Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 2,3-disubstituted indoles from alkynylanilines and 2-chlorophenols using palladium–dihydroxyterphenylphosphine catalyst

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ARTICLE INFO

Article history:
Received 13 February 2020
Revised 28 March 2020
Accepted 31 March 2020
Available online xxxx

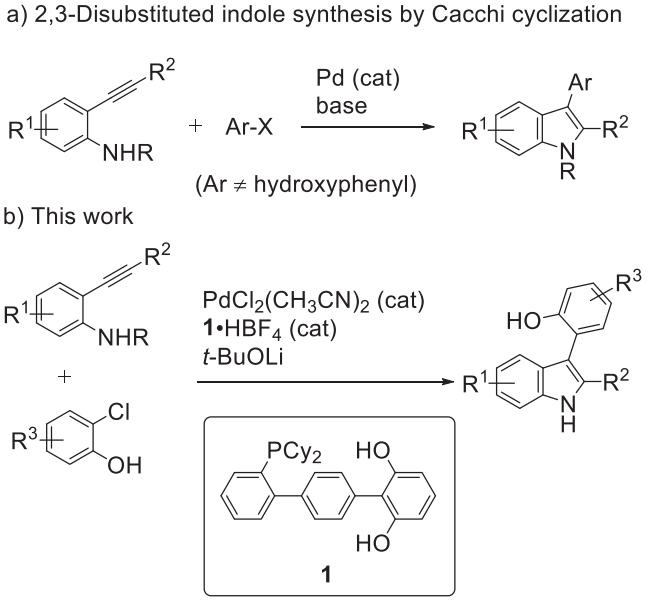
Keywords:
Indole
Palladium
Ligand
Cyclization

ABSTRACT

2,3-Disubstituted indoles bearing 2-hydroxyphenyl moieties at their C3 positions were synthesized from readily available 2-chlorophenols and alkynylanilines via aminopalladation/reductive elimination using Pd–dihydroxyterphenylphosphine catalyst. The catalyst accelerates the introduction of the 2-hydroxyphenyl group at the C3 position of the indole.

Multisubstituted indoles are often found in biologically active compounds and functional materials [1], and a variety of synthetic methods have been developed to prepare these compounds [2]. Among them, 2,3-disubstituted indoles that often bear one or more hydroxy groups have attracted considerable attention [3]. The Cacchi cyclization reaction is a useful method for the synthesis of 2,3-disubstituted indoles, which involves the palladium-catalyzed coupling of a 2-alkynylaniline and a haloarene (Scheme 1a) [4]. In this reaction, an aminopalladation/reductive-elimination sequence affords a 2,3-disubstituted indole with an aryl group at the C3 position. However, the synthesis of hydroxyaryl-group-containing indoles remains challenging, and the use of readily available and inexpensive aryl chlorides as arylating agents has been limited [5].

We previously reported the one-pot synthesis of 2,3-disubstituted benzofurans [6] from readily available 2-chlorophenols and terminal alkynes using a Pd catalyst ligated with dihydroxyterphenylphosphine (DHTP, **1**) [7]. The complexation between the hydroxy groups of the catalyst and the 2-chlorophenol via their lithium phenoxides accelerates oxidative addition of the 2-chloroaryl group to Pd, while the subsequent oxypalladation/reductive elimination affords the desired 2,3-disubstituted benzofuran bearing the 2-hydroxyphenyl group at the C3 position. We expected that the use of ligand **1** would also effectively promote the synthesis of 2,3-disubstituted indoles bearing hydroxyphenyl groups.



Scheme 1. (a) 2,3-Disubstituted indoles synthesized by the Cacchi cyclization reaction. (b) 2,3-Disubstituted indoles synthesized from 2-chlorophenols using the Pd–**1** catalyst (this work).

Herein, we report the synthesis of 2,3-disubstituted indoles bearing 2-hydroxyphenyl groups at their C3 positions from readily available 2-chlorophenols and alkynylaniline derivatives using the Pd–**1** catalyst (Scheme 1b) [8].

