Palladium(II)-Catalyzed Oxidative *ortho*-Arylation of 2-Phenylpyridines

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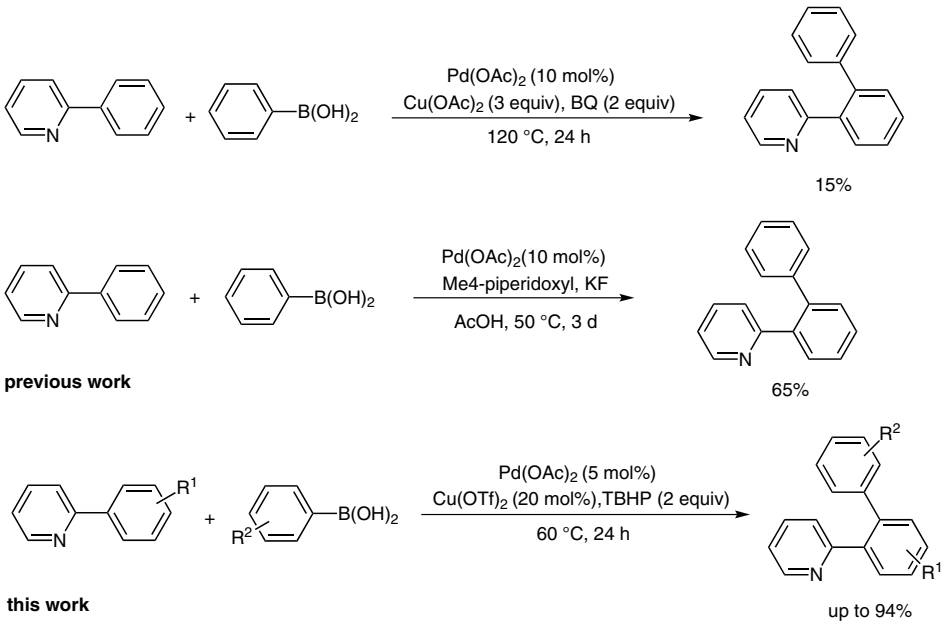
Abstract: A palladium(II)-catalyzed oxidative *ortho*-arylation of 2-phenylpyridines via direct C–H activation with aryl boric acids is described. The reaction could be conducted under mild conditions in the presence of $Pd(OAc)_2/Cu(OTf)_2$/TBHP system, and a variety of the azacyclic compounds bearing a biaryl unit were obtained with moderate to good yields.

Key words: palladium, C–H functionalization, *ortho* arylation, 2-phenylpyridines, arylboronic acid

The biaryl structural unit is present in various drugs, nature products, and key intermediates for organic synthesis.[1] Traditionally, these compounds are prepared by transition-metal-catalyzed cross-coupling reactions of aryl halides and aryl metal compounds.[2] More recently, oxidative metal-catalyzed C–H bond functionalization of heteroatom-directed aromatics, avoiding the prefunctionalization of substrates, has become a more significant and challenging method to synthesize biaryl derivatives.[3]

Transition-metal-catalyzed *ortho*-arylations of heteroatom directed aromatics with aryl electrophiles such as aryl halides, arylboronic acids, and aryl pseudo halides have been extensively studied.[4] Among all these studies, only few examples of the direct transition-metal-catalyzed coupling of boronic acid derivatives with 2-phenylpyridines and its analogues have been published to date. The reaction was initially achieved in rhodium and ruthenium catalytic systems.[5,6] Then, *ortho*-arylations of 2-phenylpyridines in $Pd(OAc)_2/Cu(OAc)_2$/BQ system and *ortho*-arylations of 2-phenylpyridines in $Pd(OAc)_2$/AcOH system were reported, respectively.[7] However, the former system is only suitable for the *ortho*-arylations of 2-phenylpyridines with potassium organotrifluoroborates instead of boronic acid derivatives, and the reactivity of the latter was poor and thus much more time was required to finish this reaction (Scheme 1). More recently, the palladium-catalyzed electrochemical iodination and one-pot arylation of aryl pyridines have been described.[8] Although many efforts have been made, harsh reaction conditions, low yields, and the limited scope of substrates are still the main issues to be addressed in these protocols.

