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PyDipSi - General and Easily Modifiable/Traceless Si-Tethered Directing Group for C-H Acyloxylation of Arenes

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Palladium-catalyzed, ligand-directed C-H functionalization has emerged as a powerful tool for direct conversion of arenes into a variety of valuable products.¹ Among these transformations, the Pd-catalyzed directed acetoxylation reactions of aromatic C-H bonds^{2,3} are particularly attractive as they allow for direct formation of oxygenated arenes.⁴ A variety of directing groups, such as pyridine,^{3a,c,g} pyrimidine,^{3e,3j} pyrazole,^{3e} oxazoline,^{3d,e} amide,^{3f,k} and oxime ether,^{3d} have been shown to be efficient in these reactions. However, despite the achieved high yields and selectivities, the acyloxylation reactions somewhat lack their generality, as the majority of the directing groups, necessary for the selective transformation, often are not easily removable from the products, thus limiting these methodologies to particular types of substrates (eq 1). Herein we wish to report a pyridyl-diisopropylsilyl (PyDipSi) as a new silicon-tethered directing group, which allows for efficient acetoxylation/pivaloxylation of aromatic C-H bonds. Most importantly, this directing group can efficiently be removed, or converted into a variety of other functional groups (eq 2).

(1)

(2)

Our approach on the design of the removable directing group is based on the employment of a temporary silicon tether to connect a good metal-coordinating group for C-H activation with an aromatic substrate of interest. We thought that employment of a silicon-tethered directing group^{5,6} would bring a certain advantage, since it is easily removable from the products of C-H functionalization. We chose pyridine as a platform for our new group design, as it is known to be superior in coordinating palladium in directed C-H activation processes.^{1j} To this end, we aimed at establishing a suitable silicon tether for the pyridine group. Accordingly, substrate **A** (Fig. 1), containing a pyridyldimethylsilyl directing group, previously developed by Yoshida⁵ for highly regio- and stereoselective Pd-catalyzed Heck arylation of vinylsilanes,^{5b} was tested first. However, the reaction with $\text{PhI}(\text{OAc})_2$ in the

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presence of 10 mol% Pd(OAc)₂ in PrCN at 80 °C **3a** resulted in total decomposition of the starting arylsilane **A** with no formation of the desired product (Table 1, entry 1). To further optimize the silicon tether, the silacyclopentane (**B**) and diisopropylsilyl (**1a**) derivatives were synthesized (Fig. 1). Similarly to **A**, compound **B** appeared to be not stable, as well (Table 1, entry 2). However, we were pleased to find that diisopropylsilyl derivative **1a** was more stable toward PhI(OAc)₂ at 80 °C, producing the desired product **2a** in 15% yield (entry 3). Increasing the temperature to 100 °C led to the slight improvement of the reaction outcome (entry 4). Addition of stoichiometric amount of Cu(OAc)₂ gave only traces of product (entry 5). Surprisingly, employment of 1 equivalent AgOAc⁷ resulted in a dramatic improvement of the reaction, affording the desired **2a** in 70% yield. Furthermore, performing the reaction at slightly higher temperature (100 °C) resulted in a better yield of **2a** (80%, entry 7). Finally, switching solvent to dichloroethane provided the highest yield (85%) of the product at lower (80 °C) temperature (entry 8). It should be mentioned that a synthesis of arylsilanes, containing PyDipSi directing group is straightforward (Scheme 1). First, pyridyldiisopropylsilane is obtained in excellent yield from commercially available 2-bromopyridine and diisopropylsilylchloride. Next, the hydride-substitution reaction in pyridyldiisopropylsilane with *in situ* generated aryllithium reagents affords arylsilanes **1** in high yields (Scheme 1).

With the optimized conditions in hand, the generality of the Pd-catalyzed acyloxylation reaction of PyDipSi-containing arenes **1** was examined (Table 2). To our delight, it was found that this transformation is highly efficient for the exclusive mono-acyloxylation of a wide range of substrates. Thus, arylsilanes **2a–x** possessing acetoxy-⁸ and even more synthetically valuable pivaloxy- group⁹ were synthesized in good to excellent yields. A variety of functional groups, such as OMe (entries **2c–e**), F (entries **2q**, **2t**), Cl (entries **2p**, **2r**, **2u**), Br (entries **2o**, **2s**), pinacol-protected aldehyde (entry **2v**), CO₂Et (entry **2w**), and CON(*i*-Pr)₂ (entry **2x**), were perfectly tolerated under these reaction conditions. Notably, substrates containing *meta* substituents displayed excellent regio-selectivity in both acetoxylation and pivaloxylation reactions, producing the corresponding oxygenated products as single regioisomers in high yields (**2c**, **2f–h**, **2n**, **2o**, **2t**, **2u**). Remarkable site selectivity was also observed in acetoxylation and pivaloxylation of 2-naphtyl derivatives, yielding the desired compounds as sole isomers (entries **2l** and **2m**).