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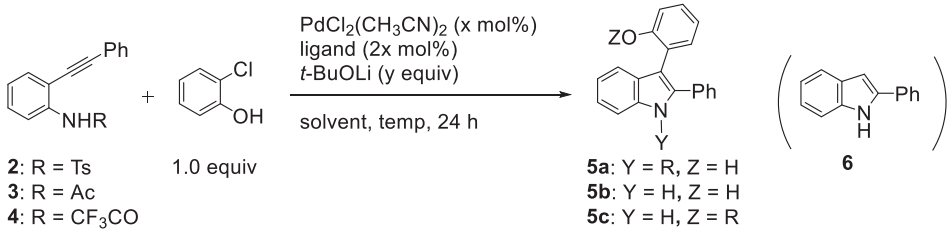
https://doi.org/10.1016/j.tetlet.2020.151896
0040-4039/

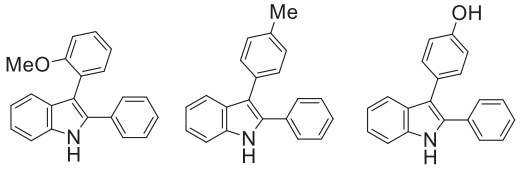
We began optimizing the reaction conditions using a catalyst derived from $PdCl_2(CH_3CN)_2$ and **1**·HBF_4. 2-(Phenylethynyl)aniline derivatives **2**–**4** and 2-chlorophenol were selected as model substrates. Based on our previous indole-synthesis study [9], lithium *tert*-butoxide was used as the base (Table 1). Tosyl- and acetyl-protected **2** and **3** did not afford the desired *N*-protected 2,3-diarylated product **5a** or *N*-deprotected **5b**; instead, only the C3-protonated indole **6** was obtained (entries 1 and 2). Trifluoroacetyl-protected **4** was found to effectively give the desired 2,3-disubstituted indole in 46% yield (entry 3). In this case, both **5b** and **5c**, in which the hydroxy group was trifluoroacetylated, were obtained. The trifluoroacetyl group of **5c** was easily cleaved by methanolysis (Scheme S1). Neither decreasing nor increasing the amount of lithium *tert*-butoxide improved the yield of **5b** (entries 4 and 5). The use of 6 mol% of the Pd catalyst significantly increased the yield of the product to 57%, with trifluoroacetylated **5c** produced as the major product (entry 6). The reaction was then conducted at a higher temperature (140 °C) by changing the solvent from toluene to xylene (entry 7). As a result, the product was obtained in 56% yield with a higher relative amount of **5b**. Mesitylene as the solvent gave the product in 50% yield (entry 8). On the other hand, the use of 1,4-dioxane did not afford any of the desired product, providing **6** in 50% yield (entry 9). Other ligands such as XPhos [10], JohnPhos [11], and $(t\text{-Bu})_3P{\cdot}HBF_4$ gave no C3-arylated products, and only byproduct **6** was obtained in moderate yields (entries 10–12). These results support our hypothesis that the ligand **1** promotes the reaction by accelerating the oxidative addition of 2-chlorophenol to Pd through the formation of a complex between the lithium phenoxides of 2-chlorophenol and **1**.

Reactions using other haloarenes were next examined. The use of 2-bromophenol instead of 2-chlorophenol resulted in a dramatic decrease in the yield of the C3-arylated product **5** to 19%, and 77% of **6** was also produced (entry 13). 2-Chloroanisole afforded the corresponding C3-arylated product **7** in only 19% yield (entry 14), while the use of 4-chlorotoluene also gave the C3-arylated product **8** in low yield (entry 15), and C3-arylation did not proceed at all in the case of 4-chlorophenol, with **6** obtained in 40% yield (entry 16). These results suggest that the *ortho* relationship between the hydroxy and chloro groups in these arylating agents plays an important role in accelerating the reaction.

Table 1
Optimizing the reaction conditions.



