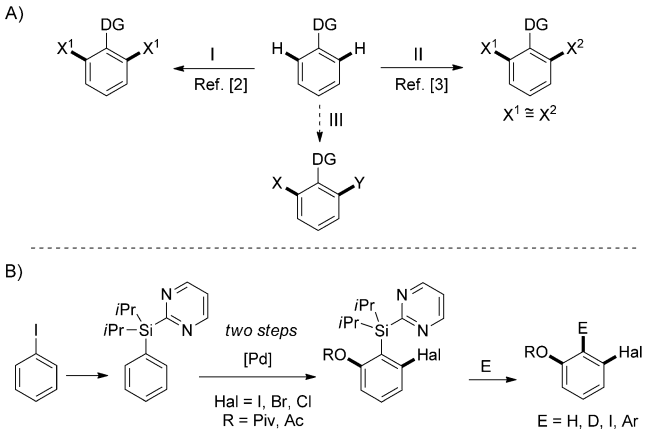
C–H Activation

DOI: 10.1002/anie.201304884

Twofold Unsymmetrical C–H Functionalization of PyrDipSi-Substituted Arenes: A General Method for the Synthesis of Substituted *meta*-Halophenols**

*Dhruba Sarkar, Ferdinand S. Melkonyan, Anton V. Gulevich, and Vladimir Gevorgyan**

Transition-metal-catalyzed heteroatom-directed C–H functionalization of arenes has emerged as a powerful and environmentally benign tool for carbon–carbon and carbon–heteroatom bond formation.[1] Moreover, twofold aromatic C–H functionalization is synthetically even more appealing as it allows for the introduction of two substituents in a one-pot or a two-step procedure. However, twofold C–H functionalization has been used only for the introduction of the same (e.g. alkenyl/alkenyl, aryl/aryl, OR/OR, Hal/Hal; Scheme 1 A, I)[2] or similar functionalities (e.g. alkenyl/alkenyl′, OAc/OPiv (Piv = pivaloyl), Cl/Br; Scheme 1 A, II).[3] To the best of our knowledge, unsymmetrical C–H functionalization with the introduction of two different functional groups is unknown (Scheme 1 A, III). If developed, this methodology would provide straightforward access to a variety of densely functionalized multisubstituted arenes. Herein, we report an unprecedented twofold unsymmetrical C–H functionalization of arenes that enables the introduction of two different functional groups (OR and Hal).[4] This concise synthesis of substituted *meta*-halophenols from aryl iodides proceeds by sequential C–H halogenation/oxygenation reactions[5,6] directed by a removable/functionalizable[7,8] pyrimidine-based silicon-tethered directing group (Scheme 1 B).

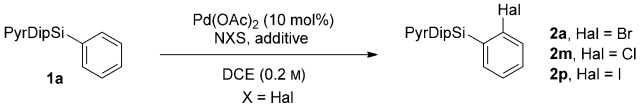


Scheme 1. Twofold C–H functionalization adjacent to a directing group (DG). A) I,II) Previously reported bisfunctionalization with two identical or similar groups; III) unsymmetrical bisfunctionalization. B) The approach developed in this study for unsymmetrical bisfunctionalization.

Recently, we developed a traceless/modifiable 2-diisopropylsilylpyrimidine (PyrDipSi) directing group for the selective mono- and bisoxygenation of arenes.[3c] Notably, this oxygenation reaction tolerated an *ortho* substituent, which makes this transformation potentially compatible with other *ortho* C–H functionalization reactions. We therefore considered the development of a twofold unnsymmetrical C–H functionalization process with this directing group. A halogenation/oxygenation sequence was chosen, as it would provide access to valuable *meta*-halophenols.[9]

First, we optimized the palladium-catalyzed C–H halogenation of PyrDipSi-substituted benzene (**1a**). The bromination of **1a** with *N*-bromosuccinimide (NBS; 2 equiv) afforded the desired product **2a** in promising 35% yield (Table 1, entry 1). Upon screening additives, we discovered that $PhI(OAc)_2$ facilitates the bromination reaction (Table 1,

Table 1: Optimization of the halogenation reactions.