To solve these problems, we herein developed a palladium-catalyzed oxidative system with TBHP as oxidant and $Cu(OTf)_2$ as co-oxidant for the couplings between 2-phenylpyridines and aryl boric acids with improved yields under mild conditions [lower temperature (60 °C), lower



Scheme 1 Pd-catalyzed *ortho*-arylation of 2-phenylpyridines with arylboronic acid

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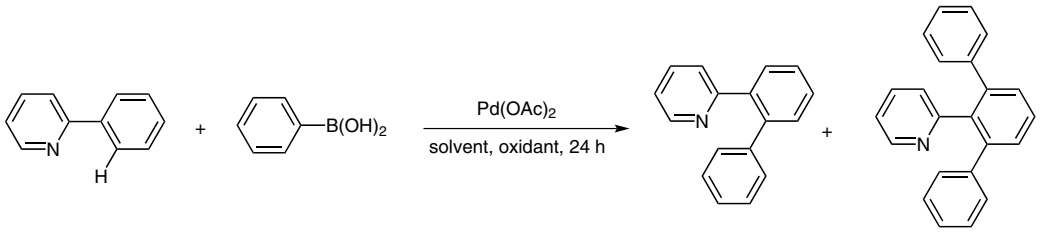
amount of additives], inhibiting the homocoupling of aryl boric acids (Scheme 1).

We commenced our studies by exploring representative oxidants and co-oxidants in the envisioned palladium-catalyzed oxidative reaction of boronic acid and 2-phenylpyridine. A variety of oxidants and additives were screened, and the results are shown in Table 1. The combination of TBHP and $Cu(OTf)_2$ were found to be the best selection for the reaction (Table 1, entry 6). Only a small amount of substrates could be converted in the absence of either of these two reagents (Table 1, entries 1 and 2). Interestingly, satisfactory yield was also obtained when the dosages of $Cu(OTf)_2$ were decreased to 0.2 equivalents (Table 1, entry 9). It is possible that TBHP works as the oxidant in this system, whereas $Cu(OTf)_2$ works as a co-oxidant which is used to accelerate the reoxidation of palladium(0).[9] After that different protic and aprotic solvents were tested, which revealed MeCN to be the reaction medium of choice (Table 1, entry 9). The temperature proved to be significant for the reaction selectivity. It was found that higher temperature was conducive to the formation of disubstituted products and the undesired biphenyl products (Table 1, entries 17 and 18), and only **3a** was produced at room temperature with poor yield (13%, Table 1, entry 16), Therefore, a slight heating (60 °C) was required to improve the conversion and retain high selectivity.

Table 1 Optimization Studies with 2-Phenylpyridine and Phenylboronic Acid[a]