Entry	R	$PdCl_2(CH_3CN)_2$ x (mol%)	Ligand	*t*-BuOLi y (equiv.)	Solvent	Temp (°C)	Yield (%)[a] **5 (5a/5b/5c)**	**6**
1	Ts (**2**)	6	**1**·HBF_4	3	toluene	reflux	nd	51[b]
2	Ac (**3**)	4	**1**·HBF_4	3.5	toluene	reflux	trace (nd/trace/nd)	16
3	CF_3CO (**4**)	4	**1**·HBF_4	3	toluene	reflux	46 (nd/23/23)	21
4	CF_3CO (**4**)	4	**1**·HBF_4	2.5	toluene	reflux	37 (nd/25/12)	34
5	CF_3CO (**4**)	4	**1**·HBF_4	3.5	toluene	reflux	44 (nd/32/12)	16
6	CF_3CO (**4**)	6	**1**·HBF_4	3	toluene	reflux	57 (nd/11/46)	3
7	CF_3CO (**4**)	6	**1**·HBF_4	3	xylene	140	56 (nd/31/25)	14
8	CF_3CO (**4**)	6	**1**·HBF_4	3	mesitylene	160	50 (nd/32/18)	28
9	CF_3CO (**4**)	4	**1**·HBF_4	3	1,4-dioxane	reflux	nd	50
10	CF_3CO (**4**)	6	XPhos	3	xylene	140	nd	55
11	CF_3CO (**4**)	6	JohnPhos	3	xylene	140	nd	58
12	CF_3CO (**4**)	6	$(t\text{-Bu})_3P{\cdot}HBF_4$	3	xylene	140	nd	55
13[c]	CF_3CO (**4**)	6	**1**·HBF_4	3	xylene	140	19 (nd/19/nd)	77
14[d]	CF_3CO (**4**)	6	**1**·HBF_4	3	xylene	140	18[e]	23
15[f]	CF_3CO (**4**)	6	**1**·HBF_4	3	xylene	140	20[g]	32
16[h]	CF_3CO (**4**)	6	**1**·HBF_4	3	xylene	140	0[i]	40



7 **8** **9**

[a] Isolated yield. nd = not detected.
[b] Obtained as 2-phenyl-1-tosyl-1*H*-indole.
[c] 2-Bromophenol was used instead of 2-chlorophenol.
[d] 2-Chloroanisole was used instead of 2-chlorophenol.
[e] **7** was obtained.
[f] 4-Chlorotoluene was used instead of 2-chlorophenol.
[g] **8** was obtained.
[h] 4-Chlorophenol was used instead of 2-chlorophenol.
[i] **9** was not obtained.

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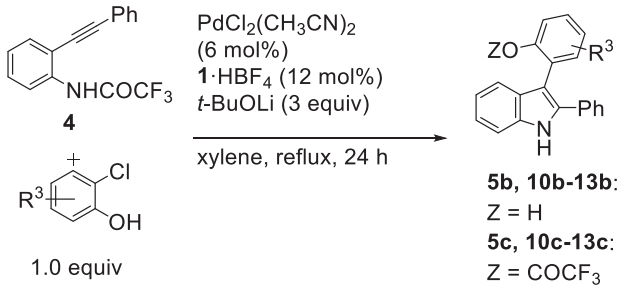
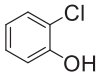
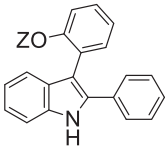
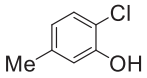
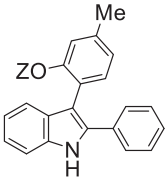
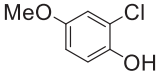
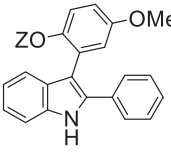
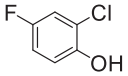
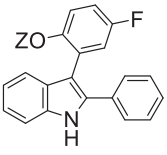
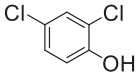
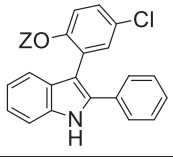
Table 2
Chlorophenol scope.[a]



Entry	2-Chlorophenol	Product	
1			56% (**5b**: 31%/**5c**: 25%)
2			51% (**10b**: 39%/**10c**: 12%)
3			31% (**11b**: 15%/**11c**: 16%)
4			45% (**12b**: 31%/**12c**: 14%)
5			69% (**13b**: 33%/**13c**: 36%)

[a] Isolated yield.

With the optimized conditions in hand, we next examined the range of 2-chlorophenols tolerated by this reaction (Table 2). The reaction proceeded smoothly when 2-chloro-5-methylphenol was used, with the corresponding 3-arylated indole **10** obtained in 51% yield (entry 2). 2-Chloro-4-methoxyphenol can also be introduced (entry 3), and the C3-arylated product **12** was obtained in 45% yield when 2-chloro-4-fluorophenol was used (entry 4). It is noteworthy that the reaction involving 2,4-dichlorophenol proceeded selectively at the 2-chloro group to give the desired indole **13** in 69% yield (entry 5). This high site-selectivity is attributable to the formation of a heteroaggregate involving the lithium phenoxides of 2,4-dichlorophenol and ligand **1** which accelerates the oxidative addition of the 2-chloro group to the Pd.