Entry	Hal	Oxidant (equiv)	Additive (equiv)	*T* [°C]	Yield [%][a,b]
1	Br	NBS (2.0)	–	60	35
2	Br	NBS (2.0)	BQ (1.0)	60	trace
3	Br	NBS (2.0)	$PhI(OAc)_2$ (1.5)	60	43
4	Br	NBS (2.0)	$PhI(OAc)_2$ (1.0)	60	40
5	Br	NBS (2.0)	$PhI(OAc)_2$ (0.5)	60	70
6	Br	NBS (1.25)	$PhI(OAc)_2$ (0.3)	60	75
7	Br	NBS (1.2)	$PhI(OAc)_2$ (0.1)	60	85
8	**Br**	**NBS (1.2)**	**$PhI(OAc)_2$ (0.1)**	**50**	**85**
9[c]	Cl	NCS (2.0)	$PhI(OAc)_2$ (0.1)	60	– (30)
10[c]	Cl	NCS (2.0)	$PhI(OAc)_2$ (1.0)	100	– (56)
11[c]	**Cl**	**NCS (5.0)**	**$PhI(OAc)_2$ (1.3)**	**100**	**75 (90)**
12[d]	**I**	**NIS (1.5)**	**–**	**60**	**94**

[a] Yield of the isolated product. [b] Yields determined by GC are given in parentheses. [c] The reaction was performed in EtCN (0.05 M solution). [d] The reaction was performed with $Pd(OAc)_2$ (5 mol%). BQ = benzoquinone, DCE = 1,2-dichloroethane.

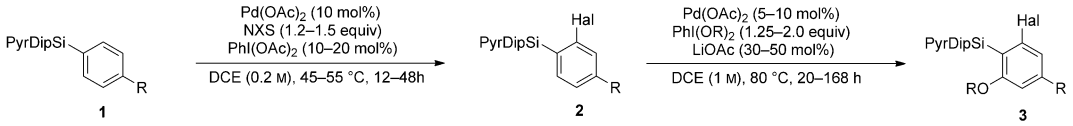
[*] D. Sarkar, Dr. F. S. Melkonyan, Dr. A. V. Gulevich, Prof. Dr. V. Gevorgyan
Department of Chemistry, University of Illinois at Chicago
845 W. Taylor Street, Rm 4500, Chicago, IL 60607 (USA)
E-mail: vlad@uic.edu
Homepage: http://www.chem.uic.edu/vggroup

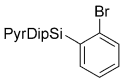
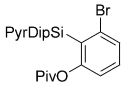
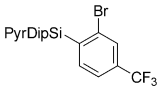
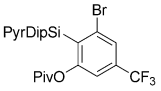
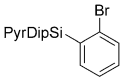
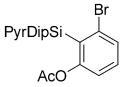
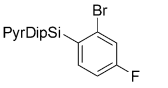
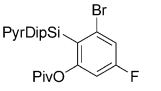
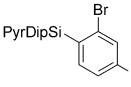
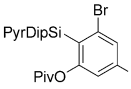
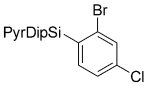
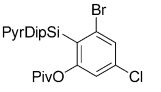
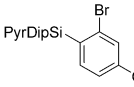
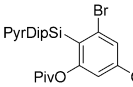
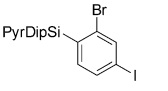
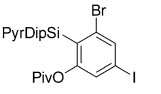
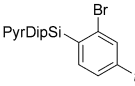
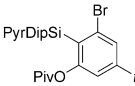
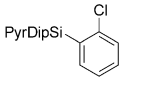
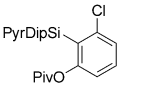
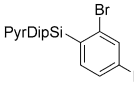
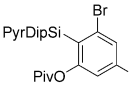
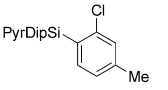
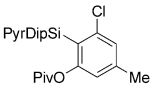
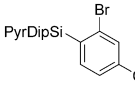
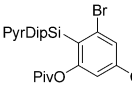
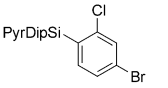
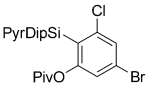
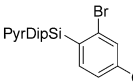
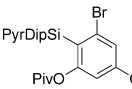
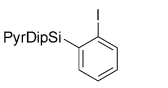
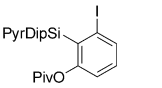
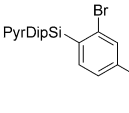
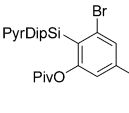
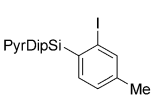
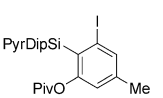
[**] The support of the NIH (GM-64444) is gratefully acknowledged. PyrDipSi = 2-diisopropylsilylpyrimidine.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304884.

