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

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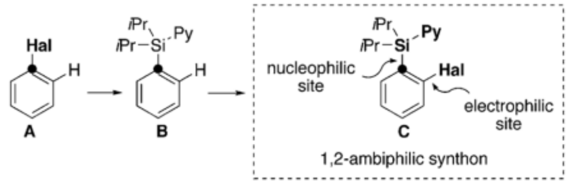
Ambiphilic aromatic synthons—compounds possessing both electrophilic and nucleophilic centers in the same molecule—are important building blocks that are widely used for a modular construction of complex molecules in organic synthesis, medicinal chemistry, and materials science.[1] Traditionally, they 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)

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

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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 (**2 f**, **2l**), ester (**2g**), and amide (**2h**) were perfectly tolerated under the halogenation reaction conditions. Iodination of *para*-substituted aryl silanes possessing both 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.

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*-bromobi-phenyl 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).

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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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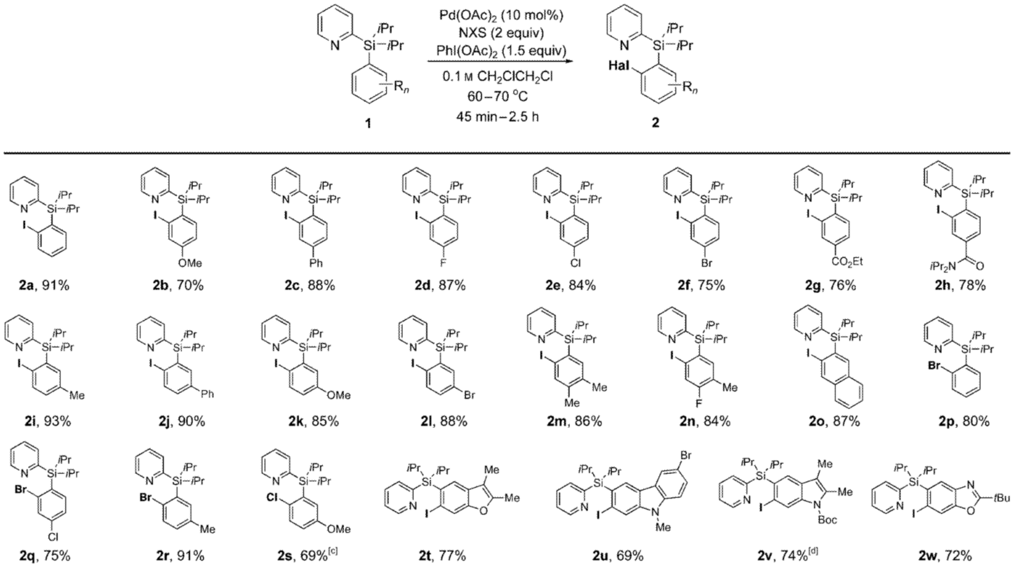
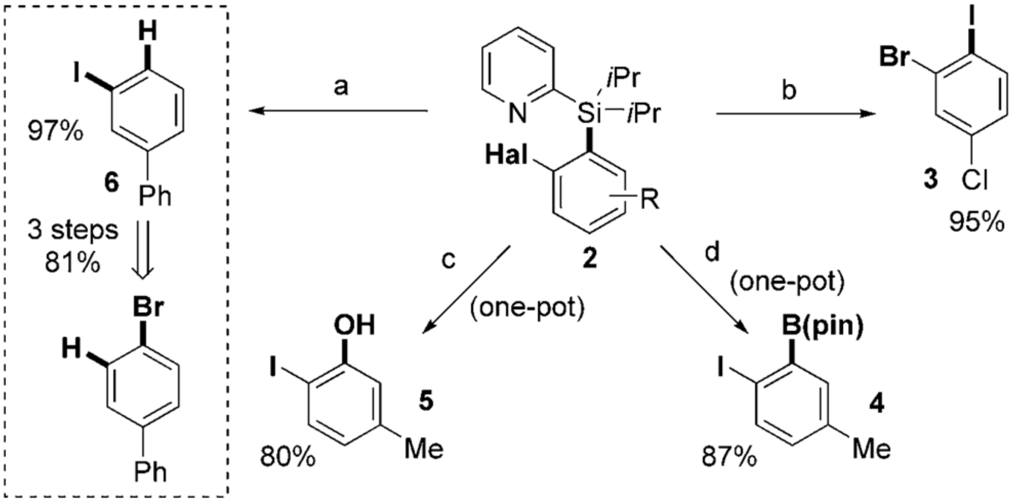


