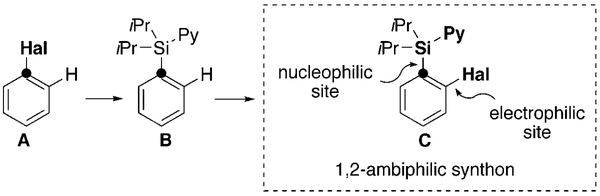
DOI: 10.1002/ange.201004426

C–H Activation

A General Strategy Toward Aromatic 1,2-Ambiphilic Synthons: Palladium-Catalyzed *ortho*-Halogenation of PyDipSi-Arenes**

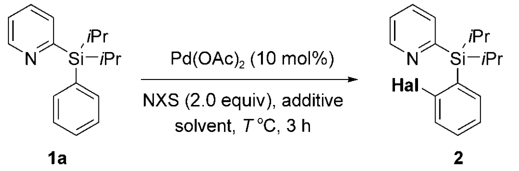
*Alexander S. Dudnik, Natalia Chernyak, Chunhui Huang, and Vladimir Gevorgyan**

Ambiphilic aromatic synthons—compounds possessing both electrophilic and nucleophilic centers in the same molecule—are important building blocks that are widely used for a modular construction of complex molecules in organic synthesis, medicinal chemistry, and materials science.[1] Traditionally, they are accessed through multistep syntheses. One of the most efficient strategies toward 1,2-ambiphilic structures involves directed *ortho*-metalation (DOM) approach.[2] Our research group has recently developed the palladium-catalyzed directed *ortho*-acyloxylation of pyridyldiisopropylsilyl (PyDipSi) arenes **B**[3] [Eq. (1)] based on a C–H activation process.[4] Most importantly, we have shown that the PyDipSi directing group[5] could efficiently participate in a variety of reactions as a nucleophilic entity. Because the acyloxy group is known to serve as an electrophilic coupling partner,[6] the *o*-acyloxylated PyDipSi-arenes can be formally considered as 1,2-ambiphiles. Taking into account the immense synthetic potential of aryl halides as electrophilic reagents, we aimed at the development of a general strategy for the synthesis of *ortho*-halogenated aryl silanes **C**, which are much more powerful 1,2-ambiphiles. Herein, we report the palladium-catalyzed *ortho*-halogenation reaction of easily accessible PyDipSi-arenes **B** into 1,2-ambiphiles **C** and their further transformations to a variety of valuable building blocks.



(1)

Table 1: Optimization of *ortho*-halogenation reaction. X = halide.



Entry	Additive (equiv)	Hal	Solvent	T [°C]	Yield [%][a]
1	none	Br	PrCN	80	50
2	none	Br	PrCN	100	65
3	AcOH (50)	Br	PrCN	80	15
4	$Cu(OAc)_2$ (1)	Br	PrCN	100	trace
5	$PhI(OAc)_2$ (1.5)	Br	PrCN	80	80
6	$PhI(OAc)_2$ (1.5)	Br	PrCN	100	65
7	**$PhI(OAc)_2$ (1.5)**	**Br**	**$C_2H_4Cl_2$**	**60**	**85**
8	**$PhI(OAc)_2$ (1.5)**	**I**	**$C_2H_4Cl_2$**	**65**	**95**
9	$PhI(OAc)_2$ (1.5)	Cl	$C_2H_4Cl_2$	65	42

[a] Yield determined by NMR spectroscopy.

First, we tested PyDipSi-arene **1a** under a variety of halogenation reaction conditions in the presence of 10 mol% of $Pd(OAc)_2$ (Table 1).[4a,7] Initially, the palladium-catalyzed bromination with 2 equivalents of NBS (*N*-bromosuccinimide) in PrCN at 80 °C afforded 50% of the desired product **2** (Table 1, entry 1; Hal = Br). Further increase of temperature to 100 °C led to a slight improvement of the reaction outcome (Table 1, entry 2). Addition of 50 equivalents of acetic acid[7a,b] resulted in significant decrease of the reaction yield (Table 1, entry 3). The employment of a stoichiometric amount of $Cu(OAc)_2$ additive gave only traces of brominated product (Table 1, entry 4). Remarkably, addition of 1.5 equivalents of $PhI(OAc)_2$ dramatically improved the reaction, and provided the bromination product in 80% yield (Table 1, entry 5). Performing the reaction at the elevated temperature (100 °C), however, gave a lower yield of **2** (Table 1, entry 6). Gratifyingly, switching solvent to 1,2-dichloroethane allowed for a better reaction yield (85%) at lower temperature (60 °C; Table 1, entry 7). Employment of NIS (*N*-iodosuccinimide) as a halogen source under these reaction conditions produced iodinated aryl silane **2** in 95% yield (Table 1, entry 8; Hal = I). On the other hand, employment of NCS (*N*-chlorosuccinimide) gave the chlorinated product in a moderate yield only (Table 1, entry 9; Hal = Cl).