entries 3 and 4). Finally, it was found that the reaction required only a catalytic amount of $PhI(OAc)_2$ (10 mol%) for the production of **2a** in high yield (Table 1, entry 8).[10] On the other hand, the C–H chlorination of **1a** required a super-stoichiometric amount of $PhI(OAc)_2$ (1.3 equiv), as well as excess *N*-chlorosuccinimide (NCS) and elevated temperatures (EtCN, 100 °C; Table 1, entry 11). The iodination of **1a** with *N*-iodosuccinimide (NIS; 1.2 equiv) afforded the iodination product **2p** in 94% yield without any additive (Table 1, entry 12). Control experiments without $Pd(OAc)_2$ did not provide any products.

Next, we attempted to use the newly found conditions for the C–H bromination process in combination with the C–H oxygenation reaction[3c] for a two-step synthesis[11] of *meta*-bromophenol derivatives (Table 2). We found that compound **1a** could be converted efficiently into bromophenol derivatives **3a** and **3aa** in a two-step sequential bromination/oxygenation procedure (Table 2, entries 1 and 2). Likewise, PyrDipSi-substituted arenes **1** bearing electron-neutral (Me, *t*Bu, Ph) and electron-donating substituents (OMe) were efficiently converted into *ortho*-bromo derivatives **2b–e**. A subsequent pivaloyloxylation furnished the corresponding products **3b–e** in good yields (Table 2, entries 3–6). Substrates possessing electron-withdrawing groups, namely, CO_2Me, COMe, and $CONiPr_2$, smoothly underwent the C–H bromination reaction (to form **2f–h**) as well as a further pivaloyloxylation reaction to produce the desired products **3f–h** (Table 2, entries 7–9). An electron-deficient CF_3-substituted arene was converted into the brominated product **2i**, which then was oxygenated to form **3i** in moderate yield (Table 2, entry 10). Notably, halo-substituted substrates underwent efficient bromination (to form **2j–l**) as well as a pivaloyloxylation reaction to produce the valuable dihalophenol derivatives **3j–l** (Table 2, entries 11–13). This halogenation/oxygenation reaction sequence was also successfully utilized for the synthesis of *meta*-chloro- and *meta*-iodophenol

Table 2: Sequential halogenation/oxygenation of PyrDipSi-substituted arenes.[a]



Entry	**2**, yield [%][b]		**3**, yield [%][b]		Entry	**2**, yield [%][b]		**3**, yield [%][b]	
1		**2a**, 85 (82)[c]		**3a**, 72 (79)[c]	10		**2i**, 58		**3i**, 51
2		**2a**, 85		**3aa**, 71	11		**2j**, 77		**3j**, 69
3		**2b**, 90		**3b**, 78	12		**2k**, 78		**3k**, 72
4		**2c**, 76		**3c**, 73	13		**2l**, 74		**3l**, 68
5		**2d**, 84		**3d**, 69	14		**2m**, 75[d]		**3m**, 65
6		**2e**, 88		**3e**, 75	15		**2n**, 64[d]		**3n**, 84
7		**2f**, 81		**3f**, 72	16		**2o**, 59[d]		**3o**, 61
8		**2g**, 74		**3g**, 59	17		**2p**, 94[e]		**3p**, 55[f]
9		**2h**, 72		**3h**, 74	18		**2q**, 80[e]		**3q**, 40[f]

