Organic LETTERS

Letter

pubs.acs.org/OrgLett

One-Pot Synthesis of 2,4-Disubstituted Indoles from *N*-Tosyl-2,3-dichloroaniline Using Palladium−Dihydroxyterphenylphosphine Catalyst

Miyuki Yamaguchi and Kei Manabe*

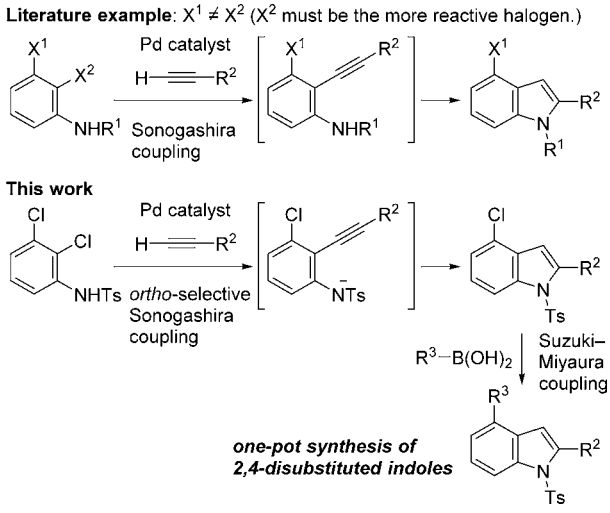
School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan

Supporting Information

ABSTRACT: 4-Chloroindoles were synthesized from readily available 2,3-dichloroaniline derivatives and terminal alkynes. The catalyst composed of palladium and dicyclohexyl(dihydroxyterphenyl)phosphine (Cy-DHTP) enabled *ortho*-selective Sonogashira coupling, and subsequent cyclization afforded 4-chloroindoles in high yields. This transformation was successfully applied to the one-pot synthesis of 2,4-disubstituted indoles via Suzuki−Miyaura coupling after indole formation.

The indole nucleus is a common heterocycle found in biologically active natural compounds[1] and pharmaceuticals;[2] accordingly, many synthetic methods for these compounds have been developed owing to its ubiquity and wide range of biological activities.[3] Among the various substitution patterns of the indole skeleton, indoles bearing 4-substitution, in particular, are challenging synthetic targets[4] due to the scarcity of efficient synthetic methods for introducing a substituent at the C-4 position of the indole ring. The main synthetic strategy for 4-substituted indoles is heteroannulation of substituted aromatic derivatives.[5] A more direct strategy, although less frequently used, is functionalization at C-4, which often requires a directing group at the C-3 position.[6] The synthesis of 4-haloindoles would be a promising strategy to provide various 4-substituted indoles through synthetic transformations such as cross-coupling.[7] Recently, a few methods for the catalytic synthesis of 4-haloindoles have been reported.[8] Among them, the Sonogashira coupling of 2,3-dihaloanilines and terminal alkynes followed by cyclization and subsequent cross-coupling is a promising route for synthesizing 2,4-disubstituted indoles.[9] However, substrates are limited to 2,3-dihaloanilines bearing different halogen atoms in order to achieve site-selective Sonogashira coupling at the position *ortho* to the amino group in the first step (Scheme 1). In addition, the presence of Br or I at the *ortho* position is crucial to achieving high reactivities; however, such dihaloanilines require multistep preparations. No examples of this sequential coupling/cyclization transformation exist using commercially available and inexpensive 2,3-dichloroaniline as the starting material. To realize the reactions of 2,3-dichloroaniline, however, two problems must be overcome: (i) the low reactivity of 2-chloroanilines due to the strong electron-donating ability of the amino group, which retards the turnover-limiting oxidative addition step, and (ii) difficulty of the site-selective Sonogashira coupling[10] that enables the reaction at the electronically deactivated and sterically hindered 2-chloro group.

Scheme 1. Synthetic Strategies of 2,4-Disubstituted Indoles from 2,3-Dihaloaniline Derivatives



We have previously reported the synthesis of benzofurans from 2-chlorophenols and terminal alkynes using Pd catalysts bearing hydroxyterphenylphosphine (HTP)[11] with cyclohexyl groups on the phosphorus atom (Cy-HTP, **1a**) (Figure 1).[12] In addition, the use of a dihydroxyterphenylphosphine such as **1b**

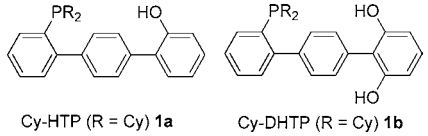


Figure 1. Hydroxylated terphenylphosphines.