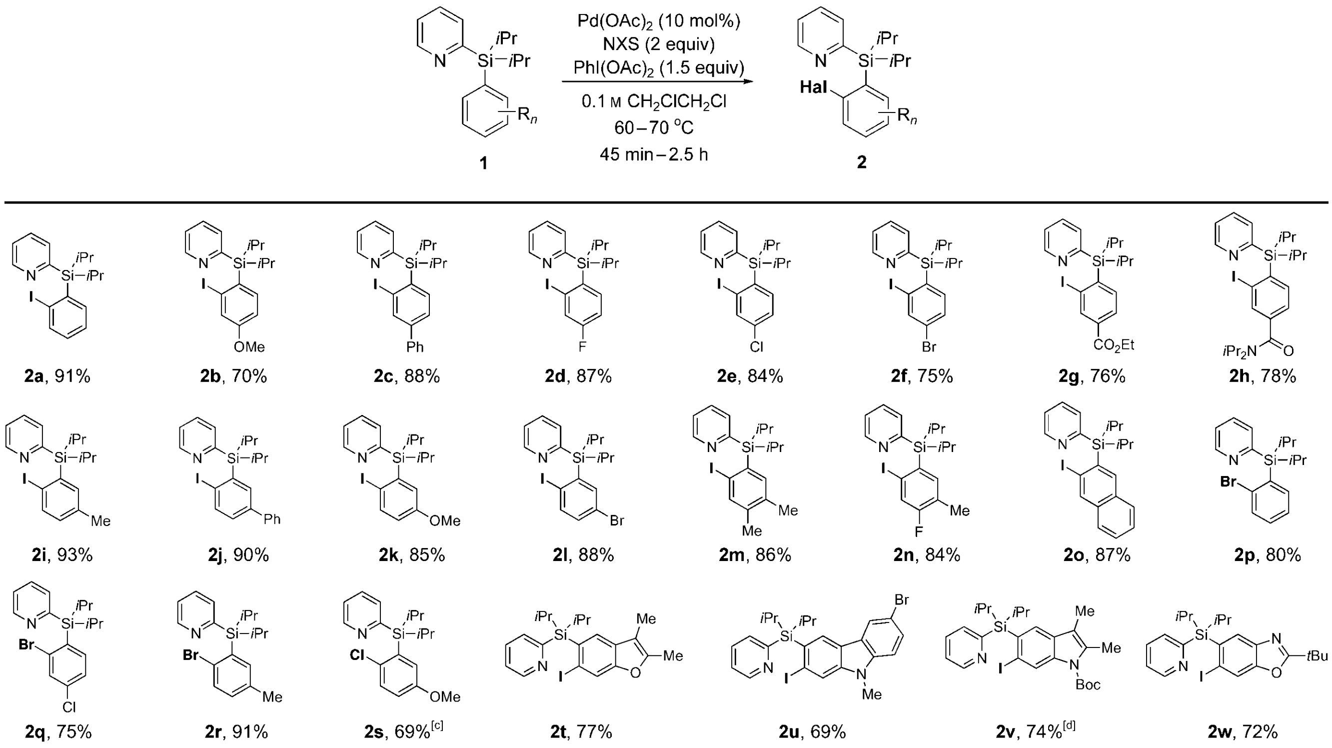
Next, the generality of the palladium-catalyzed *ortho*-halogenation of PyDipSi-arenes **1** was examined. The iodination reaction with NIS in the presence of 1.5 equivalents of $PhI(OAc)_2$ was studied first. We found this transformation to be efficient for a wide range of substrates, which allowed for the synthesis of monoiodinated aryl silanes **2a**–**w** in good to excellent yields (Scheme 1). It was found that a variety of groups, including OMe (**2b**, **2k**), F (**2d**, **2n**), Cl (**2e**), Br (**2f**, **2l**), ester (**2g**), and amide (**2h**) were perfectly tolerated under the halogenation reaction conditions. Iodination of *para*-substituted aryl silanes possessing both