[a] The reaction was carried out on a 0.4 mmol scale (see the Supporting Information for experimental details). [b] Yield of the isolated product. [c] The yield for a reaction carried out on a 5 mmol scale is given in parentheses. [d] The reaction was performed in EtCN (0.05 M solution) with NCS (5 equiv) and $PhI(OAc)_2$ (1.3 equiv) at 100 °C. [e] The reaction was performed without $PhI(OAc)_2$, with $Pd(OAc)_2$ (5 mol%) and NIS (1.5 equiv) at 60 °C. [f] The reaction was performed with $PhI(OPiv)_2$ (2 equiv).

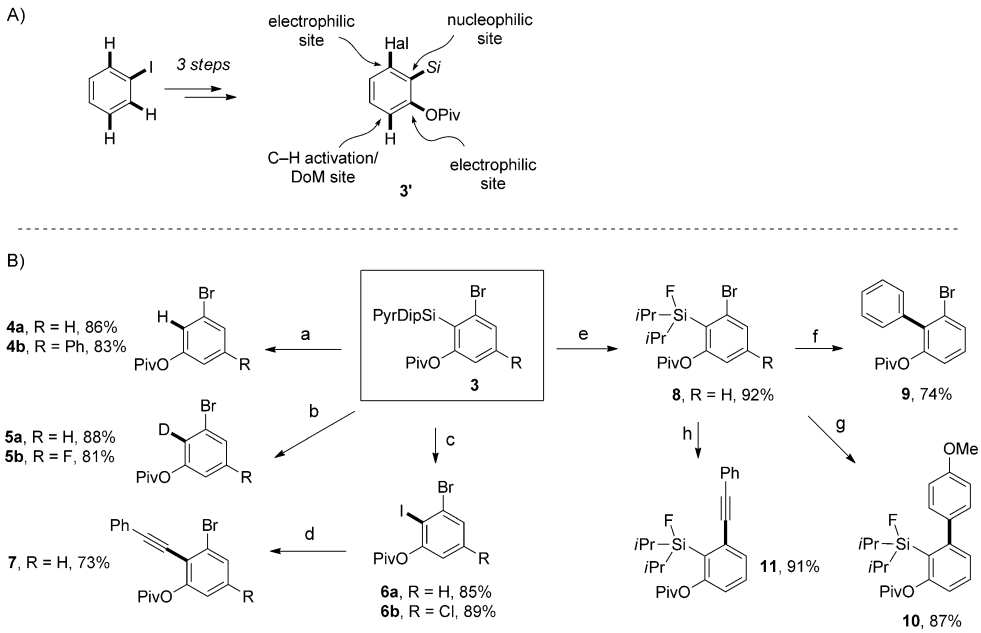
derivatives. Thus, the C–H chlorination reaction afforded 2-chloro derivatives **2m–o** in slightly diminished yields, whereas the C–H oxygenation reaction produced *meta*-chlorophenols **3m–o** in good yields (Table 2, entries 14–16). In contrast, C–H iodination proceeded uneventfully to produce the iodoarenes **2p,q** in excellent yields, whereas the subsequent pivaloyloxylation reaction was less efficient (Table 2, entries 17 and 18). The practical usefulness of the method was shown by scaling up the reaction: When **1a** was subjected to bromination and pivaloyloxylation on a 5 mmol scale, **3a** was formed in good yield. Importantly, both the PyrDipSi and the pivaloyl group can be cleaved in the obtained products **3** under mild conditions in nearly quantitative yield.[12] Thus, our newly developed two-step protocol for the synthesis of *meta*-halophenol derivatives features broad substrate scope, high functional-group tolerance, and mild reaction conditions.