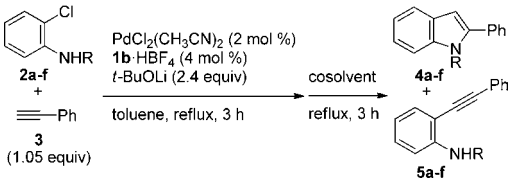
Received: March 6, 2014
Published: April 17, 2014

dx.doi.org/10.1021/ol500711z | *Org. Lett.* 2014, 16, 2386−2389

(Cy-DHTP), shown to be much more effective than HTP for *ortho*-selective cross-coupling,[13] enabled the one-pot synthesis of disubstituted benzofurans bearing substituents at different positions using various dichlorophenols.[14] This preliminary success prompted us to investigate the synthesis of 2,4-disubstituted indoles from 2,3-dichloroanilines. We expected that the use of **1b** would enable the synthesis of 4-chloroindoles and subsequent cross-coupling to afford 2,4-disubstituted indoles in one pot (Scheme 1). Herein, we present the Pd-catalyzed sequential one-pot synthesis of 2,4-disubstituted indoles from *N*-tosyl-2,3-dichloroaniline via Suzuki–Miyaura (SM) coupling of 4-chloroindoles with boronic acids.

First, we searched for catalytic conditions that sufficiently activate the chloro group *ortho* to the amino group using 2-chloroaniline derivatives **2a–f** and ethynylbenzene (**3**) as the model substrates (Table 1). According to our previous work

Table 1. Indole Synthesis from 2-Chloroaniline Derivatives



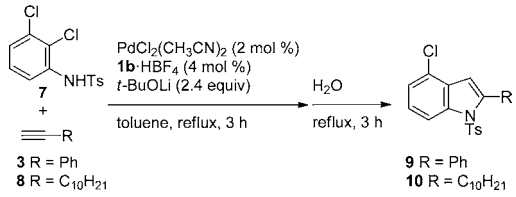
			yield[a] (%)	
entry	R	cosolvent	**4a–f**	**5a–f**
1	Ts (**2a**)	H_2O	68	nd[b]
2	H (**2b**)	H_2O	nd[b]	nd[b]
3	Ac (**2c**)	H_2O	nd[b] (12)[c]	23
4	Ms (**2d**)	H_2O	trace	nd[b]
5	Ns[d] (**2e**)	H_2O	nd[b]	nd[b]
6	Boc (**2f**)	H_2O	nd[b]	nd[b]
7[e]	Ts (**2a**)	–	trace	38
8	Ts (**2a**)	MeOH	25	trace
9[f]	Ts (**2a**)	H_2O	11	nd[b]
10[g]	Ts (**2a**)	H_2O[h]	87	nd[b]

[a]Isolated yield. [b]Not detected. [c]Yield of 2-phenyl-1*H*-indole (**6**). [d]2-Nitrobenzenesulfonyl. [e]*t*-BuOLi (3.6 equiv), 19 h. [f]**1a** instead of **1b**. [g]Mesitylene instead of toluene, 140 °C, 2 h. [h]Reflux, 1 h.

toward benzofurans,[14] the Sonogashira coupling was conducted using Pd–**1b** catalyst in the presence of *t*-BuOLi as a base. Toluene was used as the solvent, and water was added as cosolvent after the Sonogashira coupling step to promote cyclization[14] of the intermediate, 2-alkynylaniline derivative **5**. Among the 2-chloroaniline derivatives tested, *N*-tosylaniline **2a** gave the desired indole **4a** in good yield (entry 1).[15] 2-Chloroaniline (**2b**) did not afford the product (entry 2). When *N*-acetylated **2c** was used, deacylated indole **6** was obtained in low yield along with Sonogashira coupling product **5c** (entry 3). Other protecting groups (**2d–f**) were not suitable for this reaction (entries 4–6). A cosolvent is necessary to cyclize 2-alkynylaniline **5**; without the addition of water, cyclization of **5** did not proceed (entry 7). Methanol did not work well as the cosolvent for cyclization (entry 8). The use of monohydroxyterphenylphosphine **1a** instead of **1b** resulted in a low yield of the product (entry 9). In the case of other ligands commonly used in the cross-coupling of chloroarenes (such as PCy_3 or XPhos[16]), Sonogashira coupling did not proceed at all, and **2a** was fully recovered.[17] These results clearly demonstrate the effectiveness of ligand **1b**, which accelerates the turnover-limiting oxidative addition of the C–Cl bond presumably through mixed aggregate formation similar to that proposed for *ortho*-selective cross-coupling.[12−14] Mesitylene was also a good solvent, affording product **4a** at 140 °C in higher yield (entry 10).

