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

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S *Supporting Information*

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

Transition-metal-catalyzed C−H functionalization reactions represent 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−carbon[2] and carbon−heteroatom[3] bonds. However, most directing groups cannot be easily removed from the molecule after C−H functionalization, thus limiting this methodology to a particular type of substrate. Therefore, the use of removable directing groups[4] could dramatically increase the synthetic applicability of C−H functionalization processes.[5] Thus, Itami and Yoshida employed a Si-tethered pyridine group as a removable directing group for Heck and Pauson−Khand-type reactions.[6] Using this concept, we recently developed the pyridine-based 2-pyridyldiisopropylsilyl (PyDipSi) group[7] as a removable directing group for the Pd-catalyzed *mono* C−H oxygenation[8] reaction of arenes (eq 1). Feasibly, *double* C−H oxygenation could provide access
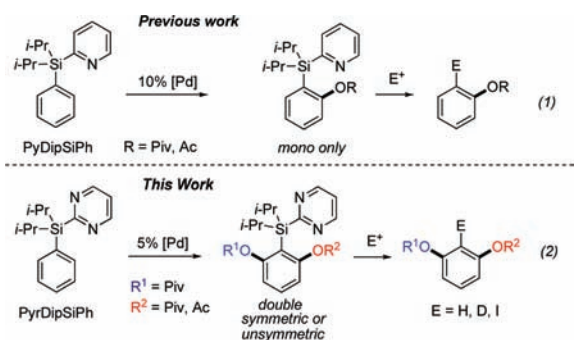

to resorcinol derivatives, which are valuable building blocks for synthesis, medicinal chemistry, and materials science.[9]

Although selected examples of double C−H acetoxylation of arenes using nonremovable directing groups, such as pyridine,[8a,f] pyrazole[8f] or ketoxime,[8h] were reported by Sanford and co-workers, the use of a cleavable/functionalizable directing group could significantly increase the synthetic applicability of the method. Herein we report the 2-pyrimidyldiisopropylsilyl (PyrDipSi) group, an efficient, easily removable/modifiable directing group for efficient Pd-catalyzed *double* C−H oxygenation of arenes into resorcinol derivatives (eq 2).

As reported earlier,[7a] the pyridine-based PyDipSi group produces monoacetoxylated product **A** in 80% yield with no double oxygenation product observed (Scheme 1). We envisioned that

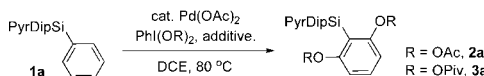## Scheme 1. Optimization of the Directing Group (DG)
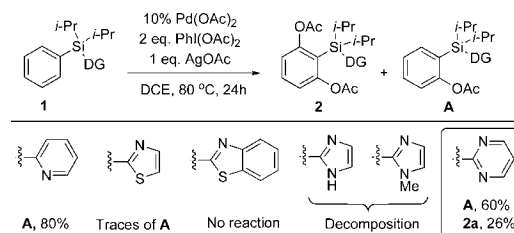
the use of a heterocycle with two heteroatoms as a directing group may facilitate the second C−H insertion reaction. Hence, we explored different Si-tethered heterocycles, including thiazole,[10] benzothiazole, imidazole, N-methylimidazole,[10] and pyrimidine,[8h,11] as potential directing groups under previously reported acetoxylation reaction conditions.[7a] It was found that thiazole- and imidazole-based directing groups were not efficient at all. To our delight, the pyrimidine-based PyrDipSi group showed promising results, producing the desired bisacetoxylated product **2a** in 26% yield (Scheme 1).

Next, optimization of the double oxygenation of PyrDipSi-benzene (**1a**) was performed (Table 1). Upon screening additives, we found that the combination of LiCl and AgOAc produced **2a** in 90% yield. Finally, LiOAc (30%) was found to be the most efficient additive, providing **2a** in almost quantitative GC yield (entry 11). However, because of its low stability toward column chromatography, we obtained a diminished isolated yield of **2a** (87%). Gratifyingly, the pivaloxylation reaction using PhI(OPiv)$_2$ under these reaction conditions produced the corresponding chromatography-stable bispivaloxylated product **3a** in almost quantitative yield (entry 11). Notably,

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	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: **1a** (0.1 mmol), catalyst, oxidant, and additive in 0.25 mL of DCE (0.4 M) were stirred at 80 °C in a sealed vial under a N$_2$ atmosphere. GC yields are given. Isolated yields are given in parentheses. [b]Concentration 1 M. [c]3 mmol scale.
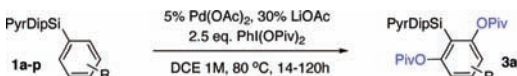
these optimized reaction conditions feature a lower amount of oxidant (1.25 equiv) and a lower catalyst loading as well as inexpensive LiOAc as a cocatalyst. The use of LiOAc was found to be crucial for the successful second C−H oxygenation, which could indicate that the reaction follows a concerted metalation−deprotonation (CMD) pathway.[12]