Traditional approaches to *meta*-halophenols[9] are mostly based on electrophilic aromatic substitution[13] or cycloaddition reactions.[14] However, these methods require multistep procedures and harsh conditions and suffer from limited scope and low selectivity. Substituted *meta*-halophenols can also be prepared from 1,3-disubstituted arenes by *meta*-selective iridium-catalyzed C–H borylation/oxidation or C–H borylation/halogenation protocols.[15] Our method can serve as a general and efficient alternative to all these methods, as it enables the synthesis of functionalized *meta*-halophenols from a monosubstituted arene (aryl iodide).[16] Furthermore, our approach utilizes a removable/modifiable[7] directing group, which offers an additional handle for further functionalization of the obtained *meta*-halophenols.

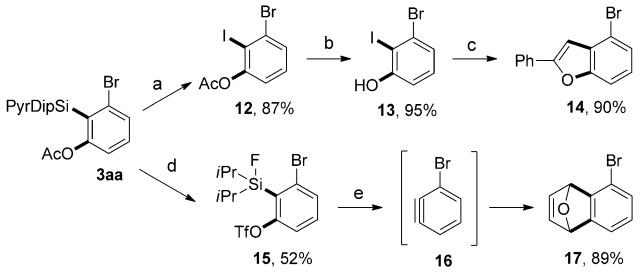
The usefulness of the developed twofold C–H functionalization method is highlighted by the concise synthesis polyfunctionalized arenes. In fact, this method can be used to transform readily available aryl iodides into a unique 3-halo-2-silaphenol scaffold **3′** (Scheme 2A). This multifunctionalized arene can potentially undergo diverse C–C, C–N, and C–O bond-forming reactions at the C–Br site through cross-coupling, *ipso* substitution or Hiyama–Denmark cross-coupling reactions at the C–Si site, C–C bond formation through cross-coupling reactions at the C–OPiv site,[17] and OPiv-directed *ortho* metalation (DoM)[18] or C–H activation reactions.[19]

Accordingly, we explored selected transformations of this building block **3** (Scheme 2B). Clearly, the PyrDipSi group can be selectively removed to provide pivaloyl-protected *meta*-bromophenols **4**. Similarly, it can be replaced with a deuterium atom to provide deuterated analogues **5**. The directing group can be readily substituted by iodide to produce valuable polyhalophenol derivatives **6** containing up to four different sites for cross-coupling reactions and thus modular functionalization of the benzene ring. Compound **6a** underwent a selective Sonogashira cross-coupling reaction at the C–I bond rather than at the less sterically hindered C–Br site to produce tolane derivative **7**.[20] The pyrimidyl group in **3** was replaced with fluoride to furnish the polyfunctional fluorosilane derivative **8**, which can be used for orthogonal cross-coupling reactions. For example, compound **8** underwent an efficient Hiyama–Denmark cross-coupling reaction at the C–Si bond with phenyl iodide to produce the biphenyl-containing building block **9**. On the other hand, the C–Br bond of **8** can be utilized in Suzuki–Miyaura as well as Sonogashira cross-coupling reactions, as demonstrated by the synthesis of derivatives **10** and **11**, respectively.

Finally, we illustrated the use of the 3-halo-2-silaphenol scaffold in the synthesis of fused systems (Scheme 3). Ready substitution of the silyl group by iodide to give **12**, followed by oxygen deprotection, furnished the 2,3-dihalophenol **13** in excellent yield. Compound **13** underwent a cascade Sonogashira coupling/5-*endo*-dig cyclization reaction with phenylacetylene to produce the 4-bromobenzofuran **14** in 90% yield.[21] Notably, our newly developed methodology provides general access to substituted 4-halobenzofurans.[21] Building



Scheme 2. A) Transformation of a simple aryl iodide into a polyfunctional arene building block **3′**. B) Transformations of arenes **3**: a) HF, THF, 0°C→RT, then AgF (2.5 equiv), H_2O in THF, room temperature; b) HF, THF, 0°C→RT, then AgF (2.5 equiv), D_2O in THF, room temperature; c) HF, THF, 0°C→RT, then AgF (2.5–3.0 equiv), NIS (3–4 equiv), THF, RT→70°C; d) phenylacetylene (1.5 equiv), $[PdCl_2(PPh_3)_2]$ (3 mol%), CuI (5 mol%), DMF, Et_2NH (1.5 equiv), 50°C; e) HF, THF, 0°C→RT; f) PhI (1.5 equiv), $[Pd(PPh_3)_4]$ (5 mol%), Ag_2O (1.1 equiv), THF, 60°C; g) 4-$MeOC_6H_4B(OH)_2$ (1.5 equiv), $[Pd_2(dba)_3]$ (5 mol%), P*t*Bu_3 (10 mol%), K_3PO_4 (2 equiv), dioxane, 90°C; h) phenylacetylene (1.2 equiv), $[Pd_2(dba)_3]$ (2.5 mol%), P*t*Bu_3 (10 mol%), Et_3N, room temperature. dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide.