---

[*] A. S. Dudnik, N. Chernyak, C. Huang, Prof. V. Gevorgyan
Department of Chemistry
University of Illinois at Chicago
845 W Taylor St, Rm 4500, Chicago, IL 60607 (USA)
Fax: (+1) 312-355-0836
E-mail: vlad@uic.edu
Homepage: http://www.chem.uic.edu/vggroup

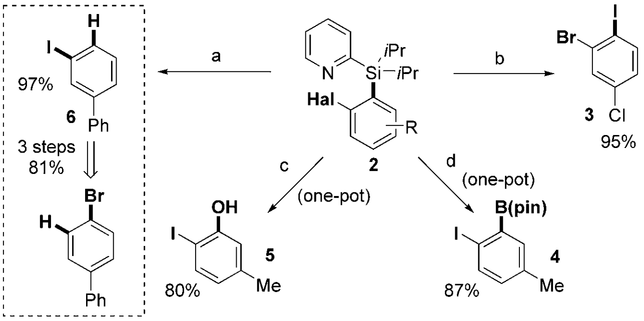
[**] The support of the NIH (GM-64444) and of the NSF (CHE-0710749) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004426.



Scheme 1. Palladium-catalyzed *ortho*-halogenation of aryl silanes. [a] Yield of isolated product. [b] See Supporting Information for experimental details. [c] Reaction was performed in PrCN at 100 °C. [d] Reaction was performed without $PhI(OAc)_2$ and with 1 equivalent of NIS. Boc = *tert*-butoxycarbonyl.

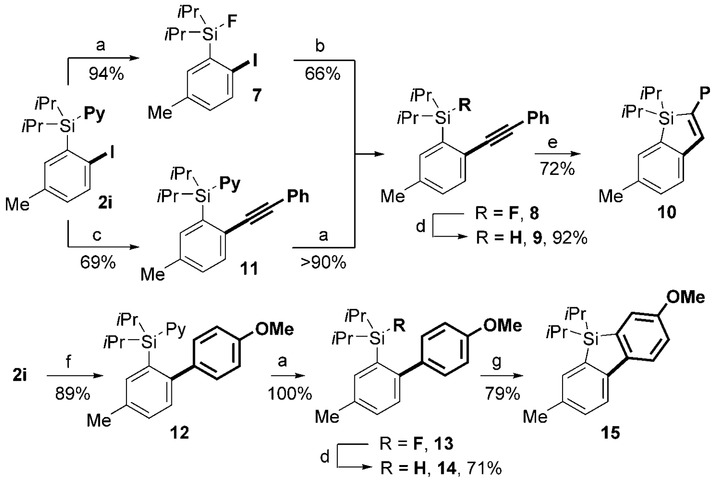
electron-donating (**2b**) and electron-withdrawing (**2d**–**h**) substituents proceeded with equal efficiency. *meta*-Substituted substrates displayed excellent site selectivity in the iodination reaction, and provided monoiodinated compounds as single regioisomers (**2i**–**l**). In addition, *ortho*-iodination of *m*-, *p*-disubstituted aryl silanes (**2m**,**n**), and 2-naphthyl derivative (**2o**) occurred uneventfully and furnished the desired products as sole regioisomers in high yields. Next, the bromination reaction of **1** allowed for efficient synthesis of *o*-bromo aryl silanes **2p**–**r**. Notably, chlorination of electron-rich aryl silane, possessing an OMe group *para* to the functionalization site, was found to be more efficient than that of electron-neutral **1a** (Table 1, entry 9), thus producing chloro-derivative **2s** in 69% yield. Finally, PyDipSi derivatives of various heterocycles, such as benzofuran (**2t**), carbazole (**2u**), indole (**2v**), and benzoxazole (**2w**), were monoiodinated in good yields. We find these results remarkable, as 6-halo derivatives of most of these heterocycles are not readily available and require multistep preparation. These derivatives now can be accessed from the 5-haloprecursors of the corresponding PyDipSi-heterocycles, which are either commercially available or can be easily synthesized in one step.