We then applied the conditions developed above to the synthesis of 4-chloroindoles from *N*-tosyl-2,3-dichloroaniline (**7**) and alkynes (Table 2). To our delight, the reaction of **7**

Table 2. Synthesis of Chloroindoles from *N*-Tosyl-2,3-dichloroaniline



	alkyne		
entry	R	equiv	yield[a] (%)
1	Ph (**3**)	1.05	74
2	Ph (**3**)	2	88
3	$C_{10}H_{21}$ (**8**)	2	83

[a]Isolated yield.

with **3** gave the desired product in good yield (entry 1). The yield was improved to 88% by increasing the amount of alkyne (entry 2). Aliphatic alkyne **8** could also be used in the reaction (entry 3). In all these cases, the Sonogashira coupling proceeded selectively at the *o*-chloro group, and the products formed through Sonogashira coupling at the *m*-chloro group were not observed. These results again demonstrate the effectiveness of the Pd–**1b** catalyst for accelerating the reaction at the electronically deactivated and sterically hindered position. It should be mentioned that this catalytic system was also applicable to *N*-tosyl-2,4- and 2,5-dichloroanilines to give the corresponding 5- and 6-chloroindoles **11–14** in moderate to high yields (Figure 2).

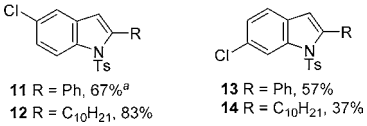


Figure 2. Synthesis of 5- and 6-chloroindoles under the conditions shown in Table 2, entries 2 and 3. [a]Alkyne 1.05 equiv, mesitylene instead of toluene, 140 °C, 2 h; H_2O, reflux, 1.5 h.

Next, we turned our attention to the transformation of the chloro group of 4-chloroindole **9** by SM coupling, a highly versatile carbon–carbon bond-forming method.[18] Compound **9** was coupled with boronic acid **15** using Pd–**1b** catalyst in the presence of K_3PO_4 as a base (Scheme 2). As expected, the reaction proceeded smoothly to give desired 2,4-disubstituted indole **16** in quantitative yield.[19]

With the optimized reaction conditions in hand, we investigated the sequential one-pot synthesis of 2,4-disubstituted indole **16** from dichloroaniline **7**, alkyne **3**, and boronic acid **15** (Table 3). We expected that the Pd–**1b** catalyst would enable 4-chloroindole formation and subsequent SM cross-coupling in one pot. First, the reaction was carried out by combining the reaction conditions developed above. Unfortu-

dx.doi.org/10.1021/ol500711z | *Org. Lett.* 2014, 16, 2386–2389

Scheme 2. Suzuki–Miyaura Coupling of 4-Chloroindole

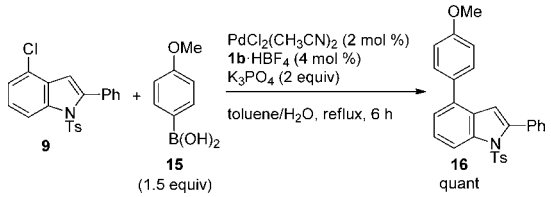
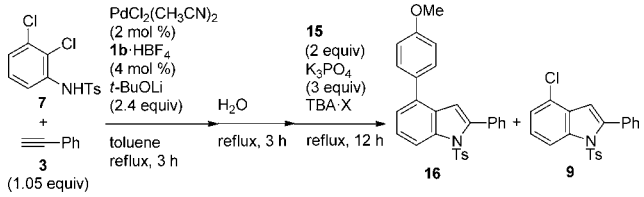


Table 3. One-Pot Synthesis of 2,4-Disubstituted Indole



		yield[a] (%)	
entry	TBAX (equiv)	**16**	**9**
1	–	nd[b]	15
2	TBAC (2)	29	19
3[c]	–	13	4
4[c]	TBAC (2)	1	2
5	TBAC (1)	16	41
6	TBAC (0.5)	52	11
7	TBAC (0.25)	61	<10
8	TBAB (0.25)	49	<10[d]
9	TBAOH (0.25)	24	25[d]
10[e]	TBAC (0.5)	69	trace