Scheme 3. Synthesis of fused heterocycles: a) HF, THF, 0 °C→RT, then AgF (3 equiv), NIS (4 equiv), THF, RT→70 °C; b) Cs_2CO_3 (1 equiv), MeOH, 0 °C→RT; c) phenylacetylene (1.1 equiv), [$PdCl_2(PPh_3)_2$] (5 mol%), CuI (10 mol%), DMF, piperidine (1 equiv), 60 °C; d) Cs_2CO_3 (10 mol%), MeOH, 0 °C→RT, then Tf_2O (1.1 equiv), Et*N*iPr_2 (2 equiv), CH_2Cl_2, room temperature, then HF, THF, 0 °C→RT; e) CsF (3 equiv), CH_3CN, then furan (5 equiv), room temperature. Tf = trifluoromethanesulfonyl.

block **3aa** contains the C–Si bond next to the C–O bond on the benzene ring, and this arrangement can be used for the generation of bromobenzyne **16**. Thus, **3aa** was readily converted into the benzyne precursor **15**. The treatment of **15** with CsF produced bromobenzyne **16**, which was trapped through a [4+2] cycloaddition reaction with furan to produce 5-bromo-1,4-dihydroepoxynaphthalene (**17**).[22] Therefore, this method is also useful for the generation of halo-substituted benzynes for broad application in synthesis.

In conclusion, we have developed a general and efficient twofold unsymmetrical C–H functionalization of arenes, namely, a C–H halogenation/oxygenation reaction, with a PyrDipSi directing group. This protocol enables the efficient preparation of substituted *meta*-halophenols as well as polyfunctionalized arenes from simple aryl iodides. The obtained molecules were shown to undergo a variety of synthetically useful transformations to produce diversely functionalized aromatic compounds, such as iodoarenes, biaryl compounds, tolanes, and fused heterocycles.

Received: June 6, 2013
Published online: ■■ ■■, ■■■■

Keywords: C–H activation · cross-coupling · halogenation · oxygenation · palladium

[1] For a review on the transition-metal-catalyzed C–H activation of arenes, see: *C–H Activation*, *Topics in Current Chemistry*, *Vol. 292* (Eds.: J.-Q. Yu, Z. Shi), Springer, Berlin, **2010**.

[2] For selected examples of the transition-metal-catalyzed symmetrical bisfunctionalization of arenes, see: a) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300; b) O. Daugulis, Z. G. Zaitsev, *Angew. Chem.* **2005**, *117*, 4114; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; c) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123; d) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483; e) E. W. Kalberer, S. R. Whitfield, M. S. Sanford, *J. Mol. Catal. A* **2006**, *251*, 108; f) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285; g) P. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2009**, *11*, 1871; h) X. Zheng, B. Song, G. Li, B. Liu, H. Deng, B. Xu, *Tetrahedron Lett.* **2010**, *51*, 6641; i) S. Mo, Y. Zhu, Z. Shen, *Org. Biomol. Chem.* **2013**, *11*, 2756; j) X. Zhao, C. S. Yeung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837; k) H. Wang, N. Schröder, F. Glorius, *Angew. Chem.* **2013**, *125*, 5495; *Angew. Chem. Int. Ed.* **2013**, *52*, 5386.

