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Two-fold Unsymmetrical C-H Functionalization of PyrDipSi-Arenes: A General Method For Synthesis of Substituted *meta*-Halophenols**

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Abstract

Two-fold unsymmetrical functionalization of arenes, which includes sequential halogenation/oxygenation reactions, has been developed. This transformation allows for a general and efficient synthesis of substituted *meta*-halophenols from simple aryl iodides. Importantly, the PyrDipSi (2-diisopropylsilylpyrimidine) group can be easily removed or efficiently converted into valuable functionalities.

Keywords

C-H activation; arenes; palladium; halogenation; oxygenation; cross-coupling

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, two-fold aromatic C-H functionalization is synthetically even more appealing as it allows for introduction of two substituents using a one-pot or a two step procedure. However, two-fold C-H functionalization has been used only for introduction of the same (e.g. alkenyl/alkenyl, aryl/aryl, OR/OR, Hal/Hal; eq 1, a)^[2] or similar (e.g. alkenyl/alkenyl', OAc/OPiv, Cl/Br; eq 1, b)^[3] functionalities. To the best of our knowledge, unsymmetrical C-H functionalization with introduction of *two different functional groups* is unknown (Equation 1, c). If developed, this methodology would open a straightforward access to a variety of densely functionalized multisubstituted arenes. Herein, we wish to

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report an unprecedented two-fold unsymmetrical C-H functionalization of arenes, which allows for introduction of *two different functional groups* (OR and Hal).^[4] This method features a concise synthesis of substituted *meta*-halophenols starting from aryl iodides via a sequential C-H halogenation/oxygenation reactions^[5,6] using removable/functionalizabile^[7,8] pyrimidine-based silicon-tethered directing group (Equation 2).

(1)

(2)

Recently, we have developed a traceless/modifiable PyrDipSi directing group for selective mono- and bis-oxygenation of arenes.^[3c] Notably, this oxygenation reaction tolerated an *ortho*-substituent, which makes this transformation potentially compatible with other *ortho*-C-H functionalizations. Based on this, we thought of developing a two-fold unsymmetrical C-H functionalization process using this directing group. A halogenation/oxygenation sequence was chosen, as it would open access to valuable *meta*-halophenols.^[9]

First, we performed optimization of the Pd-catalyzed C-H halogenation reactions of PyrDipSi-benzene (**1a**). The bromination of **1a** with NBS (2 equiv) afforded the desired product **2a** in promising 35% yield (Table 1, entry 1). Upon screening additives we uncovered that PhI(OAc)₂ facilitates the bromination reaction (entries 3–4). Finally, it was found that the reaction required only catalytic amounts of PhI(OAc)₂ (10 mol %), producing **2a** in high yield (entry 8).^[10] On the other hand, C-H chlorination (entry 11) of **1a** required superstoichiometric amounts of PhI(OAc)₂ (1.3 equiv), as excess NCS, and elevated temperatures (EtCN, 100 °C). Iodination of **1a** using NIS (1.2 equiv) afforded iodination product **2p** in 94% yield without any additive (entry 12). Control experiments without Pd(OAc)₂ did not provide any products.

Next, we attempted to use the newly found conditions for C-H bromination process in combination with C-H oxygenation reaction^[3c] for two-step synthesis^[11] of *meta*-bromophenol derivatives (Table 2). Delightfully, we found that compound **1a** could efficiently be converted into bromophenol derivatives **3a** and **3aa** using a two-step sequential bromination/oxygenation protocol (entries 1–2). Likewise, PyrDipSi-arenes **1** bearing electron-neutral (Me, ^tBu, Ph) and electron-donating (OMe) substituents were efficiently converted into *ortho*-bromo derivatives **2b–e**. A subsequent pivaloxylation furnished the corresponding products **3b–e** in good yields (entries 3–6). Substrates possessing electron-withdrawing groups, namely CO₂Me, COMe and CON(ⁱPr)₂, smoothly underwent the C-H bromination reaction (**2f–h**), as well as further pivaloxylation reaction, to produce the desired products **3f–h** (entries 7–9). Electron-deficient CF₃-substituted arene was converted into brominated product **2i**, which then was oxygenated to form **3i** in moderate yield (entry 10). Notably, halo-substituted substrates efficiently underwent bromination (**2j–l**), as well as pivaloxylation reactions, producing valuable dihalophenol derivatives **3j–l** (entries 11–13). This halogenation/oxygenation reaction sequence was also successfully utilized for synthesis of *meta*-chloro- and *meta*-iodophenol derivatives. Thus, C-H chlorination reaction afforded 2-chloro-derivatives **2m–o** in slightly diminishing yields, whereas C-H oxygenation reaction produced *meta*-chlorophenols **3m–o** in good yields (entries 14–16). In contrast, C-H iodination proceeded uneventfully produces the iodoarenes **2p,q** in excellent yields, albeit the subsequent pivaloxylation reaction was less efficient (entries 17–18). The practical usefulness of the method was shown by scaling up the reaction up to 5 mmol, provided **3a** without diminishing yield. Importantly, both the PyrDipSi and 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 synthesis of *meta*-halophenol derivatives features broad substrate scope, high functional group tolerance, and mild reaction conditions.

