

# Synthesis of Unsymmetrical *o*-Biphenols and *o*-Binaphthols via Silicon-Tethered Pd-Catalyzed C–H Arylation

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## ABSTRACT



A mild, practical, and efficient method for the synthesis of unsymmetrical *o*-biphenols (including *o*-phenol-naphthols and *o*-binaphthols) has been developed. Unsymmetrical bis-aryloxy silanes, which were readily prepared in a semi-one-pot fashion, underwent the Pd-catalyzed intramolecular arylation followed by a routine TBAF desilylation step to furnish valuable unsymmetrical biphenols without necessity of isolation of seven-membered intermediates. The excellent functional group tolerance allows for synthesis of a variety of functionalized *o*-biphenols and *o*-binaphthols from easily available starting materials.

The *o*-biphenol framework is a key unit found in natural and synthetic bioactive molecules<sup>1</sup> and in various ligand families.<sup>2</sup> Due to the favorable single-electron phenolic oxidation,<sup>3</sup> the strategies toward assembly of biphenols largely concentrate on the oxidative phenol coupling reactions. Nonetheless, the synthesis of biphenols via these approaches is limited to symmetrical and electron-rich

systems, often employing toxic heavy metal oxidants.<sup>4</sup> The synthesis of unsymmetrical biphenols via oxidative cross-coupling of phenols suffers from significant amounts of self-coupling byproducts and undesired oligomers.<sup>3c,5</sup> There are a few reports on the synthesis of unsymmetrical biphenols employing a silicon tether,<sup>6</sup> yet these reactions are limited to electron-rich substrates. Recently, we<sup>7</sup> reported the Pd-catalyzed arylation of phenols<sup>8</sup> via an easy-on and -off silicon-tethered strategy,<sup>9</sup> which allowed assembly of unsymmetrical biphenol **C** via further oxidation of a six-membered

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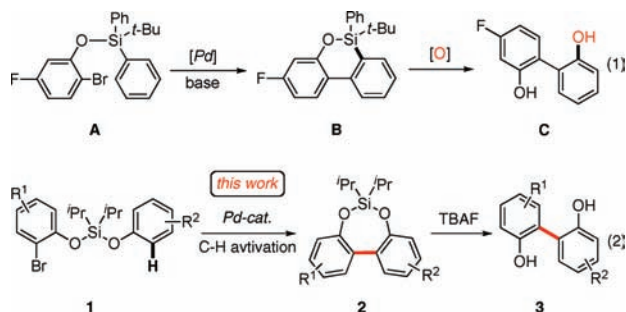
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oxasilacycle **B** (eq 1). However, oxidation of the C–Si bond required harsh conditions and is limited to the particular substitution pattern. Herein, we wish to report a mild, general, and efficient method for the synthesis of unsymmetrical biphenols **3** via intramolecular Pd-catalyzed C–H arylation<sup>7,10</sup> of **1** to form **2**, followed by a routine desilylation step (eq 2).



We hypothesized that if intramolecular C–H arylation<sup>10f–k</sup> of easily available bis-aryloxy silane **1** would be efficient to form seven-membered<sup>11</sup> silacycles **2**, it would provide an easy route to biphenols **3** via a simple deprotection. To test this hypothesis, we subjected **1a** to the previously reported arylation conditions.<sup>7</sup> However, under these conditions only reductive debromination occurred, with trace amounts of **2a** produced. Fagnou showed the possibility of seven-membered ring formation employing bulky electron-deficient bidentate ligands combined with palladium acetate.<sup>10i,j</sup> Still, employment of these conditions did not give any arylation product in the silicon-tethered case, as only reductive product **4** was obtained. After extensive screening of reaction parameters, including palladium sources, ligands, bases, and solvents,<sup>12</sup> we found that bulky electron-deficient monodentate ligand P(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> in nonpolar solvents is capable of suppressing the C–Br reduction process. Employment of bases K<sub>3</sub>PO<sub>4</sub> and Ag<sub>2</sub>CO<sub>3</sub> resulted in higher efficiency of arylation (Table 1, entries 2, 3). Application of additives did not cause improvement (entries 4, 5). Gratifyingly, the combination of K<sub>3</sub>PO<sub>4</sub>