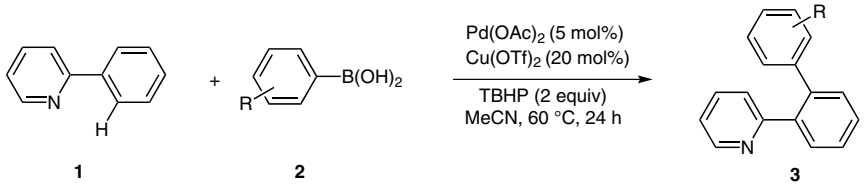


3a **4a**

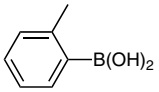
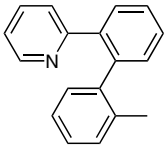
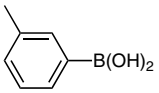
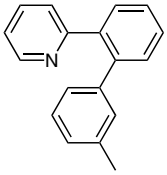
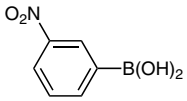
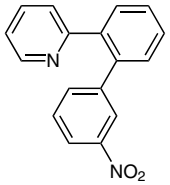
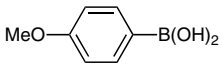
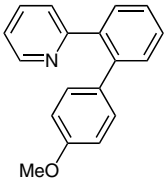
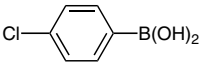
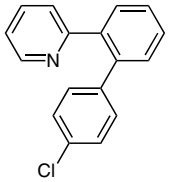
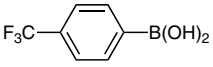
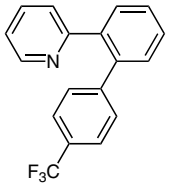
Entry	Oxidant/co-oxidant	Solvent	Temp (°C)	Yield of **3a**/**4a** (%)[b]
1[c]	$Cu(OTf)_2$ (2 equiv)	MeCN	60	6/0
2	TBHP	MeCN	60	3/0
3	$K_2S_2O_8/Cu(OTf)_2$	MeCN	60	52/5
4	$K_2S_2O_8$/AgOAc	MeCN	60	76/7
5	BQ/$Cu(OTf)_2$	MeCN	60	19/0
6[c]	TBHP/$Cu(OTf)_2$	MeCN	60	95/3
7	TBHP/$Cu(OAc)_2$	MeCN	60	23/0
8	TBHP/AgOAc	MeCN	60	67/11
9	TBHP/$Cu(OTf)_2$	MeCN	60	91/6
10	TBHP/$Cu(OTf)_2$	DCE	60	0/0
11	TBHP/$Cu(OTf)_2$	AcOH	60	3/0
12	TBHP/$Cu(OTf)_2$	MeOH	60	20/0
13	TBHP/$Cu(OTf)_2$	DMSO	60	56/4
14	TBHP/$Cu(OTf)_2$	1,4-dioxane	60	0/0
15	TBHP/$Cu(OTf)_2$	DMF	60	45/2
16	TBHP/$Cu(OTf)_2$	MeCN	r.t.	13/0
17	TBHP/$Cu(OTf)_2$	MeCN	80	43/35
18	TBHP/$Cu(OTf)_2$	MeCN	110[d]	32/36

[a] Reaction conditions: 2-phenylpyridine(0.5 mmol), phenylboronic acid (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), oxidants (1.0 mmol), co-oxidants (0.1 mmol), solvent (2 mL).
[b] Based on GC–MS results.
[c] $Cu(OTf)_2$ (1 mmol, 2 equiv) was added.
[d] In a sealed tube.

Table 2 Arylation of 2-Phenylpyridine with Arylboronic Acids[a]



1 **2** **3**

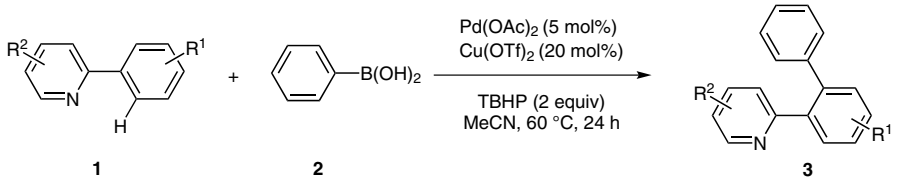
Entry	Substrate **2**	Product **3**	Yield (%)[b]
1	 **2b**	 **3b**	56[c]
2	 **2c**	 **3c**	78 (84)[c]
3	 **2d**	 **3d**	69 (73)[c]
4	 **2e**	 **3e**	90 (94)[c]
5	 **2f**	 **3f**	77 (83)[c]
6	 **2g**	 **3g**	17[c]

[a] Reaction conditions: 2-phenylpyridine(1.0 mmol), aryl boric acids (2.0 mmol), $Pd(OAc)_2$ (0.05 mmol), TBHP (2.0 mmol), $Cu(OTf)_2$ (0.2 mmol), MeCN (2 mL), at 60 °C.
[b] Isolated yields.
[c] Based on GC–MS results.