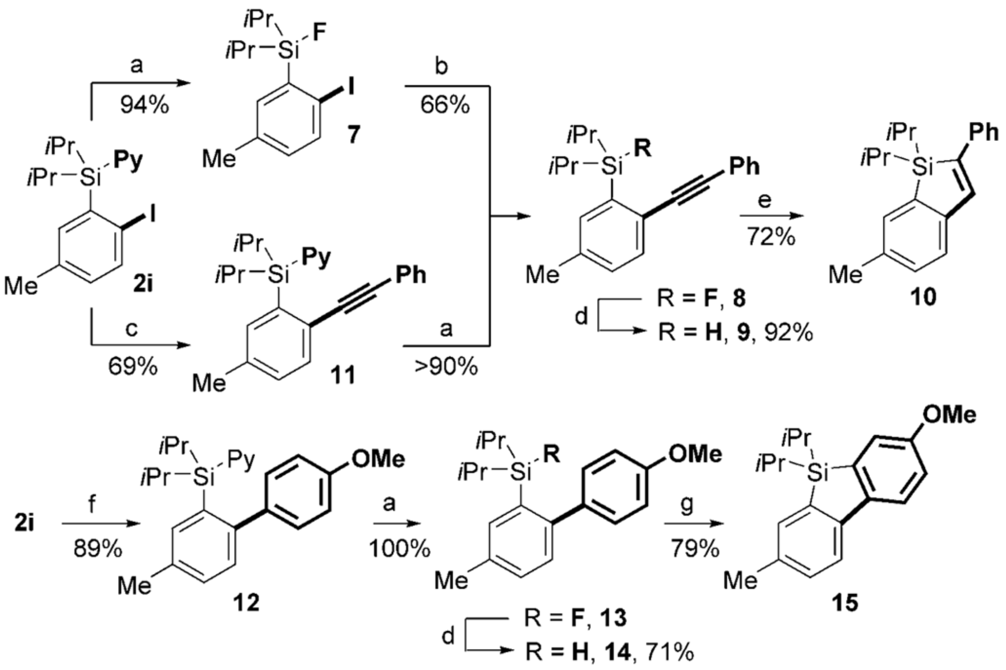
Scheme 1.

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.



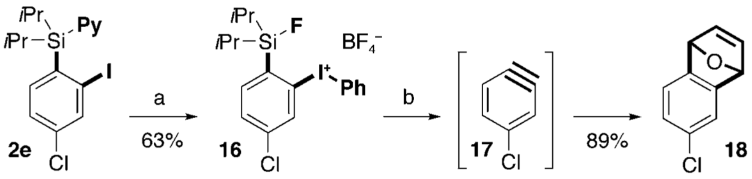
Scheme 2.

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.



Scheme 3.

Synthesis of benzannulated siloles **10** and **15**. Reagents and conditions: a) HF, THF, RT, 1 h; b) PhCCH, [{Pd(CH$_3$CN)$_2$}Cl$_2$] (3 mol%), *t*Bu$_3$P (6 mol%), CuI (2 mol%), *i*Pr$_2$NH, 1,2-dioxane, 60 °C, 12 h; c) PhCCBF$_3$K, [{Pd(dppf)}Cl$_2$]·DCM (10 mol%), Cs$_2$CO$_3$, 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$_6$H$_4$B(OH)$_2$ (1.2 equiv), [Pd$_2$(dba)$_3$] (5 mol%), *t*Bu$_3$P (10 mol%), K$_3$PO$_4$, 1,2-dioxane, 70°C, 12 h; g) Ph$_3$CB(C$_6$F$_5$)$_4$, 1,6-lutidine, CH$_2$Cl$_2$, RT, 1 h. dba = *trans*,*trans*-dibenzylideneacetone, DME = 1,2-dimethoxyethane, dppf =1,1′-bis(diphenylphosphanyl)ferrocene, Py =pyridine.

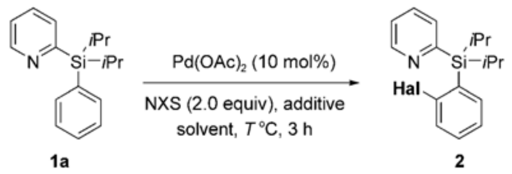


Scheme 4.

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 $BF_3 \cdot Et_2O$ (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.

Table 1

Optimization of *ortho*-halogenation reaction. X =halide.



Entry	Additive (equiv)	Hal	Solvent	*T* [8C]	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.