**Table 1.** Optimization of Reaction Conditions<sup>a</sup>

no.	R	base (equiv)	additive (equiv)	yield, % <sup>b</sup>	<b>2:4</b> <sup>c</sup>
1	H ( <b>1a</b> )	K <sub>2</sub> CO <sub>3</sub> <sup>d</sup> (2)	none	25	5:1
2	<b>1a</b>	K <sub>3</sub> PO <sub>4</sub> (2)	none	31	14:1
3	<b>1a</b>	Ag <sub>2</sub> CO <sub>3</sub> (2)	none	49	15:1
4	<b>1a</b>	K <sub>3</sub> PO <sub>4</sub> (2)	PivOH (0.3)	42	15:1
5	<b>1a</b>	K <sub>3</sub> PO <sub>4</sub> (2)	3-NO <sub>2</sub> -Py (0.3)	43	17:1
6	<b>1a</b>	K <sub>3</sub> PO <sub>4</sub> (2)	none	66	26:1
7	<b>1a</b>	Ag <sub>2</sub> CO <sub>3</sub> (0.5)	none	73	41:1
8	<b>1a</b>	K <sub>3</sub> PO <sub>4</sub> (1)	Ag <sub>2</sub> CO <sub>3</sub> (1.5)	78	32:1
9	<b>1a</b>	K <sub>3</sub> PO <sub>4</sub> ( <b>2</b> )	Ag <sub>2</sub> CO <sub>3</sub> ( <b>1</b> )	<b>85 (73)</b>	<b>34:1</b>
10	<i>p</i> -OMe ( <b>1b</b> )	K <sub>3</sub> PO <sub>4</sub> (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	(70)	>99:1
11	<i>p</i> -CF <sub>3</sub> ( <b>1c</b> )	K <sub>3</sub> PO <sub>4</sub> (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	(90)	>99:1
12	<i>o</i> -Me ( <b>1d</b> )	K <sub>3</sub> PO <sub>4</sub> (2)	Ag <sub>2</sub> CO <sub>3</sub> (1)	(80)	100:0

<sup>a</sup> See Supporting Information for details. <sup>b</sup> GC yields of **2**, isolated yields are in parentheses. <sup>c</sup> GC ratio. <sup>d</sup> *p*-Xylene was used as a solvent.

and Ag<sub>2</sub>CO<sub>3</sub> dramatically improved the yield and the arylation/reduction ratio, resulting in 73% isolated yield of **2a** and high arylation/reduction ratio (entry 9). Next, these conditions were tested on substrates **1b–d** (entries 10–12). In all cases, the yields were high with negligible amounts of debromination byproducts **4** obtained. Naturally, the standard TBAF deprotection protocol afforded **3a** quantitatively.<sup>12</sup> Semi-one-pot procedure from **1a** to **3a** demonstrated the same efficiency (Table 2, entry 1). For easier separation, all other biphenols were isolated as acetates without loss of the yields.

Next, the scope of this protocol toward synthesis of unsymmetrical biphenols, phenol-naphthols, and binaphthols was examined (Table 2). Gratifyingly, it was found that this method is general and efficient, regardless on the electronic properties of substituents on either phenol ring. Thus, a variety of functional groups, such as MeO, F, Cl, CF<sub>3</sub>, CHO, NO<sub>2</sub>, and even Br, can be perfectly tolerated under these reaction conditions producing the unsymmetrical biphenol acetates in 3-step semi-one-pot in high to excellent overall yields. As expected, *meta*-substituted phenols gave mixtures of regioisomers. The regioselectivity was affected by both electronics and sterics. For example, although CF<sub>3</sub> and Me groups are comparable in size, the substrate **1k**, possessing an electron-withdrawing group (R = CF<sub>3</sub>), reacted more regioselectively compared to Me-substituted **1j**. Expectedly, the steric effect on the regioselectivity of arylation has also been observed. Thus, differently O-protected resorcinol