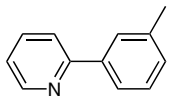
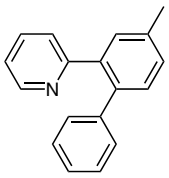
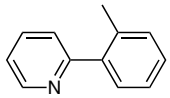
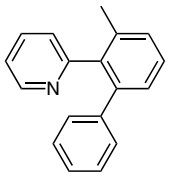
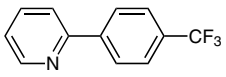
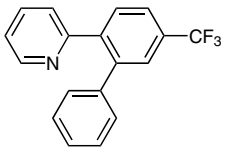
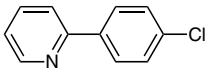
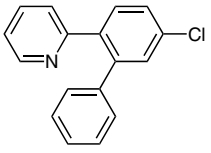
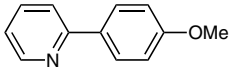
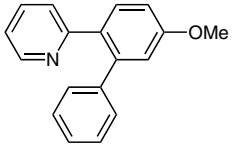
With the optimized reaction conditions in hand, we firstly probed its applicability in the oxidative arylation of 2-phenylpyridine and utilizing different phenylboronic acid derivatives. Most reactions proceeded smoothly, providing their corresponding mono *ortho*-arylated products in good yields (Table 2, entries 1–5). Comparatively, arylboronic acids bearing electron-donating groups show higher activity than electron-withdrawing ones. The lower yield observed in the case of 2-methyl phenylboronic acid compared to *meta*-substituted groups is possibly due to the steric hindrance of the *ortho*-methyl group in 2-methylphenylboronic acid (Table 2, entries 1 and 2). As for 4-trifluoromethylphenylboronic acid (**2g**), the homocoupling suppressed the *ortho*-arylations affording more self-coupling products (Table 2, entry 6).

Substituted 2-phenylpyridines **1b**–**m** compatibility studies are then examined. As expected, a series of substitutions including methyl, methoxy, chloro, and trifluoromethyl on the phenyl ring were compatible under the optimal reaction conditions (Table 3, entries 1–5). But compared to 2-phenylpyridine, substituent in the phenyl ring have negative effects on the product yields for both

Table 3 Arylation of 2-Phenylpyridine with Arylboronic Acids[a]



1 **2** **3**

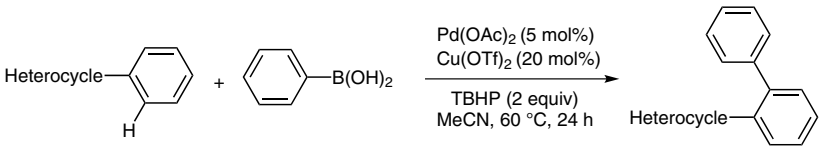
Entry	Substrate **1**	Product **3**	Yield (%)[b]
1	 **1h**	 **3h**	75 (81)[c]
2	 **1i**	 **3i**	34 (46)[c]
3	 **1j**	 **3j**	41 (54)[c]
4	 **1k**	 **3k**	56 (61)[c]
5	 **1l**	 **3l**	63 (69)[c]

[a] Reaction conditions: 2-phenylpridine(0.5 mmol), aryl boric acids (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), TBHP (1.0 mmol), $Cu(OTf)_2$ (0.1 mmol), MeCN (2 mL), at 60 °C.
[b] Isolated yields.
[c] Based on GC–MS results.

electron-donating groups and electron-withdrawing groups. It is probably because the substituent may have negative effects on the coordinating ability of the pyridine and the formation of the pyridine palladacycle.