[a]Isolated yield. [b]Not detected. [c]XPhos (4 mol %) was added at the beginning. [d]Determined by ^{1}H NMR. [e]Alkyne (2 equiv).

nately, SM coupling did not proceed at all and 4-chloroindole **9** remained (entry 1). After a screening of additives, quaternary ammonium salts were found to be effective for promoting the SM coupling step.[20] We assume that quaternary ammonium salts work as a phase-transfer agent and transport boronic acid back to the organic phase. The use of tetra-*n*-butylammonium chloride (TBAC) afforded desired product **16** with an amount of unreacted **9** (entry 2). When a two-ligand system consisting of **1b** and XPhos (effective in our benzofuran synthesis[14]) was used, the yield of **16** was not improved (entries 3 and 4). Decreasing the amount of TBAC gave better results (entries 5–7). Examining the counteranions bromide and hydroxide gave the product in moderate yields (entries 8 and 9). Finally, conditions using 2 equiv of alkyne **3** and 0.5 equiv of TBAC led to the best yield (69%) of **16** (entry 10).

The scope and generality of this method was next examined by using various alkynes and boronic acids (Figure 3). Both alkyl- and arylalkynes afforded the corresponding products (**16**, **21**–**23**, and **31**) in moderate to high yield. Phenylboronic acid having either an electron-donating or electron-withdrawing group at the *para* position reacted well (**16**–**19**, **23**–**26**). *Ortho*- or *meta*-substituted phenylboronic acid also gave the corresponding 2,4-disubstituted indoles (**27**, **28**) in good yield. 3-Thienyl (**20**, **29**) and alkenyl (**30**) groups could also be introduced.

In summary, we have developed an efficient synthetic method toward 4-chloroindoles from readily available 2,3-dichloroaniline derivatives and terminal alkynes using the dihydroxyterphenylphosphine-based catalyst Pd–**1b**. This catalytic system was successfully applied to the one-pot

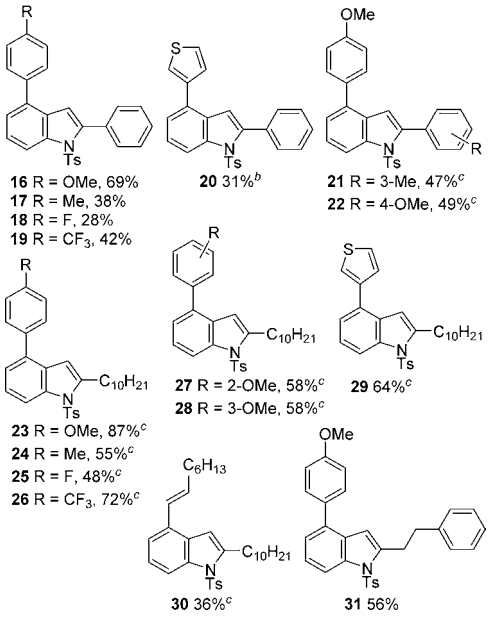


Figure 3. Substrate scope. Conditions: (i) alkyne (2 equiv), $PdCl_2(CH_3CN)_2$ (2 mol %), **1b**·HBF_4 (4 mol %), *t*-BuOLi (2.4 equiv), toluene, reflux, 3 h; (ii) H_2O, reflux, 3 h; (iii) boronic acid (2 equiv), K_3PO_4 (3 equiv), TBAC (0.5 equiv), reflux, 12 h. [b]Boronic acid (3 equiv), K_3PO_4 (4.5 equiv), SM coupling 20 h. [c]Alkyne (1.05 equiv).

synthesis of 2,4-disubstituted indoles via 4-chloroindole formation followed by subsequent SM coupling. This work provides a facile synthetic route for indoles with the less explored 4-substitution pattern.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: manabe@u-shizuoka-ken.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by Grants-in-Aid for Young Scientists (B) (Grant No. 24750036) from the Japan Society for the Promotion of Science (JSPS) and Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Haruka Katsumata (University of Shizuoka) for the initial experiments and Kohei Suzuki (University of Shizuoka) for the preparation of ligand **1b**.

■ REFERENCES

(1) Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; p 221.

(2) (a) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (b) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (c) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620.

