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Double-Fold C-H Oxygenation of Arenes Using PyrDipSi: a General and Efficient Traceless/Modifiable Silicon-Tethered Directing Group

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Abstract

The efficient Pd-catalyzed double-fold C-H oxygenation of arenes into resorcinols using newly developed 2-pyrimidylisopropylsilyl (PyrDipSi) directing group is described. Its employment allows for a sequential introduction of OAc and OPiv groups in a *one-pot* manner to produce orthogonally protected resorcinol derivatives. PyrDipSi group is superior over the previously developed 2-pyridylisopropylsilyl (PyDipSi) group, as it is efficient for monooxygenation of *ortho*-substituted arenes. Notably, PyrDipSi group can be easily installed into arene molecule and can be easily removed or modified after the oxygenation reaction.

Transition metal-catalyzed C-H functionalization represents a very powerful tool for straightforward modification of various organic molecules.¹ Among these reactions, C-H functionalization of arenes can be efficiently used for formation of new carbon-carbon² and carbon-heteroatom³ bonds. However most directing groups cannot be easily removed from the molecule after C-H functionalization, thus limiting this methodology to particular type of substrates. Therefore, employment of removable directing groups⁴ could dramatically increase synthetic applicability of the C-H functionalization processes.⁵ Thus, Itami and Yoshida employed silyl ethered pyridine group as a removable directing group for Heck and Pauson-Khand-type reactions.⁶ Using this concept, we have recently developed the pyridine-based PyDipSi group⁷ as a removable directing group for the Pd-catalyzed *mono* C-H oxygenation⁸ reaction of arenes (eq. 1). Feasibly, *double* C-H oxygenation could provide an access to resorcinol derivatives, valuable building blocks for synthesis, medicinal chemistry and material science.⁹ Although, selected examples of double C-H acetoxylation of arenes using non-removable directing groups, such as pyridine,^{8a,f} pyrazole^{8f} or ketoxime,^{8h} were reported by Sanford et al., employment of cleavable/functionalizable directing group could significantly increase synthetic applicability of the method. Herein we wish to report the PyrDipSi, an efficient easily removable/modifiable directing group for efficient Pd-catalyzed *double* C-H oxygenation of arenes into resorcinol derivatives (eq. 2).

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ASSOCIATED CONTENT Supporting Information. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

As reported earlier,^{7a} pyridine-based PyDipSi group produces mono acetoxylation product **A** in 80% yield with no double oxygenation product observed (Scheme 1). We envisioned that employment of heterocycle with two heteroatoms as a directing group may facilitate the second C-H insertion reaction. Hence, we explored different Si-tethered heterocycles including thiazole,¹⁰ benzothiazole, *NH*-imidazole, *NMe*-imidazole,¹⁰ and pyrimidine^{8h,11} as potential directing groups under previously reported acetoxylation reaction conditions.^{7a} It was found that employment of thiazole- and imidazole-based directing groups was not efficient et al. To our delight, the pyrimidine-based PyrDipSi group showed promising results, producing the desired bis-acetoxylation product **2a** in 26% yield (Scheme 1).

Next, optimization of double oxygenation of PyrDipSi benzene **1a** was performed (Table 1). Upon screening additives, we found that the combination of LiCl and AgOAc produces the corresponding bis-acetoxylation product **2a** in 90% yield. Finally, LiOAc (30%) was found to be the most efficient additive, providing bisacetoxylation product **2a** in almost quantitative GC yield (entry 11). However, due to low stability toward column chromatography, we obtained diminished isolated yield (87%) of **2a**. Gratifyingly, pivaloylation reaction using PhI(OPiv)₂ under these reaction conditions produced the corresponding chromatography-stable bis-pivaloxylated product **3a**, in almost quantitative yield (entry 11). Notably, these optimized reaction conditions feature lower amount of oxidant (1.25 eq.), lower catalyst loading, as well as inexpensive LiOAc as a co-catalyst. Employment of LiOAc is crucial for the successful second C-H oxygenation, which could indicate that the reaction follows a concerted metallation-deprotonation (CMD) pathway.¹²