We also attempted to extend our catalytic system to more phenyl-substituted heterocyclic compounds. 2,6-Diphenylpyridine was firstly tried. 2-[(1,1′-Biphenyl)-2-yl]-6-phenylpyridine (**3m**) was obtained with 82% yield using two equivalents phenylboronic acid (Table 4, entry 1), whereas three products 2-[(1,1′-biphenyl)-2-yl]-6-phenylpyridine (**3m**, 11% yield), 2-[(1,1′:3′,1″-terphenyl)-2′-yl]-6-phenylpyridine (**3n** 45% yield), and 2,6-di[(1,1′-biphenyl)-2-yl]pyridine (**3o**, 15% yield, Table 4, entries 2 and 3) were obtained when the dosage of phenylboronic acid was increased to five equivalents (Table 4, entries 1 and 2). Probably due to the crowed structure, only trace amount of trisubstituted or tetrasubstituted products could be observed.

Table 4 Arylation of Heterocycle Derivatives with Phenylboronic Acid[a]



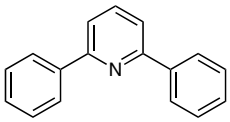
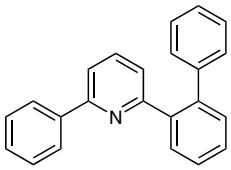
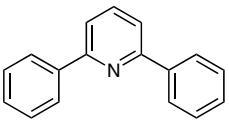
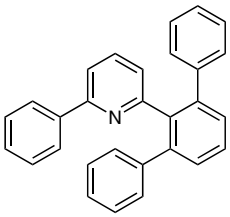
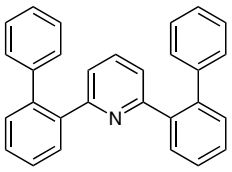
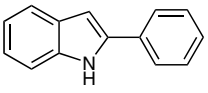
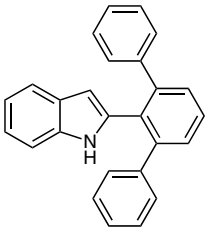
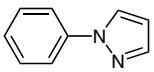
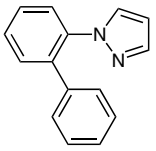
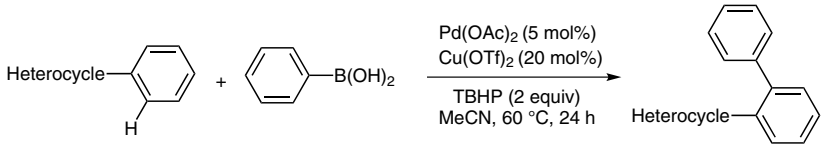
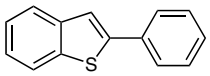
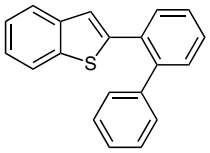
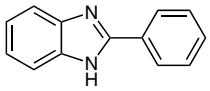
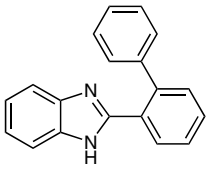
Entry	Substrate **1**	Product **3**	Yield (%)[b]
1	 **1m**	 **3m**	77 (82)[c]
2	 **1m**	 **3n**	40 (45)[c]
		 **3o**	15[c]
3	 **1p**	 **3p**	80 (84)[c]
4	 **1p**	 **3q**	81 (85)[c]

Table 4 Arylation of Heterocycle Derivatives with Phenylboronic Acid[a] (continued)