Scheme 2. Transformations of the PyDipSi group in haloarene derivatives. Reagents and conditions: a) AgF (4 equiv), H_2O (6 equiv), THF, RT, 12 h; b) AgF (4 equiv), NIS (4 equiv), THF, RT, 12 h; c) 1. BCl_3 (4.4 equiv), DCM, 0 °C, RT, 6 h; 2. 30 wt% H_2O_2/3 wt% NaOH (excess), H_2O, RT, 12 h; d) 1. BCl_3 (4.4 equiv), DCM, 0 °C, RT, 6 h; 2. pinacol (excess), Et_3N/DCM (1:1), RT, 12 h. THF = tetrahydrofuran.

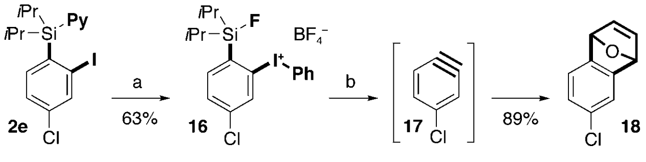
Naturally, after the development of efficient palladium-catalyzed halogenation of aryl silanes, we investigated possible transformations of the PyDipSi directing group (Scheme 2).[8] First, the reaction of **2c** with AgF/H_2O (2:3) in THF resulted in efficient removal of the directing group, thus affording *m*-iodobiphenyl (**6**) in 97% yield.[9] Interestingly, the overall three-step transformation of *p*-bromobiphenyl into *m*-iodobiphenyl constitutes an example of a formal Finkelstein/“1,2-halogen dance” reaction. Next, the iododesilylation reaction of chlorobromoaryl silane **2e** with NIS in the presence of AgF in THF allowed for efficient preparation of 1-cloro-3-bromo-4-iodobenzene (**3**), which is a synthetically useful and versatile building block for modular functionalization of the benzene ring. Furthermore, iodoaryl silane **2i** was efficiently converted into *o*-iodoaryl boronate **4**,[10] which is another powerful 1,2-ambiphile, in 87% yield by a one-pot sequence involving borodesilylation with BCl_3, and subsequent protection with pinacol.[11,12] Furthermore, borodesilylation of **2i** and subsequent oxidation with H_2O_2/NaOH afforded *o*-iodophenol **5** in 80 % yield.

Further utility of *o*-halogenated PyDipSi-arene derivatives was demonstrated by a convergent synthesis of unsymmetrically substituted benzo[*b*]silole **10** and dibenzosilole **15** (Scheme 3). First, treatment of **2i** with HF at room temperature led to selective substitution of the pyridine group with fluoride,[13] thus providing fluorosilane **7** in excellent yield. Next, *o*-iodoaryl fluorosilane **7** was alkynylated with potassium phenylethynyltrifluoroborate under Suzuki reaction conditions[14] and produced **8** in 66 % yield. Alternatively, alkynylated aryl silane **8** can be accessed from **2i** through a sequence involving Sonogashira reaction[15] with phenylacetylene and subsequent substitution of the pyridine group with fluoride. A subsequent reduction of silylfluoride **8** with $LiAlH_4$ furnished silylhydride **9**. 5-*Endo*-dig cyclization of the latter in the presence of KH in DME[16] provided **10** in 72 % yield. En route to dibenzosilole derivative **15**, *o*-iodoaryl silane **2i** was subjected to Suzuki coupling[17] with 4-methoxyphenylboronic acid and gave biphenylsilane **12** in 89 % yield. Next, substitution of the pyridine group in **12** with fluoride produced silylfluoride **13** quantitatively. Smooth reduction of **13** into hydride **14** and its subsequent electrophilic cyclization reaction with trityl tetrakis(pentafluorophenyl)borate[18] resulted in formation of dibenzosilole **15** in 71 % yield (Scheme 3).