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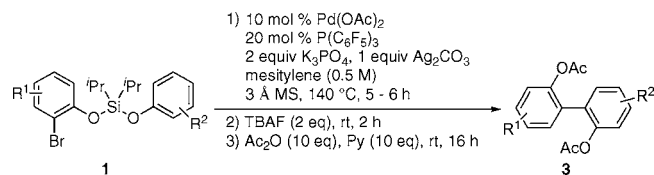
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**Table 2.** Synthesis of Unsymmetrical *o*-Biphenols, *o*-Phenol-naphthols, and *o*-Binaphthols via Silicon-Tethered C–H Arylation (3-Steps, Semi-one-pot)<sup>a,b</sup>



no.	substrates (1)	products (3)	yield, [%]	no.	substrates (1)	products (3)	yield, [%]
1			<b>a</b> 72 (100) <sup>c</sup>	14			<b>n</b> 66 <sup>e,f</sup> (9:1)
2			<b>b</b> 81	15			<b>o</b> 72
3			<b>e</b> 82	16			<b>p</b> 61
4			<b>f</b> 86	17			<b>q</b> 89
5			<b>c</b> 83	18			<b>r</b> 86
6			<b>g</b> 74	19			<b>s</b> 96
7			<b>h</b> 51	20			<b>t</b> 83
8			<b>d</b> 68	21			<b>u</b> 89
9			<b>i</b> 56 <sup>d</sup>	22			<b>v</b> 80
10			<b>j</b> 72 <sup>e</sup> (2.6:1)	23			<b>w</b> 90
11			<b>k</b> 80 <sup>e</sup> (7:1)	24			<b>x</b> 77
12			<b>l</b> 79 <sup>e</sup> (1:1.2)	25			<b>y</b> 97 (1.7:1)
13			<b>m</b> 67 <sup>e,f</sup> (5:1)				<b>y'</b>

<sup>a</sup> Isolated yields. <sup>b</sup> To simplify isolation, the biphenols were further converted to their corresponding acetates. <sup>c</sup> Two-step semi-one-pot procedure gave unprotected 2,2'-biphenol in 72% yield; yield in the parentheses is desilylation from **2a** to **3a**. <sup>d</sup> <sup>1</sup>H NMR yield (against CH<sub>2</sub>Br<sub>2</sub> as an internal standard). <sup>e</sup> Major regioisomer shown. <sup>f</sup> 4 equiv of TBAF, 15 equiv of Ac<sub>2</sub>O, and 15 equiv of pyridine were used; **3m** = **3n**.

provided varied regioselectivity increasing with bulkier protecting groups (**1l** < **1m** < **1n**). 1-Naphthols and 2-naphthols could efficiently be employed in this arylation reaction, as well (entries 15–25). Thus, differently substituted 2-bromophenols underwent smooth arylation with 1-naphthol producing unsymmetrical phenol-naphthols in 61–96% yields. The unsymmetrical mixed 1- and 2-naphthol products (**3v**, **3w**) were also obtained highly efficiently. It deserves mentioning that **3w** represents the core structure of a series of small molecule inhibitors of Stat3 oncogene.<sup>1c</sup> Arylation of **1y** afforded a 1.7:1 mixture of unsymmetrical 2,2'-BINOL<sup>13</sup> derivative (**3y**) and 1,2'-binaphthyl-2,3'-diol derivative (**3y'**) in excellent overall yield (entry 25).

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In summary, a mild, practical, and efficient method for the synthesis of symmetrical and unsymmetrical *o*-biphenols, *o*-phenol-naphthols, and *o*-binaphthols has been developed. The method involves a Pd-catalyzed intramolecular C–H arylation of unsymmetrical bis-aryloxy silanes to give the seven-membered oxasilacycles, which via a consecutive routine TBAF deprotection furnishes valuable unsymmetrical *o*-biphenols and *o*-binaphthols. The method allows for easy synthesis of a wide variety of functionalized symmetrical and unsymmetrical *o*-biphenols and *o*-binaphthols from easily available starting materials.

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

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