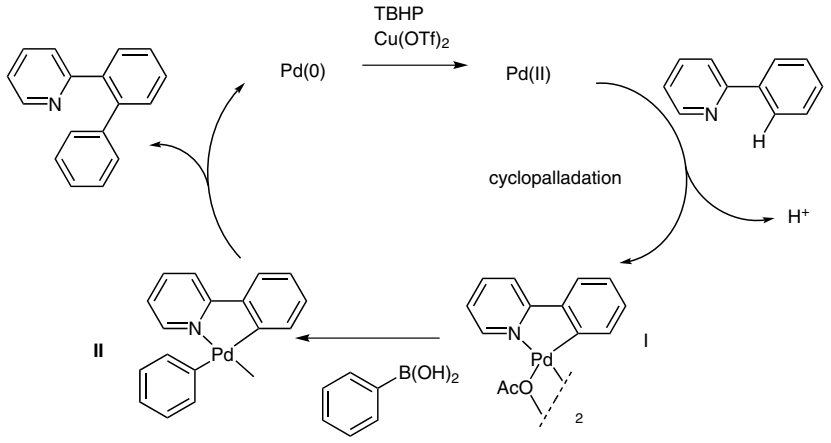
Entry	Substrate **1**	Product **3**	Yield (%)[b]
5[d]	 **1q**	 **3r**	3[c]
6[d]	 **1r**	 **3s**	13[c]

[a] Reaction conditions: 2-phenylpyridine (1.0 mmol), aryl boric acids (2.0 mmol), $Pd(OAc)_2$ (0.05 mmol), TBHP (2.0 mmol), $Cu(OTf)_2$ (0.2 mmol), MeCN (2mL), at 60 °C.
[b] Isolated yields.
[c] Based on GC–MS results.
[d] The reaction was conducted at 110 °C in sealed tube.

After that, 2-phenylindole was tested which showed high activity under the optimized conditions, affording the di-substituted product with 84% yield instead of the mono-substituted one (Table 4, entry 3). Good results were also obtained with phenylpyrazole in 85% yield (Table 4, entry 4). 2-Phenylbenzothiophene and 2-phenylbenzoimidazole were also examined; however, unfortunately, only small amount of substrates converted (Table 4, entries 5 and 6).

Finally, a possible mechanism for the present palladium(II)-catalyzed *ortho*-arylation of 2-phenylpyridine via C–H bond activation is proposed. As shown in Scheme 2, the transformation was initiated from *ortho*-cyclopalladation directed by pyridine to generate the cyclopalladium species. Subsequently, the aryl group of phenylboronic acid bonds to the palladium center of the pyridine palladacycle via ligand exchange. At last, the intermediate **II** is further converted into the *ortho*-arylated product. In addition, the released palladium(0) is reoxidized effciently by $Cu(OTf)_2$ and TBHP under mild conditions to regenerate palladium(II), which could continue the catalytic cycle.

In conclusion, we have described a palladium-catalyzed oxidative *ortho*-arylation of 2-phenylpyridines with arylboronic acids The reaction could be conducted in relatively mild conditions (60 °C, 24 h) in the presence of $Pd(OAc)_2$ (5 mol%), $Cu(OTf)_2$ (20 mol%), and TBHP. Moreover, the reaction system could be extended to some other azacyclics with good results.



Scheme 2 Proposed mechanism for *ortho*-arylation of 2-phenylpyridines

General Procedure for *ortho*-Arylated 2-Phenylpyridine Derivatives

A sealed tube was charged with 2-phenylpyridine (0.5 mmol), phenylboronic acid (1 mmol), $Cu(OTf)_2$ (0.1 mmol), TBHP (1 mmol), and $Pd(OAc)_2$ (0.025 mmol) in MeCN (5 mL) The mixture was heated to 60 °C and stirred violently at this temperature for 24 h. After being cooled to r.t., the mixture was filtered. The filtrate was evaporated under vacuum. Subsequently, the residue was purified by chromatography (silica gel; *n*-hexane–EtOAc, 10:1).

Analytical Data of New Compounds

2-[5-Chloro-(1,1′-biphenyl)-2-yl]pyridine (3k)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 4.8 Hz, 1 H), 7.67 (d, *J* = 8.9 Hz, 1 H), 7.46 (dd, *J* = 6.2, 2.1 Hz, 2 H), 7.40 (d, *J* = 1.7 Hz, 1 H), 7.27–7.25 (m, 2 H), 7.19–7.08 (m, 4 H), 6.86 (d, *J* = 7.9 Hz, 1 H).^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.34, 149.72, 142.44, 140.30, 138.10, 135.56, 134.57, 132.12, 130.55, 129.74, 128.45, 127.89, 127.47, 125.53, 121.83. MS (EI$^+$): *m/z* = 265 $[M + H]^+$.