We next conducted reactions using various 2-alkynylanilines and 2-chlorophenol (Table 3), with the corresponding 2,3-diarylated indoles obtained in moderate yields (entries 1–4). An improved yield was obtained for the 2-decyl-substituted indole, with **18** obtained in 72% yield (entry 5), while the 2-phenethyl-substituted indole **19** was also obtained in good yield (entry 6). However, a low (19%) yield of the 5-methyl-substituted indole **20** was obtained, with 46% of the C3-protonated indole produced (entry 7), while the 5-trifluoromethyl-substituted indole **21** was also obtained in a low yield (entry 8). It should be noted that the 5-chloro substituted indole **22** was obtained in 32% yield with 39% of the C3-protonated indole produced and no other byproducts observed (entry 9). This result reveals that ligand **1** selectively accelerates the oxidative addition of 2-chlorophenol to Pd. Although the reason is unclear, the introduction of substituents on the aniline lowered the yield of the product **20**–**22**.

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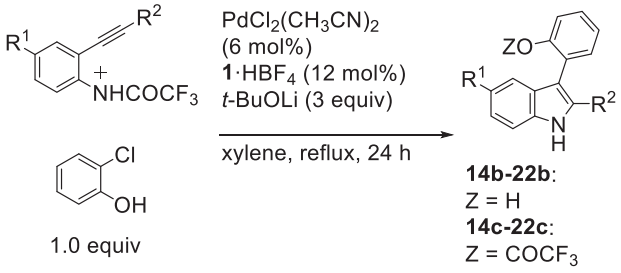
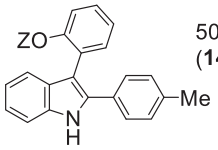
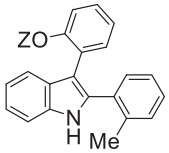
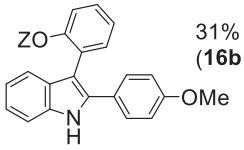
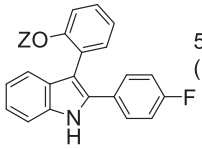
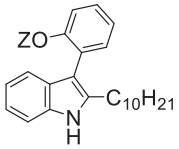
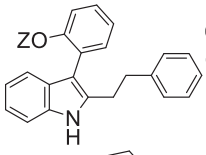
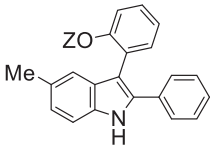
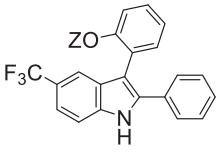
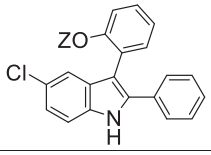
Table 3
2-Alkynylaniline scope.[a]



Entry	R^1 / R^2	Product	
1	R^1 = H R^2 = 4-MeC_6H_4		50% (**14b**: 37%/**14c**: 13%)
2	R^1 = H R^2 = 2-MeC_6H_4		45% (**15b**: 35%/**15c**: 10%)
3	R^1 = H R^2 = 4-$MeOC_6H_4$		31% (**16b**: 25%/**16c**: 6%)
4	R^1 = H R^2 = 4-FC_6H_4		54% (**17b**: 43%/**17c**: 11%)
5	R^1 = H R^2 = $C_{10}H_{21}$		72% (**18b**: 47%/**18c**: 25%)
6	R^1 = H R^2 = $PhCH_2CH_2$		65% (**19b**: 50%/ **19c**: 15%)
7	R^1 = Me R^2 = Ph		19% (**20b**: 19%/**20c**: nd)
8	R^1 = CF_3 R^2 = Ph		14% (**21b**: 11%/**21c**: 3%)
9	R^1 = Cl R^2 = Ph		32% (**22b**: 32%/**22c**: nd)

[a] Isolated yield.