It should be mentioned that the traditional approaches to *meta*-halophenols^[9] are mostly based on electrophilic aromatic substitution^[13] or cycloaddition reactions.^[14] However, these methods require multistep procedures, harsh conditions, and suffer from limited scope and low selectivity. In addition, substituted *meta*-halophenols can be prepared from 1,3-disubstituted arenes using *meta*-selective Ir-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 allows for synthesis of functionalized *meta*-halophenols from monosubstituted arene (aryl iodide).^[16] In addition, our approach utilizes a removable/modifiable^[7] directing group, which offers an additional handle for further functionalization of the obtained *meta*-halophenols.

Usefulness of the developed two-fold C-H functionalization method could be highlighted in concise synthesis polyfunctionalized arenes. In fact, starting from readily available aryl iodides, this method affords a unique 3-halo-2-silaphenol scaffold **3'** (Scheme 1A). This multifunctionalized arene can potentially undergo a diverse C-C, C-N, C-O bond formation at the C-Hal site via cross-coupling reactions, *ipso* substitution reaction or Hiyama-Denmark cross-coupling reaction at the C-Si site, C-C bond formation via the cross-coupling

reactions at 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 1B). Obviously, PyrDipSi group can be selectively removed to provide the pivaloyl protected *meta*-bromophenols **4**. Similarly, it can be replaced with D-atom providing a deuterated analog **5**. The directing group can be easily substituted with iodide to produce valuable polyhalophenol derivatives **6**, containing up to four different sites for cross-coupling reactions, which can be used for a modular functionalization of the benzene ring. The C-I bond of **6a** can undergo a selective Sonogashira cross-coupling reaction over the less sterically hindered C-Br site to produce tolane **7**.^[20] The pyrimidyl group in **3** could be replaced with fluoride furnishing polyfunctional fluorosilane derivative **8**, which can be used for orthogonal cross-coupling reactions. For example, the C-Si bond of **8** underwent efficient Hiyama-Denmark cross-coupling reaction with phenyl iodide to produce biphenyl-containing building block **9**. On the other hand, the C-Br bond of **8** can be utilized in Suzuki-Miyaura, as well as in Sonogashira cross-coupling reactions, affording derivatives **10** and **11**, respectively.

Finally, we illustrated the utilization of the scaffold **3** in the synthesis of fused systems (Scheme 2). An easy substitution of “Si”-group with iodide (**12**), followed by oxygen deprotection furnished 2,3-dihalophenol **13** in excellent yield. The latter could undergo a cascade Sonogashira coupling/5-*endo-dig* cyclization reaction with phenylacetylene producing 4-bromobenzofuran **14** in 90% yield.^[21] Noteworthy, our newly developed methodology makes this benzofuran synthesis^[21] more valuable since it provides a general access to substituted 4-halobenzofurans. Building block **3aa** contains the C-Si bond next to the C-O bond in the benzene ring, which can be used for generation of bromo-benzyne **16**. Thus, **3aa** was easily converted into the benzyne precursor **15**. Treatment of **15** with CsF produced Br-benzyne **16**, which was trapped via a [4+2] cycloaddition reaction with furan to produce 5-bromo-1,4-dihydroepoxynaphthalene **17**.^[22] Therefore, this method is also useful for generation of halo-substituted benzynes for broad applications in synthesis.

