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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 staring materials.

The *o*-biphenol framework is a key unit found in natural and synthetic bioactive molecules[1] and in various ligand families.[2] Due to the favorable single-electron phenolic oxidation,[3] 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.[4] The synthesis of unsymmetrical biphenols via oxidative cross-coupling of phenols suffers from significant amounts of self-coupling byproducts and undesired oligomers.[3c,5] There are a few reports on the synthesis of unsymmetrical biphenols employing a silicon tether,[6] yet these reactions are limited to electron-rich substrates. Recently, we[7] reported the Pd-catalyzed arylation of phenols[8] via an easy-on and -off silicon-tethered strategy,[9] which allowed assembly of unsymmetrical biphenol **C** via further oxidation of a six-membered

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(7) Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844.

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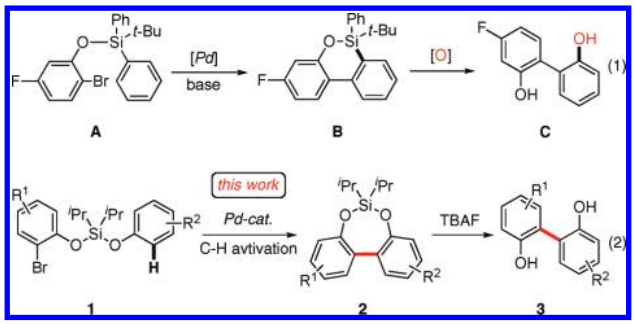
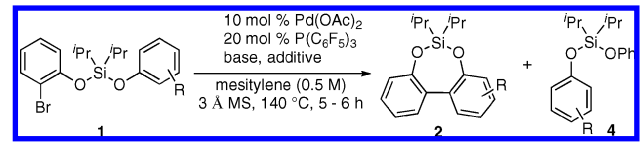
oxasilacylce **B** (eq 1). However, oxidation of the C−Si bond required harsh conditions and is limited to the particular substitution pattern. Herein, we wish to report a mild, general, and efficient method for the synthesis of unsymmetrical biphenols **3** via intramolecular Pd-catalyzed C−H arylation[7,10]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



We hypothesized that if intramolecular C−H arylation[10f−k] of easily available bis-aryloxy silane **1** would be efficient to form seven-membered[11] 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.[7] 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.[10i,j] 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,[12] we found that bulky electron-deficient monodentate ligand $P(C_6F_5)_3$ in nonpolar solvents is capable of suppressing the C−Br reduction process. Employment of bases K_3PO_4 and Ag_2CO_3 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_3PO_4 and Ag_2CO_3 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.[12] 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.

Table 1. Optimization of Reaction Conditions[a]



no.	R	base (equiv)	additive (equiv)	yield, %[b]	**2**:**4**[c]
1	H (**1a**)	K_2CO_3[d] (2)	none	25	5:1
2	**1a**	K_3PO_4 (2)	none	31	14:1
3	**1a**	Ag_2CO_3 (2)	none	49	15:1
4	**1a**	K_3PO_4 (2)	PivOH (0.3)	42	15:1
5	**1a**	K_3PO_4 (2)	3-NO_2-Py (0.3)	43	17:1
6	**1a**	K_3PO_4 (2) Ag_2CO_3 (0.5)	none	66	26:1
7	**1a**	K_3PO_4 (2) Ag_2CO_3 (1.5)	none	73	41:1
8	**1a**	K_3PO_4 (1) Ag_2CO_3 (1)	none	78	32:1
9	**1a**	**K_3PO_4 (2) Ag_2CO_3 (1)**	**none**	**85 (73)**	**34:1**
10	*p*-OMe (**1b**)	K_3PO_4 (2) Ag_2CO_3 (1)	none	(70)	>99:1
11	*p*-CF_3 (**1c**)	K_3PO_4 (2) Ag_2CO_3 (1)	none	(90)	>99:1
12	*o*-Me (**1d**)	K_3PO_4(2) Ag_2CO_3 (1)	none	(80)	100:0

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

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_3, CHO, NO_2, 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_3 and Me groups are comparable in size, the substrate **1k**, possessing an electron-withdrawing group (R = CF_3), 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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(9) (a) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054. For a review, see, for example: (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813.