[3] For examples of unsymmetrical bisfunctionalization with the introduction of similar functionalities, see: a) N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 7094; b) K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2010**, *122*, 6305; *Angew. Chem. Int. Ed.* **2010**, *49*, 6169; c) A. V. Gulevich, F. S. Melkonyan, D. Sarkar, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 5528; d) C. Cong, J. You, G. Gao, J. Lan, *Chem. Commun.* **2013**, *49*, 662; e) X. Sun, G. Shan, Y. Sun, Y. Rao, *Angew. Chem.* **2013**, *125*, 4536; *Angew. Chem. Int. Ed.* **2013**, *52*, 4440.

[4] During the preparation of this manuscript, examples of unsymmetrical bisfunctionalization with the introduction of two different functionalities were reported: a) W. Hengbin, G. Li, K. M. Engle, J.-Q. Yu, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 6774; b) B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, D. D. Dixon, J.-Q. Yu, P. S. Baran, *Angew. Chem.* **2013**, *125*, 7458; *Angew. Chem. Int. Ed.* **2013**, *52*, 7317.

[5] For selected examples of the transition-metal-catalyzed C–H halogenation of arenes, see Ref. [2a,d] and: a) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416; b) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 5293; *Angew. Chem. Int. Ed.* **2008**, *47*, 5215; c) D. C. Powers, T. Ritter, *Nat. Chem.* **2009**, *1*, 302; d) T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140; e) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama, T. Tanabe, *J. Am. Chem. Soc.* **2009**, *131*, 11310; f) Z. Shen, Y. Lu, R. Wang, X. Qiao, *Synlett* **2011**, 1038; g) R. B. Bedford, M. F. Haddow, C. J. Mitchell, R. L. Webster, *Angew. Chem.* **2011**, *123*, 5638; *Angew. Chem. Int. Ed.* **2011**, *50*, 5524; h) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298; i) X. T. Ma, S.-K. Tian, *Adv. Synth. Catal.* **2013**, *355*, 337; j) A. S. Dudnik, N. Chernyak, C. Huang, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 8911; *Angew. Chem. Int. Ed.* **2010**, *49*, 8729; k) C. Huang, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Adv. Synth. Catal.* **2011**, *353*, 1285.

[6] For selected examples of the C–H oxygenation of arenes, see: a) A. R. Dick, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 12790; b) D. Kalyani, M. S. Sanford, *Org. Lett.* **2005**, *7*, 4149; c) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141; d) G.-W. Wang, T.-T. Yuan, X.-L. Wu, *J. Org. Chem.* **2008**, *73*, 4717; e) J. M. Racowski, R. Dick, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 10974; f) K. J. Stowers, M. S. Sanford, *Org. Lett.* **2009**, *11*, 4584; g) S. Gu, C. Chen, W. Chen, *J. Org. Chem.* **2009**, *74*, 7203; h) F.-R. Gou, X.-C. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan, Y.-M. Liang, *Org. Lett.* **2009**, *11*, 5726; i) N. Chernyak, A. S. Dudnik, C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 8270; j) C. Huang, N. Ghavtadze, B. Chattopadhyay, V. Gevorgyan, *J. Am. Chem. Soc.* **2011**, *133*, 17630; k) C. Huang, N. Ghavtadze, B. Godoi, V. Gevorgyan, *Chem. Eur. J.* **2012**, *18*, 9789; l) P. Sun, W. Li, *J. Org. Chem.* **2012**, *77*, 8362; and Ref. [2f].

[7] For recent reviews on removable/modifiable directing groups, see: a) S. Bracegirdle, E. A. Anderson, *Chem. Soc. Rev.* **2010**, *39*, 4114; b) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450; c) Y. Huang, C. Wang, *Synlett* **2013**, *24*, 145.

[8] For the use of pyridine-based silicon-tethered directing groups in Heck reactions, see: a) K. Itami, K. Mitsudo, T. Nokami, T. Kamei, T. Koike, J.-i. Yoshida, *J. Organomet. Chem.* **2002**, *653*, 105.