In conclusion, we have developed a general and efficient twofold unsymmetrical C-H functionalization of arenes, namely C-H halogenations/oxygenation reaction, using PyrDipSi directing group. This protocol allows for efficient preparation of substituted *meta*-halophenols, as well as polyfunctionalized arenes, from simple aryl iodides. The obtained molecules could undergo a variety of synthetically useful transformations producing diversely functionalized aromatic compounds such as iodoarenes, biaryls, tolanes, and fused heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Transformations of arenes **3**. Reagents and conditions: a) HF, THF, 0 °C to rt then AgF (2.5 equiv), H₂O in THF, rt. b) HF, THF, 0 °C to rt then AgF (2.5 equiv), D₂O in THF, rt. c) HF, THF, 0 °C to rt then AgF (2.5–3.0 equiv), NIS (3–4 equiv), THF, rt to 70 °C. d) Phenylacetylene (1.5 equiv), PdCl₂(PPh₃)₂ (3 mol%), CuI (5 mol%), DMF, Et₂NH (1.5 equiv), 50 °C. e) HF, THF, 0 °C to rt. f) PhI (1.5 equiv), Pd(PPh₃)₄ (5 mol %), Ag₂O (1.1 equiv), THF, 60 °C. g) 4-MeOC₆H₄B(OH)₂ (1.5 equiv), Pd₂(dba)₃ (5 mol %), P^tBu₃ (10 mol %), K₃PO₄ (2 equiv), Dioxane, 90 °C. h) Phenylacetylene (1.2 equiv), Pd₂(dba)₃ (2.5 mol %), P^tBu₃ (10 mol %), Et₃N, rt.

Scheme 2.

Synthesis of fused heterocycles. Reagents and conditions: a) HF, THF, 0 °C to rt then AgF (3 equiv), NIS (4 equiv), THF, rt to 70 °C. b) Cs₂CO₃ (1 equiv), MeOH, 0 °C to rt. c) Phenylacetylene (1.1 equiv), PdCl₂(PPh₃)₂ (5 mol %), CuI (10 mol %), DMF, piperidine (1 equiv), 60 °C. d) Cs₂CO₃ (10 mol%), MeOH, 0 °C to rt then Tf₂O (1.1 equiv), EtNⁱPr₂ (2 equiv), DCM, rt. then HF, THF, 0 °C to rt. e) CsF (3 equiv), CH₃CN then furan (5 equiv), rt.

Table 1

Optimization of 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] Isolated yields are given.

^[b] GC yields are given in parentheses.

^[c] Reactions were performed in EtCN (0.05M).

^[d] Reaction was performed with Pd(OAc)₂ (5 mol%)

Table 2Sequential halogenation/oxygenation of PyrDipSi-Arenes.^[a]

Ent.	Halogenated product	Yield ^[b]	Oxygenated product	Yield ^[b]
1		2a , 85% (82%) ^[c]		3a , 72% (79%) ^[c]
2				3aa , 71%
3		2b , 90%		3b , 78%
4		2c , 76%		3c , 73%
5		2d , 84%		3d , 69%
6		2e , 88%		3e , 75%
7		2f , 81%		3f , 72%
8		2g , 74%		3g , 59%
9		2h , 72%		3h , 74%
10		2i , 58%		3i , 51%

Ent.	Halogenated product	Yield ^[b]	Oxygenated product	Yield ^[b]
11		2j , 77%		3j , 69%
12		2k , 78%		3k , 72%
13		2l , 74%		3l , 68%
14		2m , 75% ^[d]		3m , 65%
15		2n , 64% ^[d]		3n , 84%
16		2o , 59% ^[d]		3o , 61%
17		2p , 94% ^[e]		3p , 55% ^[f]
18		2q , 80% ^[e]		3q , 40% ^[f]

^[a] 0.4 mmol scale, see Supporting Information for experimental details.

^[b] Isolated yields.

^[c] 5 mmol scale.

^[d] Reactions were performed in 0.05M EtCN with 5 equiv NCS and 1.3 equiv $\text{PhI}(\text{OAc})_2$ at 100 °C.

^[e] Reactions were performed without $\text{PhI}(\text{OAc})_2$, 5 mol % $\text{Pd}(\text{OAc})_2$ and 1.5 equiv NIS at 60 °C.

^[f] 2 equiv of $\text{PhI}(\text{OPiv})_2$ was used.