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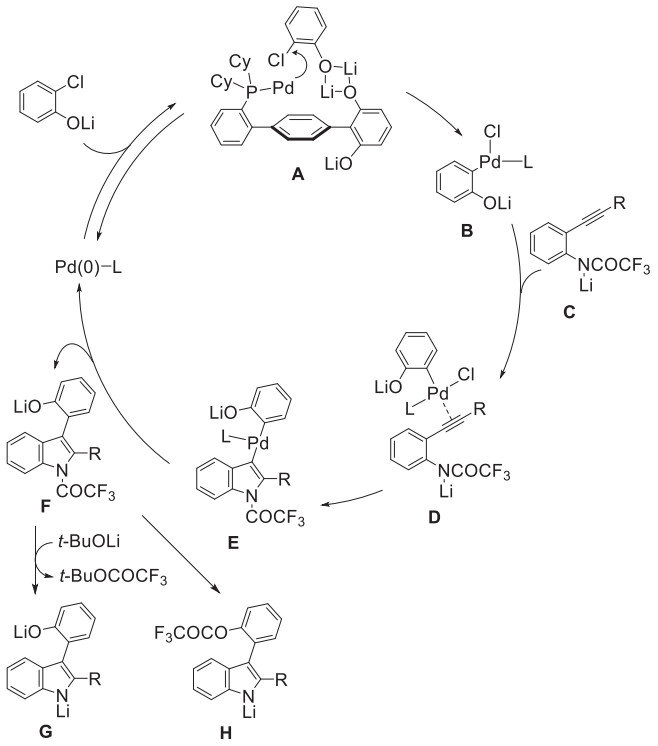

Scheme 2. Proposed reaction pathways.

We assume that reaction pathways involved in this chemistry are as shown in Scheme 2. The lithium salts of **1** and 2-chlorophenol form a heteroaggregate **A**, in which the palladium is located close to the 2-chloro group of the 2-chlorophenoxide. Therefore, the 2-chloro group oxidatively adds selectively and efficiently to the Pd to give intermediate **B**, which subsequently coordinates to the alkyne moiety of the 2-alkynylaniline **C**. The resulting intermediate **D** undergoes aminopalladation to give the σ-indolylpalladium intermediate **E**, and subsequent reductive elimination/detrifluoroacetylation gives the desired product **F**. Detrifluoroacetylation by *t*-BuOLi then affords **G**. The *O*-trifluoroacetylated product **H** is also formed through intermolecular *O*-trifluoroacetylation.

In summary, we synthesized 2,3-disubstituted indoles bearing 2-hydroxyphenyl groups at their C3 positions from readily available 2-alkynylanilines and 2-chlorophenols using Pd–**1** as the catalyst. Various 2-alkynylanililnes bearing either aryl or alkyl groups can be used for this reaction, and substrates having alkyl groups gave the products in higher yield. Ligand **1** accelerates oxidative addition at the 2-chloro group of the 2-chlorophenol, resulting in the formation of the target 2,3-disubstituted indole in moderate-to-good yield.

Acknowledgments

This work was partially supported by JSPS KAKENHI (Grant Numbers 15H04634 and 17K08214), the Hamamatsu Foundation for Science and Technology Promotion, and the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery, and Life Science Research (BINDS)) from the Japan Agency for Medical Research and Development (AMED).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151896.