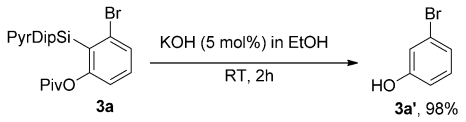
[9] For the importance of *meta*-halophenols, see: a) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, **1996**; b) *Ullmann's Encyclopedia of Industrial Chemistry*, *5th ed.*, Wiley-VCH, Weinheim, **1998**; c) C. G. Hartung, V. Snieckus,

Modern Arene Chemistry (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**.

[10] Although the exact role of $PhI(OAc)_2$ in the C–H halogenation is currently unclear, it presumably helps to maintain the reactive Pd species.

[11] Attempts at a one-pot bromination/oxygenation reaction sequence were not successful. We attribute this lack of success to potential deactivation of the palladium catalyst by succinimide formed in the halogenation reaction.

[12] Compound **3a** underwent smooth double deprotection to give *meta*-bromophenol (**3a′**):



3a **3a'**, 98%

[13] For an approach to *meta*-bromophenols based on electrophilic substitution, see: C. F. Koelsch, *J. Am. Chem. Soc.* **1939**, *61*, 969.

[14] For a nonselective synthesis of substituted *meta*-halophenols by cycloaddition chemistry, see: a) J. W. Patterson, *J. Org. Chem.* **1995**, *60*, 560; b) S. Choudhury, F. A. Khan, *Eur. J. Org. Chem.* **2010**, 2954.

[15] For the synthesis of substituted *meta*-bromophenols by iridium-catalyzed C–H activation, see: a) R. E. Maleczka, Jr., F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.* **2003**, *125*, 7792; b) J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434; c) B. M. Partridge, J. F. Hartwig, *Org. Lett.* **2013**, *15*, 140.

[16] For an example of the *meta* functionalization of phenol, see: H.-X. Dai, G. Li, X.-G. Zhang, A. F. Stepan, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 7567.

[17] For examples of cross-coupling reactions of aryl pivalates, see: a) K. W. Quasdorf, X. Tian, N. K. Garg, *J. Am. Chem. Soc.* **2008**, *130*, 14422; b) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 14468; c) B.-J. Li, Y.-J. Li, X.-Y. Lu, J. Liu, B.-T. Guan, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 10278; *Angew. Chem. Int. Ed.* **2008**, *47*, 10124.

[18] For a general review on directed *ortho* metalation for the synthesis of polysubstituted aromatic compounds, see: V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.

[19] For examples of pivalate-directed C–H activation, see: a) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 468; b) T. Gensch, M. Rönnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer, H.-J. Knölker, *Chem. Eur. J.* **2012**, *18*, 770.

[20] R. Sanz, V. Guilarte, N. García, *Org. Biomol. Chem.* **2010**, *8*, 3860.

[21] R. Sanz, M. P. Castroviejo, Y. Fernández, F. J. Fañanás, *J. Org. Chem.* **2005**, *70*, 6548.

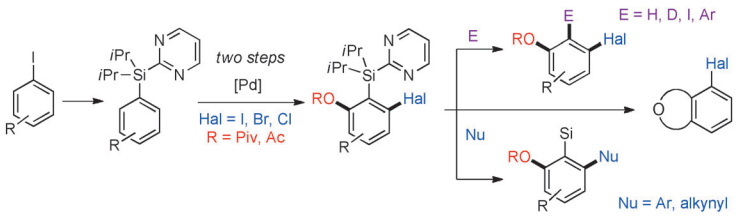
[22] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

Communications

C–H Activation

D. Sarkar, F. S. Melkonyan, A. V. Gulevich, V. Gevorgyan* ——— ■■■■–■■■■

Twofold Unsymmetrical C–H Functionalization of PyrDipSi-Substituted Arenes: A General Method for the Synthesis of Substituted *meta*-Halophenols



And the world is your oyster... Sequential halogenation/oxygenation reactions of 2-diisopropylsilylpyrimidine-substituted arenes provide a general and efficient synthesis of substituted *meta*-halophenols from simple aryl iodides (see scheme; Piv = pivaloyl). The products are poised to undergo diverse C–C, C–N, and C–O bond-forming reactions that enable the transformation of their framework and the introduction of valuable functionalities.