Scheme 3. Synthesis of benzannulated siloles **10** and **15**. Reagents and conditions: a) HF, THF, RT, 1 h; b) PhCCH, [{Pd($CH_3CN)_2$}Cl_2] (3 mol%), tBu_3P (6 mol%), CuI (2 mol%), iPr_2NH, 1,2-dioxane, 60°C, 12 h; c) $PhCCBF_3K$, [{Pd(dppf)}Cl_2]·DCM (10 mol%), Cs_2CO_3, THF, reflux, 48 h; d) $LiAlH_4$ (2.5 equiv), THF, reflux, 12 h; e) KH (1.4 equiv), DME, 5 h; f) 4-MeO-$C_6H_4B(OH)_2$ (1.2 equiv), [$Pd_2(dba)_3$] (5 mol%), tBu_3P (10 mol%), K_3PO_4, 1,2-dioxane, 70°C, 12 h; g) $Ph_3CB(C_6F_5)_4$, 1,6-lutidine, CH_2Cl_2, RT, 1 h. dba = *trans,trans*-dibenzylideneacetone, DME = 1,2-dimethoxyethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Py = pyridine.

Definitely, *o*-benzyne is one of the most synthetically attractive 1,2-ambiphiles.[19] Because *o*-silylphenyliodonium triflates are known to efficiently generate benzynes in the presence of TBAF,[20,21] we decided to convert the iodide functionality in PyDipSi-arenes **2** into a better leaving iodonium group. Accordingly, substrate **2e**, after exchange of the pyridine group to fluoride, was smoothly converted into the corresponding iodonium tetrafluoroborate **16** (Scheme 4).[22] Treatment of the latter with TBAF in CH_2Cl_2 allowed for the efficient generation of benzyne **17**, trapping of which with furan provided 1,4-epoxydihydronaphthalene **18** in 89 % yield. To the best of our knowledge, the above sequence, taken together with the *o*-iodination of PyDipSi-arenes, represents the first example of benzyne synthesis featuring C–H activation strategy.



Scheme 4. Conversion of PyDipSi-iodoarenes into benzyne. Reagents and conditions: a) 1. 48 wt% HF (excess), THF, RT, 1 h; 2. m-CPBA (1.2 equiv), DCM, then $BF_3·Et_2O$ (2.5 equiv), RT, 1 h; 3. $PhB(OH)_2$ (1.1 equiv), 0°C, RT, 30 min ; b) TBAF (1.2 equiv), furan (5 equiv), DCM, RT, 1 h. *m*-CPBA = *meta*-chloroperbenzoic acid, TBAF = tetra-*n*-butylammonium fluoride.

In conclusion, we have developed a general and efficient strategy for the synthesis of 1,2-ambiphilic aromatic and heteroannulated aromatic synthons. This method features installation of the removable/modifiable PyDipSi directing group on haloarenes and subsequent palladium-catalyzed directed *ortho*-halogenation reaction to give the *o*-halogenated PyDipSi-arene derivatives. Synthetic usefulness of these 1,2-ambiphilic building blocks was demonstrated in a variety of transformations, involving participation of both nucleophilic aryl silane and electrophilic aryl iodide moieties. These transformations include protio-, halo-, borodesilylations, and conversion of the PyDipSi group into the OH functionality, as well as Suzuki and Sonogashira cross-coupling reactions of the aryl iodide unit. Finally, the unique reactivity of these 1,2-ambiphiles was illustrated in convergent syntheses of benzannulated silole derivatives, as well as in the efficient generation of *o*-benzyne.

Received: July 20, 2010

Keywords: benzynes · C–H activation · halogenation · palladium · siloles

---

[1] For selected examples on importance of ambiphilic synthons, see: a) A. K. Yudin, R. Hili, *Chem. Eur. J.* **2007**, *13*, 6538; b) D. Tejedor, G. Méndez-Abt, J. González-Platas, M. A. Ramírez, F. García-Tellado, *Chem. Commun.* **2009**, 2368; c) T. B. Samarakoon, M. Y. Hur, R. D. Kurtz, P. R. Hanson, *Org. Lett.* **2010**, *12*,

2182; d) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716, and references therein.