Our initial mechanistic studies indicated that electron-rich arenes were acyloxylated faster than electron-deficient ones.^{10–11} In addition, the substantial value of k_H/k_D (6.7) was observed in intramolecular KIE studies of the pivaloxylation reaction of **1a–d₁** (Scheme 2).¹² It is believed that the present Pd-catalyzed acyloxylation reaction follows the C-H activation pathway.^{3b,e,h,i,,13}

Naturally, after the development of the efficient directed C-H acyloxylation of arylsilanes, we explored further transformations of the PyDipSi group of the product **2g** (Scheme 3). First, it was found that the reaction of **2g** with AgF¹⁴ in methanol resulted in efficient deprotection of the directing group, affording tolylpivalate **3** in 92% yield. Moreover, treatment of **2g** with AgF in THF/D₂O produced the deuterated arylpivalate **3-d₁** in 95% yield. Remarkably, a combination of AgF/NIS allowed for a quantitative conversion of the PyDipSi group into iodide functionality. The latter transformation, taken together with the installation and pivaloxylation steps, represents a formal 3-step *ortho*-oxygenation of 3-iodotoluene.¹⁵ Furthermore, **2g** was converted into a synthetically valuable arylboronate **5**¹⁶ in 94% yield via a one-pot borodesilylation with BCl₃/protection with pinacol sequence.¹⁷ In addition, borodesilylation of **2g**, followed by oxidation in the presence of H₂O₂/NaOH, produced substituted catechol **6** in excellent yield. Finally, it was found that the acetoxy-derivative **2a** underwent an efficient Hiyama-Denmark cross-coupling¹⁸ with

phenyl iodide and subsequent hydrolysis of acetoxy-group, providing 2-phenylphenol **7** in 93% yield (Scheme 3).

In summary, we have shown that PyDipSi group can serve as new, general directing group for the Pd-catalyzed acyloxylation of arenes, providing access to a variety of acetoxylation and pivaloxylation aromatic compounds in good yields. Most importantly, it was shown that this newly designed directing group could efficiently be cleaved, as well as converted into other valuable functional groups, such as iodide and boronate. Finally, borodesilylation of this directing group under oxidative conditions allows for preparation of substituted catechol, whereas the Hiyama-Denmark coupling provides direct access to *ortho*-hydroxybiphenyl.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Substrates for optimization of silicon tether.

Scheme 1.
Synthesis and Installation of PyDipSi Directing Group

Scheme 2.
Intramolecular Kinetic Isotope Effect Studies

Scheme 3.
Further Transformations of PyDipSi Group

Table 1

Optimization of *ortho*-Acetoxylation Reaction Conditions

entry	substrate	additive (equiv)	solvent	T, °C	yield, % ^a
1	A	none	PrCN	80	<i>b</i>
2	B	none	PrCN	80	<i>b</i>
3	1a	none	PrCN	80	15 (2a) ^b
4	1a	none	PrCN	100	30 (2a) ^b
5	1a	Cu(OAc) ₂ (1)	PrCN	100	trace (2a)
6	1a	AgOAc (1)	PrCN	80	70 (2a)
7	1a	AgOAc (1)	PrCN	100	80 (2a)
8	1a	AgOAc (1)	DCE	80	85 (2a)

^aNMR yield.^bDecomposition of starting arylsilane was observed.

Table 2

Pd-Catalyzed *ortho*-Acyloxylation of Arylsilanes ^{a,b}

2a 80% R=Ac	2c 60%	2d 84% R=Ac
2b 80% R=Piv		2e 78% R=Piv
<hr/>		
2f 88% R ¹ Ac Me	2g 93% R ¹ Piv Me	2h 79% R ¹ Piv Ph
2i 93% R ¹ Ac Me	2j 78% R ¹ Piv Me	2k 81% R ¹ Piv Ph
<hr/>		
2l 90% R=Ac	2m 83% R=Piv	2n 90%
		2o 60%
<hr/>		
2p 64% R Hal Ac Cl	2q 82% R Hal Piv F	2r 74% R Hal Piv Cl
2s 77% R Hal Piv Br		
<hr/>		
2v 68%	2w 67%	2x 79%

^a Isolated yields.^b See Supporting Information for details.