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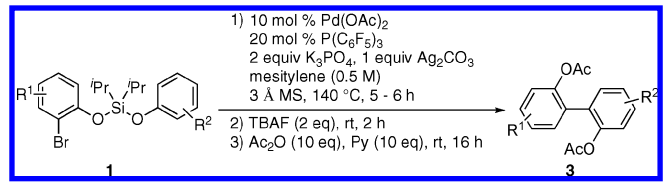
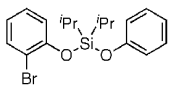
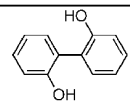
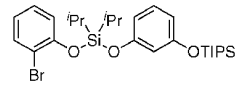
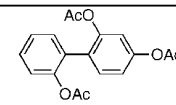
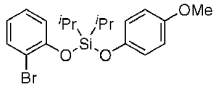
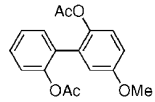
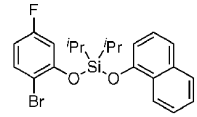
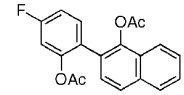
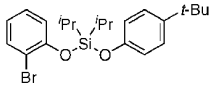
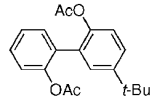
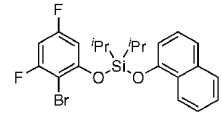
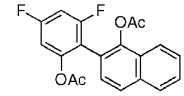
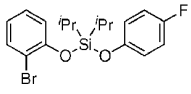
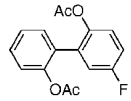
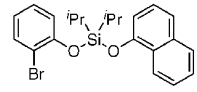
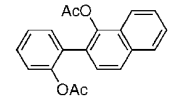
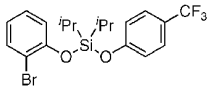
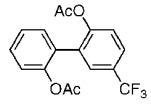
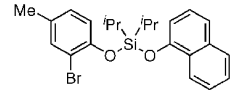
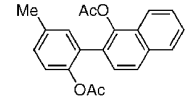
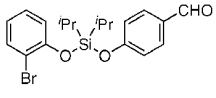
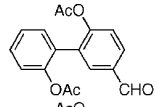
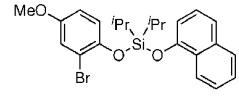
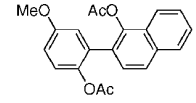
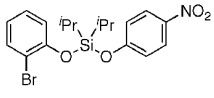
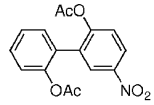
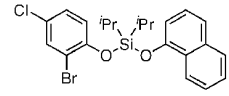
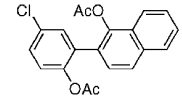
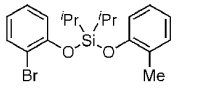
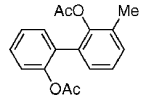
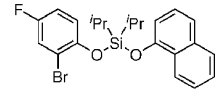
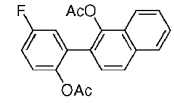
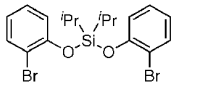
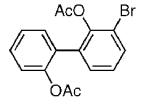
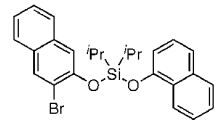
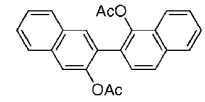
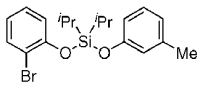
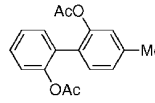
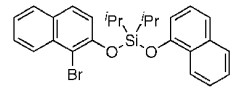
(11) For challenges in formation of a seven-membered ring via C−H arylation, see refs 10i, j.

(12) See the Supporting Information for details.

Table 2. Synthesis of Unsymmetrical *o*-Biphenols, *o*-Phenol-naphthols, and *o*-Binaphthols via Silicon-Tethered C−H Arylation (3-Steps, Semi-one-pot)[a,b]



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

[a] Isolated yields. [b] To simplify isolation, the biphenols were further converted to their corresponding acetates. [c] Two-step semi-one-pot procedure gave unprotected 2,2′-biphenol in 72% yield; yield in the parentheses is desilylation from **2a** to **3a**. [d] ^{1}H NMR yield (against CH_2Br_2 as an internal standard). [e] Major regioisomer shown. [f] 4 equiv of TBAF, 15 equiv of Ac_2O, 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.[1c] Arylation of **1y** afforded a 1.7:1 mixture of unsymmetrical 2,2′-BINOL[13] derivative (**3y**) and 1,2′-binaphthyl-2,3′-diol derivative (**3y′**) in excellent overall yield (entry 25).

(13) For a review, see 1a For examples, see: (a) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137. (b) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856. (c) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927. (d) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082. (e) Hovorka, M.; Ščigel, R.; Guterová, J.; Tichý, M.; Závada, J. *Tetrahedron* **1992**, *48*, 9503.

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 staring 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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