We also developed a simple and scalable procedure for installation of PyrDipSi onto aryl iodides. First, PyrDipSiH was prepared from 2-iodopyrimidine and commercially available diisopropylchlorosilane. Thus, formation of the pyrimidylmagnesium compound[13] followed by reaction with the chlorosilane afforded PyrDipSiH in high yield. Subsequent Rh-catalyzed coupling of aryl iodides with PyrDipSiH provided a number of PyrDipSi arenes **1** in good yields (Scheme 2).[14]

Scheme 2. Installation of the PyrDipSi Group
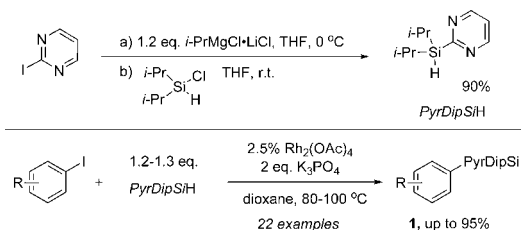
With an efficient method for installation of the PyrDipSi group and optimized conditions for double pivaloxylation in hand, we investigated the scope of the reaction (Table 2). It was found that a variety of arenes bearing alkyl or aryl substituents produced the corresponding resorcinol derivatives in 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 (entry 11) groups, 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] Because of the additional steric hindrance, 3-substituted PyrDipSi arenes exhibited substantially lower reactivities. Thus, only PyrDipSi-benzene **1p**, possessing a small F

Table 2. Double Pivaloxylation of PyrDipSiAr[a]

Ent.	Product	Yield	Ent.	Product	Yield
1	**3a**	97%	9	**3i**	65%
2	**3b**	95%	10	**3j**	60%
3	**3c**	88%	11	**3k**	86%
4	**3d**	74%	12	**3l**	80%
5	**3e**	80%	13	**3m**	83%
6	**3f**	90%	14	**3n**	95%
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.

substituent at the meta position, underwent the double oxygenation reaction to give resorcinol **3p**, although in diminished yield (entry 16).

Next, we aimed at achieving nonsymmetrical bisfunctionalization of PyrDipSi arenes via a sequential C−H acetoxylation/pivaloxylation reaction (Scheme 3). Thus, acetoxylation of **1a**

Scheme 3. Nonsymmetric Double-Fold C−H Oxygenation
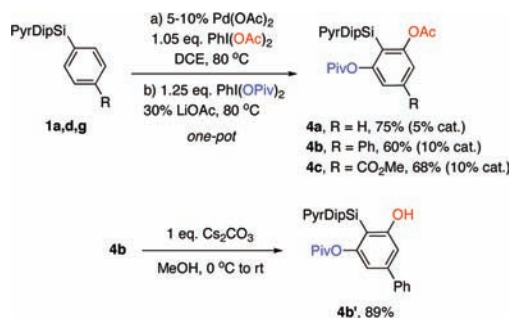
with PhI(OAc)$_2$ followed by a *one-pot* pivaloxylation reaction of the intermediate using PhI(OPiv)$_2$ in the presence of LiOAc (30%) furnished the corresponding product **4a** in good yield. This protocol enabled the preparation of differently substituted, orthogonally protected resorcinol derivatives **4a−c** in good yields. As expected, the acetyl group could be selectively cleaved in the presence of the pivaloxy group, thus producing monoprotected resorcinol derivative **4b′** in high yield (Scheme 3).

We also investigated the monopivaloxylation reaction of ortho-substituted PyrDipSi arenes (Scheme 4). It was found