References

[1] (a) A.J. Kochanowska-Karamyan, M.T. Hamann, Chem. Rev. 110 (2010) 4489–4497;
(b) S.M. Bronner, G.-Y.J. Im, N.K. Garg. In: K.C. Majumdar, S.K. Chattopadhyay (eds.), Heterocycles in Natural Product Synthesis, Wiley-VCH Verlag & Co. KGaA: Weinheim, 2011, p. 221.;
(c) V. Sharma, P. Kumar, D. Pathak, J. Heterocycl. Chem. 47 (2010) 491–502;
(d) N.K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C.H. Kim, A.K. Verma, E.H. Choi, Molecules 18 (2013) 6620–6662;
(e) T.V. Sravanthi, S.L. Manju, Eur. J. Pharm. Sci. 91 (2016) 1–10;
(f) A. Kumari, R.K. Singh, Bioorg. Chem. 89 (2019) 103021.
[2] (a) S. Cacchi, G. Fabrizi, Chem. Rev. 105 (2005) 2873–2920;
(b) G.R. Humphrey, J.T. Kuethe, Chem. Rev. 106 (2006) 2875–2911;
(c) S. Cacchi, G. Fabrizi, Chem. Rev. 111 (2011) PR215–PR283;
(d) G.W. Gribble, Indole Ring Synthesis: From Natural Products to Drug Discovery, John Wiley & Sons Ltd., West Sussex, 2016;
(e) Resent reports concerning the synthesis of 2.3-disubstituted indoles:B. Zhou, Z. Wu, D. Ma, X. Ji, Y. Zhang, Org. Lett. 20 (2018) 6440–6443;
(f) H. Yuan, L. Guo, F. Liu, Z. Miao, L. Feng, H. Gao, ACS Cat. 9 (2019) 3906–3912;
(g) C. Lu, H. Huang, X. Tuo, P. Jiang, F. Zhang, G.-J. Deng, Org. Chem. Front. 6 (2019) 2738–2743;
(h) Y. Shang, K. Jonnada, S.L. Yedage, H. Tu, X. Zhang, X. Lou, S. Huang, W. Su, Chem. Comm. 55 (2019) 9547–9550;
(i) J. Yang, L. Wu, H. Xu, H. Gao, Z. Zhou, W. Wei Yi, Org. Lett. 21 (2019) 9904–9908;
(j) F. Jafarpour, M. Ghasemi, F. Mohaghegh, S. Asgari, A. Habibi, Org. Lett. 21 (2019) 10143–10148;
(k) G. Zhao, M. Zhu, O. Provot, M. Alami, S. Messaoudi, Org. Lett. 22 (2020) 57–61.
[3] (a) Examples of 2,3-disubstituted indoles containing 2-hydroxyphenyl groups at their C3 positions: M.C. Pirrung, K. Park, Z. Li Org. Lett. 3 (2001) 365–367;
(b) J.S. Yadav, B.V.S. Reddy, T. Swamy, Tetrahedron Lett. 44 (2003) 9121–9124;
(c) M.C. Pirrung, Z. Li, E. Hensley, Y. Liu, A. Tanksale, B. Lin, A. Pai, N.J.G. Webster, J. Comb. Chem. 9 (2007) 844–854;
(d) Z. Chai, J.-N. Chen, Z. Liu, X.-F. Li, P.-J. Yang, J.-P. Hu, G. Yang, Org. Biomol. Chem. 14 (2016) 1024–1030;
(e) R. Jillella, C.H. Oh, RSC Adv. 8 (2018) 22122–22126.
[4] (a) Review: G. Battistuzzi, S. Cacchi, G. Fabrizi Eur. J. Org. Chem. (2002) 2671–2681;
(b) Selected examples:A. Arcadi, S. Cacchi, F. Marinelli, Tetrahedron Lett. 33 (1992) 3915–3918;
(c) S. Cacchi, G. Fabrizi, D. Lamba, F. Marinelli, L.M. Parisi, Synthesis (2003) 728–734;
(d) S. Cacchi, G. Fabrizi, L.M. Parisi, Synthesis (2004) 1889–1894.
[5] (a) S. Cacchi, G. Fabrizi, A. Goggiamani, Adv. Synth. Cat. 348 (2006) 1301–1305;
(b) B.Z. Lu, H.-X. Wei, Y. Zhang, W. Zhao, M. Dufour, G. Li, V. Farina, C.H. Senanayake, J. Org. Chem. 78 (2013) 4558–4562.
[6] M. Yamaguchi, H. Ozawa, H. Katsumata, T. Akiyama, K. Manabe, Tetrahedron Lett. 59 (2018) 3175–3178.
[7] S. Ishikawa, K. Manabe, Angew. Chem. Int. Ed. 49 (2010) 772–775.
[8] The one-pot synthesis of 2,3-disubstituted indole **5** from **4**, ethynylbenzene, and 2-chlorophenol was conducted using the Pd**1** catalyst. However, C3-arylation did not proceed and only the C3-protonated indole **6** was obtained in 33% yield (Scheme S2).
[9] (a) M. Yamaguchi, K. Manabe, Org. Lett. 16 (2014) 2386–2389;
(b) M. Yamaguchi, K. Manabe, Org. Biomol. Chem. 15 (2017) 6645–6655.
[10] X. Huang, K.W. Anderson, D. Zim, L. Jiang, A. Klapars, S.L. Buchwald, J. Am. Chem. Soc. 125 (2003) 6653–6655.
[11] A. Aranyos, D.W. Old, A. Kiyomori, J.P. Wolfe, J.P. Sadighi, S.L. Buchwald, J. Am. Chem. Soc. 121 (1999) 4369–4378.