(3) (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Barluenga, J.; Rodríguez, F.; Fañanás, F. J. *Chem.—Asian J.* **2009**, *4*, 1036. (e) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29.
(4) (a) Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267. (b) Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. *Synlett* **2013**, *24*, 1025.
(5) For example: (a) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797. (b) Stoll, A. H.; Knochel, P. *Org. Lett.* **2008**, *10*, 113.
(6) Selected examples: (a) Somei, M.; Yamada, F.; Kunimoto, M.; Kaneko, C. *Heterocycles* **1984**, *22*, 797. (b) Iwao, M. *Heterocycles* **1993**, *36*, 29. (c) Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983. (d) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. (e) Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060. (f) Liu, Q.; Li, Q.; Ma, Y.; Jia, Y. *Org. Lett.* **2013**, *15*, 4528. (g) Lanke, V.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 6262. (h) Gritsch, P. J.; Leitner, C.; Pfaffenbach, M.; Gaich, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 1208.
(7) (a) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (b) Kalinin, A. V.; Chauder, B. A.; Rakhit, S.; Snieckus, V. *Org. Lett.* **2003**, *5*, 3519.
(8) (a) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501. (b) Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851. (c) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058. (d) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnáiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713. (e) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031. (f) Stokes, B. J.; Liu, S.; Driver, T. G. *J. Am. Chem. Soc.* **2011**, *133*, 4702. (g) Wang, Y.-Z.; Ye, L.-W.; Zhang, L.-M. *Chem. Commun.* **2011**, *47*, 7815. (h) Huleatt, P. B.; Lau, J.; Chua, S.; Tan, Y. L.; Duong, H. A.; Chai, C. L. L. *Tetrahedron Lett.* **2011**, *52*, 1339. (i) Flanagan, J. C. A.; Dornan, L. M.; McLaughlin, M. G.; McCreanor, N. G.; Cook, M. J.; Muldoon, M. J. *Green Chem.* **2012**, *14*, 1281.
(9) (a) Sanz, R.; Guilarte, V.; García, N. *Org. Biomol. Chem.* **2010**, *8*, 3860. (b) Guilarte, V.; Castroviejo, M. P.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *J. Org. Chem.* **2011**, *76*, 3416.
(10) Reviews of site-selective cross coupling: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (b) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 103. (c) Wang, J.-R.; Manabe, K. *Synthesis* **2009**, 1405.
(11) (a) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1302. (b) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1304. (c) Ishikawa, S.; Manabe, K. *Org. Lett.* **2007**, *9*, 5593. (d) Manabe, K.; Ishikawa, S. *Chem. Commun.* **2008**, 3829. (e) Ishikawa, S.; Manabe, K. *Tetrahedron* **2010**, *66*, 297.
(12) Wang, J.-R.; Manabe, K. *J. Org. Chem.* **2010**, *75*, 5340.
(13) (a) Ishikawa, S.; Manabe, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 772. (b) Ishikawa, S.; Manabe, K. *Tetrahedron* **2011**, *67*, 10156.
(14) Yamaguchi, M.; Katsumata, H.; Manabe, K. *J. Org. Chem.* **2013**, *78*, 9270.
(15) An early example of the use of an *N*-sulfonylaniline for indole synthesis: Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305.
(16) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
(17) For details of optimization studies, see Tables S1 and S2 (Supporting Information).
(18) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Examples of SM coupling of 4-chloroindole: (b) Tanaka, M.; Li, X.; Hikawa, H.; Suzuki, T.; Tsutsumi, K.; Sato, M.; Takikawa, O.; Suzuki, H.; Yokoyama, Y. *Bioorg. Med. Chem.* **2013**, *21*, 1159. (c) Tichý, M.; Pohl, R.; Tloušťová, E.; Weber, J.; Bahador, G.; Lee, Y.-J.; Hocek, M. *Bioorg. Med. Chem.* **2013**, *21*, 5362.
(19) SM coupling also proceeded quantitatively when XPhos was used as the ligand.
(20) Selected examples of uses of quaternary ammonium salts for SM coupling: (a) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170. (b) Castanet, A.-S.; Colobert, F.; Desmurs, J.-R.; Schlama, T. *J. Mol. Catal. A: Chem.* **2002**, *182*−*183*, 481. (c) Amadio, E.; Scrivanti, A.; Bortoluzzi, M.; Bertoldini, M.; Beghetto, V.; Matteoli, U.; Chessa, G. *Inorg. Chim. Acta* **2013**, *405*, 188.