Scheme 4. Pivaloxylation of Ortho-Substituted PyrDipSiAr
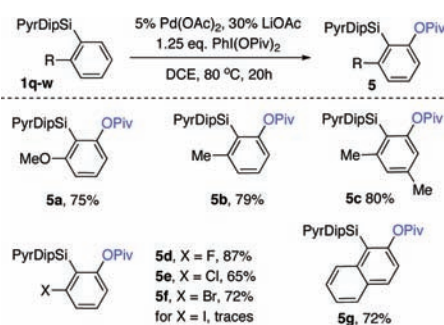
that various ortho-substituted PyrDipSi arenes **1q**−**w** underwent smooth pivaloxylation, producing the corresponding products **5** in good yields. Thus, methoxy (entry **5a**) and methyl (entries **5b** and **5c**) as well as fluorine (entry **5d**), chlorine (entry **5e**), and bromine (entry **5f**) were tolerated at the ortho position of the arene. Likewise, 1-PyrDipSi-naphthalene afforded the corresponding product **5g** in good yield. In contrast, the previously developed PyDipSi group did not appear to be efficient at all in the oxygenation of ortho-substituted arenes. Thus, *o*-Br-PyDipSi-benzene, under the same reaction conditions, did not produce detectable amounts of oxygenated product **5f′**, the PyDipSi analogue of **5f** (Scheme 4).[16] Although at this point the dramatic difference in the directing abilities of the PyrDipSi and PyDipSi groups remains unclear, it is most likely attributable to the different basicity/binding properties of these groups.[17]

Finally, we showed that the PyrDipSi group can be easily removed from the bisoxygenated products **4** to provide the corresponding protected resorcinols **6** or deuterated analogues **7** in almost quantitative yields (Scheme 5). Moreover, the PyrDipSi group can

Scheme 5. Modification of the PyrDipSi Group in the Obtained Resorcinols[a]
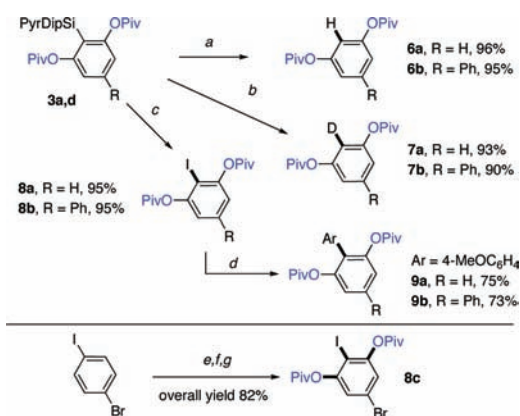
[a]Conditions: (a) HF, 1.2 equiv of AgF, MeOH/THF, rt. (b) HF, THF, 0 °C to rt, then 1.2 equiv of AgF, D₂O/THF, rt. (c) HF, THF, rt, then 2 equiv of NIS, 1.2 equiv of AgF, THF, rt. (d) 1.5 equiv of 4-MeOC₆H₄B(OH)₂, 5% Pd₂(dba)₃, 10% PPh₃, 2 equiv of K₃PO₄, dioxane, 100 °C. (e) 1.5 equiv of PyrDipSiH, 2.5% Rh₂(OAc)₄, 2 equiv of K₃PO₄, dioxane, 100 °C. (f) 5% Pd(OAc)₂, 2.5 equiv of PhI(OPiv)₂, 30% LiOAc, DCE, 80 °C. (g) HF, THF, rt, then 2 equiv of NIS, 1.2 equiv of AgF, THF, rt.

be easily substituted with iodide (entries **8a** and **8b**), which opens broad opportunities for subsequent modification. As an example, iodides **8** readily undergo Miyaura−Suzuki cross-coupling reactions, providing biaryls **9** in high yields. Furthermore, the synthetic

usefulness of the developed methodology is further illustrated by the efficient three-step conversion of 4-iodobromobenzene into the corresponding resorcinol **8c** (Scheme 5).[16]

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

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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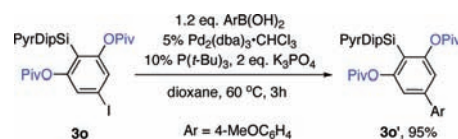
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(14) For transition-metal-catalyzed coupling of aryl iodides and silanes, see ref 7b and references therein. For optimization of the arylation reaction and preparation of **1**, see the Supporting Information.

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

PyrDipSi OPiv / PivO / 3o
1.2 eq. ArB(OH)$_2$
5% Pd$_2$(dba)$_3$·CHCl$_3$
10% P(*t*-Bu)$_3$, 2 eq. K$_3$PO$_4$
dioxane, 60 °C, 3h
Ar = 4-MeOC$_6$H$_4$
PyrDipSi OPiv / PivO / Ar / 3o', 95%

(16) See the Supporting Information for details.

(17) Sanford and co-workers did not observe a strong correlation between directing ability and basicity (for directing groups of different sizes) in the Pd-catalyzed C−H oxygenation reaction.[8h] Here, however, because of the steric similarity of PyrDipSi and PyDipSi, their basicity[18] could play a role in the reaction. Also, we observed that even catalytic amounts of pyridine suppress the second C−H oxygenation reaction (Table 1, entry 3). For the influence of the electron-withdrawing nature of pyrimidine on the Pd-catalyzed C−H trifluoromethylation reaction, see ref 10.

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