We have also developed a simple and scalable procedure for installation of PyrDipSi group onto aryl iodides. First, PyrDipSiH was prepared from easily available 2-iodopyrimidine and commercially available diisopropylchlorosilane. Thus, formation of pyrimidylmagnesium compound¹³ followed by reaction with chlorosilane afforded PyrDipSiH in high yield. A subsequent Rh-catalyzed coupling of aryl iodides with PyrDipSiH, provided a number of PyrDipSi arenes **1** in good yields (Scheme 2).¹⁴

With the efficient method for installation of PyrDipSi group and optimized conditions for double pivaloylation in hand, we investigated the scope of the reaction (Table 2). It was found that a variety of arenes bearing alkyl or aryl substituents produced the corresponding resorcinol derivatives in excellent yields. Moreover, different functional groups, such as

methoxy (entry 6), carbomethoxy (entry 7), amide (entry 8), and acetyl (entry 9) were also tolerated. Notably, formyl (entry 10) and styryl groups (entry 11), which are prone to oxidation, furnished the corresponding products in good yields. All halogens were compatible with the reaction conditions (entries 12-15), thus providing compounds bearing an additional handle for a subsequent functionalization.¹⁵ Due to the additional steric hindrance, 3-substituted PyrDipSi arenes exhibited substantially lower reactivity. Thus, only PyrDipSi benzene **1p**, possessing a small F-substituent at the meta-position, underwent double oxygenation reaction to give resorcinol **3p**, although in diminished yield (entry 16).

Next, we aimed at achieving nonsymmetrical bis-functionalization of PyrDipSi arenes via a sequential C-H acetoxylation/pivaloxylation reaction (Scheme 3). Thus acetoxylation of *PyrDipSiPh* **1a** with PhI(OAc)₂ followed by a *one-pot* pivaloxylation reaction of the intermediate using PhI(OPiv)₂ in the presence of LiOAc (30%) furnished the corresponding product **4a** in good yield. This protocol allowed for preparation of differently substituted orthogonally protected resorcinol derivatives **4a-c** in good yields. As expected, the acetyl group could selectively be cleaved in the presence of pivaloxy group, thus producing mono-protected resorcinol derivative **4b'** in high yield (Scheme 3).

We also investigated mono pivaloxylation reaction of *ortho*-substituted PyrDipSi arenes (Scheme 4). It was found that various *ortho*-substituted PyrDipSi arenes **1q-w** underwent smooth pivaloxylation, producing the corresponding products **5** in good yields. Thus, methoxy (entry **5a**), methyl (entries **5b,c**), as well as fluorine (entry **5d**), chlorine (entry **5e**) and bromine (entry **5f**) can be tolerated at the *ortho*-position of arene. Likewise, 1-PyrDipSi naphthalene afforded the corresponding product **5g** in good yield. In contrast, the previously developed PyDipSi group appeared to be not efficient in oxygenation of *ortho*-substituted arenes at all. Thus, *ortho*-Br-PyDipSi benzene, under the same reaction conditions, did not produce detectable amounts of oxygenated product **5f'**, a PyDipSi analog of **5f** (Scheme 4).¹⁶ Although, at this point, the dramatic difference in directing abilities of PyrDipSi and Py-DipSi groups remains unclear, it is most likely to be attributed to different basicity/binding properties of these groups.¹⁷

Finally, we have shown that PyrDipSi group can be easily removed from *bis*-oxygenated products **4** to provide the corresponding protected resorcinols **6** or deuterated analogs **7** in almost quantitative yields (Scheme 5). Moreover, PyrDipSi group can be easily substituted with iodide (entries **8a,b**), which opens broad opportunities for a subsequent modification. As an example, we have shown that iodides **8** readily undergo Miyaura-Suzuki cross-coupling reaction, providing biaryls **9** in high yields. Furthermore, a synthetic usefulness of the developed methodology can further be illustrated by the efficient 3-step conversion of 4-iodobromobenzene into the corresponding resorcinol **8c** (Scheme 5).¹⁶

In conclusion, we have developed the PyrDipSi, a new general and efficient silicon tethered directing group, which can be easily installed at aryl iodides using the Rh-catalyzed coupling with PyrDip-SiH. Employment of this new directing group allowed for mild and efficient Pd-catalyzed double C-H oxygenation of arenes, producing valuable resorcinol derivatives. Moreover, the developed convenient protocol for *one-pot* acetoxylation/pivaloxylation reaction is efficient for synthesis of orthogonally protected resorcinols. In contrast to the previously developed PyDipSi group, the PyrDipSi group is also efficient for mono oxygenation of *ortho*-substituted arenes. Finally, we have shown that this new directing group can be easily removed or converted to valuable aryl iodides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- (15). For example, compound 3o readily undergoes Miyaura-Suzuki cross-coupling reaction:

- (16). See Supporting Information for details.
- (17). Although Sanford et al. did not observe strong correlation between directing ability and basicity of a directing group (for directing groups of different sizes) in the Pd-catalyzed C-H oxygenation reaction,^{8h} in our case, due to steric similarity of *PyrDipSi* and *PyDipSi* groups, their basicity¹⁸ could play certain role in the reaction. Additionally, we observed that even catalytic amounts of pyridine suppress the second C-H oxygenation reaction (Table 1, entry 3). For influence of electron-withdrawing nature of pyrimidine on the Pd-catalyzed C-H trifluoromethylation reaction, see ref. 10.
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Scheme 1.
Optimization of directing group (DG)

Scheme 2.
Installation of PyrDipSi group

Scheme 3.
Nonsymmetric double-fold C-H oxygenation

Scheme 4.
Pyvaloxylation of *o*-substituted PyrDipSi arenes

Scheme 5.

Modification of PyrDipSi group in obtained resorcinols

(a) HF, 1.2 eq. AgF, MeOH/THF, rt. (b) HF, THF, 0 °C to rt, then 1.2 eq. AgF, D₂O/THF, rt. (c) HF, THF rt, then 2 eq. NIS, 1.2 eq. AgF, THF, rt. (d) 1.5 eq. 4-MeOC₆H₄B(OH)₂, 5% Pd₂(dba)₃, 10% PPh₃, 2 eq. K₃PO₄, dioxane, 100 °C. (e) 1.5 eq. PyrDipSiH, 2.5% Rh₂(OAc)₄, 2 eq. K₃PO₄, dioxane, 100 °C. (f) 5% Pd(OAc)₂, 2.5 eq. PhI(OPiv)₂, 30% LiOAc, DCE, 80 °C. (g) HF, THF, rt, then 2 eq. NIS, 1.2 eq. AgF, THF, rt.

Table 1

Optimization of the double oxygenation reaction^a

Ent.	Cat.	Oxidant, eq.	Additive, eq.	Yield, %
1	10%	PhI(OAc) ₂ , 4.0	AgOAc, 1.0	60
2	10%	PhI(OAc) ₂ , 4.0	None	40
3	10%	PhI(OAc) ₂ , 4.0	Py, 10%	10
4	10%	PhI(OAc) ₂ , 4.0	Air	34
5	10%	PhI(OAc) ₂ , 4.0	AgOAc/LiCl, 1.0	90
6	10%	PhI(OAc) ₂ , 4.0	LiOAc, 1.0	91
7	5%	PhI(OAc) ₂ , 4.0	LiOAc, 1.0	90
8	5%	PhI(OAc) ₂ , 4.0	LiOAc, 0.3	95
9 ^d	5%	PhI(OAc) ₂ , 2.5	LiOAc, 0.3	95 ^b
10	5%	PhI(OAc) ₂ , 2.5	LiOAc, 0.3	97(87) ^b
11	5%	PhI(OPiv) ₂ , 2.5	LiOAc, 0.3	99(97) ^b
12	5%	PhI(OPiv) ₂ , 2.5	LiOAc, 0.3	98(95) ^{b,c}

^a Conditions: 0.1 mmol **1a**, catalyst, oxidant, and additive in 0.25 mL DCE (0.4M) were stirred at 80 °C in sealed vial under N₂ atmosphere. GC yields are given. Isolated yield is given in parenthesis.

^b Concentration 1M.

^c 3 mmol scale.

Table 2

Double pivaloxylation of PyrDipSiAr^a

Ent.	Product	Yield	Ent.	Product	Yield
1		97%	9		65%
2		95%	10		60%
3		88%	11		86%
4		74%	12		80%
5		80%	13		83%
6		90%	14		95%

Ent.	Product	Yield	Ent.	Product	Yield
7	3g	98%	15	3o	82%
8	3h	69%	16	3p	41% ^b

^a 0.2 mmol scale, isolated yields are given.

^b 10% cat.