2-[(1,1′-Biphenyl)-2-yl]-6-phenylpyridine (3m)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84–7.80 (m, 3 H), 7.57 (t, *J* = 3.9 Hz, 2 H), 7.53–7.48 (m, 3 H), 7.45–7.39 (m, 3 H), 7.31–7.29 (m, 1 H), 7.28–7.23 (m, 4 H), 7.05–7.00 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.95, 155.79, 140.90, 139.98, 138.67, 138.56, 135.26, 129.72, 129.68, 128.76, 127.76, 127.55, 127.06, 126.59, 126.02, 125.58, 122.28, 117.06. MS (EI$^+$): *m/z* = 308 $[M + H]^+$.

2-[(1,1′:3′,1″-Terphenyl)-2′-yl]-6-phenylpyridine (3n)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 9.7, 8.3 Hz, 5 H), 7.60–7.53 (m, 6 H), 7.50–7.45 (m, 4 H), 7.39 (d, *J* = 2.5 Hz, 2 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.15 (d, *J* = 2.5 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.95, 150.77, 147.31, 135.04, 127.73, 127.71, 127.01, 126.36, 125.47, 124.78, 123.20, 121.52, 119.70, 113.82, 110.93, 104.30. MS (EI$^+$): *m/z* = 384 $[M + H]^+$.

2-[(1,1′:3′,1″-Terphenyl)-2′-yl]-1*H*-indole (3p)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.52 (dd, *J* = 6.6, 3.0 Hz, 2 H), 7.49–7.42 (m, 2 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.18 (m, 8 H), 7.02 (d, *J* = 8.1 Hz, 1 H), 6.95 (t, *J* = 7.6 Hz, 1 H), 6.82 (t, *J* = 7.4 Hz, 1 H), 6.74 (d, *J* = 8.2 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.27, 136.17, 134.55, 128.75, 127.29, 126.77, 126.77, 126.52, 125.80, 124.43, 121.41, 120.60, 119.04, 118.23, 111.30, 109.71. MS (EI$^+$): *m/z* = 346 $[M + H]^+$.

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

References

(1) (a) Roncali, J. *Chem. Rev.* **1992**, *92*, 711. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (c) Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 402. (d) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384. (f) MaGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.

(2) Selected reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6723. (c) Negishi, E.-i. *Angew. Chem. Int. Ed.* **2011**, *50*, 6738. (d) Farina, V.; Krishnamurphy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1.

(3) Selected reviews: (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (e) Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2009**, *15*, 5874. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (i) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1351. (j) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778.

(4) Selected reviews: (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (c) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (d) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5554. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (h) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (i) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 1275. (j) Xiao, B.; Fu, Y.; Xu, J.; Gong, T. J.; Dai, J. J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468. (k) Gandeepan, P.; Parthasarathy, K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2010**, *132*, 8569. (l) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032. (m) Karthikeyan, J.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 9880.

(5) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 130.

(6) Hong, L.; Wei, W.; Yuan, X.; Chao, Z.; Xiaobing, W. *Chem. Commun.* **2011**, *47*, 1497.

(7) (a) Chu, J.-H.; Tsai, S.-L.; Wu, M.-J. *Synthesis* **2009**, 3757. (b) Sylvia, K.; Thomas, V.; Armido, S. *Synlett* **2008**, 2841.

(8) Aiso, H.; Kochi, T.; Mutsutani, H.; Tanabe, T.; Nishiyama, S.; Kakiuchi, F. *J. Org. Chem.* **2012**, *77*, 7718.

(9) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183.