **2001**, 3, 4295.
- [6] C. Zhang, J. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, 64, 3804.
- [7] a) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, 120, 9722; see also: b) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, 125, 6653; c) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, 127, 4685.
- [8] S. Cacchi, G. Fabrizi, P. Pace, *J. Org. Chem.* **1998**, 63, 1001.