[2] For a review on directed *ortho*-metalation, see: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; for recent examples of employment of DOM group in cross-coupling reactions, see: b) K. W. Quasdorf, M. Riener, K. V. Petrova, N. K. Garg, *J. Am. Chem. Soc.* **2009**, *131*, 17748; c) A. Antoft-Finch, T. Blackburn, V. Snieckus, *J. Am. Chem. Soc.* **2009**, *131*, 17750.

[3] N. Chernyak, A. S. Dudnik, C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 8270.

[4] For selected recent reviews on transition-metal-catalyzed C−H activation of arenes, see: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; e) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; f) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074.

[5] For employment of pyridyldimethylsilyl directing group in Heck arylations, see: a) K. Itami, K. Mitsudo, T. Kamei, T. Koike, T. Nokami, J.-I. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 12013; b) K. Itami, T. Nokami, J.-I. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 5600; for employment of dimethylhydrosilyl directing group in iridium-catalyzed C−H borylations, see: c) D. W. Robbins, T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 4068; d) T. A. Boebel, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 7534.

[6] For review on cross-coupling reactions of pivalates, see: L. J. Gooßen, K. Gooßen, C. Stanciu, *Angew. Chem.* **2009**, *121*, 3621; *Angew. Chem. Int. Ed.* **2009**, *48*, 3569.

[7] For representative examples of palladium-catalyzed directed C−H halogenation of arenes, see: a) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483; b) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, *8*, 2523; c) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 5293; *Angew. Chem. Int. Ed.* **2008**, *47*, 5215; d) D. C. Powers, T. Ritter, *Nat. Chem.* **2009**, *1*, 302; e) T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140; f) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama, T. Tanabe, *J. Am. Chem. Soc.* **2009**, *131*, 11310; g) O. S. Andrienko, V. S. Goncharov, V. S. Raida, *Russ. J. Org. Chem.* **1996**, *32*, 79.

[8] For an excellent example of ruthenium-catalyzed *o*-silylation of arenes using a removable boron-tethered directing group, see: H. Ihara, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 7502.

[9] a) A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto, H. Yamamoto, *Angew. Chem.* **1999**, *111*, 3916; *Angew. Chem. Int. Ed.* **1999**, *38*, 3701; b) K. Itami, M. Mineno, T. Kamei, J.-I. Yoshida, *Org. Lett.* **2002**, *4*, 3635.

[10] Recently, it was shown that boronic acids could be *ortho*-iodinated under Friedel–Crafts reaction conditions. However, the reported method is limited to electron-rich substrates only, see: R. M. Al-Zoubi, D. G. Hall, *Org. Lett.* **2010**, *12*, 2480.

[11] a) K. Itami, T. Kamei, J.-I. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670; b) T. Kamei, K. Itami, J.-I. Yoshida, *Adv. Synth. Catal.* **2004**, *346*, 1824; c) Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, *7*, 2523; d) M. Rottländer, N. Palmer, P. Knochel, *Synlett* **1996**, 573.

[12] For a review on C−B bond formation through a C−H activation, see: I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890.

[13] R. S. Brown, H. Slebocka-Tilk, J. M. Buschek, J. G. Ulan, *J. Am. Chem. Soc.* **1984**, *106*, 5979.

[14] G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416.

[15] T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2000**, *2*, 1729.

[16] L. Ilies, H. Tsuji, E. Nakamura, *Org. Lett.* **2009**, *11*, 3966.

[17] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

[18] S. Furukawa, J. Kobayashi, T. Kawashima, *J. Am. Chem. Soc.* **2009**, *131*, 14192.

[19] For reviews, see: a) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem.* **2003**, *115*, 518; *Angew. Chem. Int. Ed.* **2003**, *42*, 502; b) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701.

[20] Our initial attempts on direct conversion of the *o*-iodo derivatives **2** into benzynes were unsuccessful.

[21] For selected examples on employment of *o*-(trimethylsilyl)phenyliodonium triflates as precursors for the preparation of benzyne, see: a) S. Kitamura, M. Yamane, *J. Chem. Soc. Chem. Commun.* **1995**, 983; b) T. Kitamura, M. Yamane, K. Inoue, M. Todaka, N. Fukatsu, Z. Meng, Y. Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 11674.

[22] M. Bielawski, D. Aili, B. Olofsson, *J. Org. Chem.* **2008**, *73*, 4602.