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Article

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Catalytic Reductive ortho-C–H Silylation of Phenols with Traceless, Versatile Acetal Directing Groups and Synthetic Applications of Dioxasilines

Yuanda Hua,[§] Parham Asgari,[§] Thirupataiah Avullala, and Junha Jeon*

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ABSTRACT: A new, highly selective, bond functionalization strategy, achieved via relay of two transition metal catalysts and use of traceless acetal directing groups, has been employed to provide facile formation of C–Si bonds, and concomitant functionalization of a silicon group, in a single vessel. Specifically, this approach involves the relay of Ir-catalyzed hydrosilylation of inexpensive and readily available phenyl acetates, exploiting disubstituted silyl synthons, to afford silyl acetals and Rh-catalyzed *ortho*-C–H silylation to provide dioxasilines. A subsequent nucleophilic addition to silicon removes the acetal directing groups and directly provides unmasked phenol products and, thus, useful functional groups at silicon achieved in a single vessel. This traceless acetal directing group strategy for catalytic *ortho*-C–H silylation of phenols was also successfully applied to preparation of multi-substituted arenes. Remarkably, a new, formal α-chloroacetyl directing group has been developed which allows catalytic reductive C–H silylation of sterically hindered phenols. In particular, this new method permits to access to highly versatile and nicely differentiated 1,2,3-trisubstiuted arenes that are difficult to access by other catalytic routes. In addition, the resulting dioxasilines can serve as chromatographically stable halosilane equivalents which allow not only removal of acetal directing groups, but also introduce useful functional groups leading to silicon-bridged biaryls. We demonstrated that this catalytic C–H bond silylation strategy has powerful synthetic potential by creating direct applications of dioxasilines to other important transformations, examples of which include aryne chemistry, Au-catalyzed direct arylation, sequential orthogonal cross-couplings, and late-stage silylation of phenolic bioactive molecules and BINOL scaffolds.

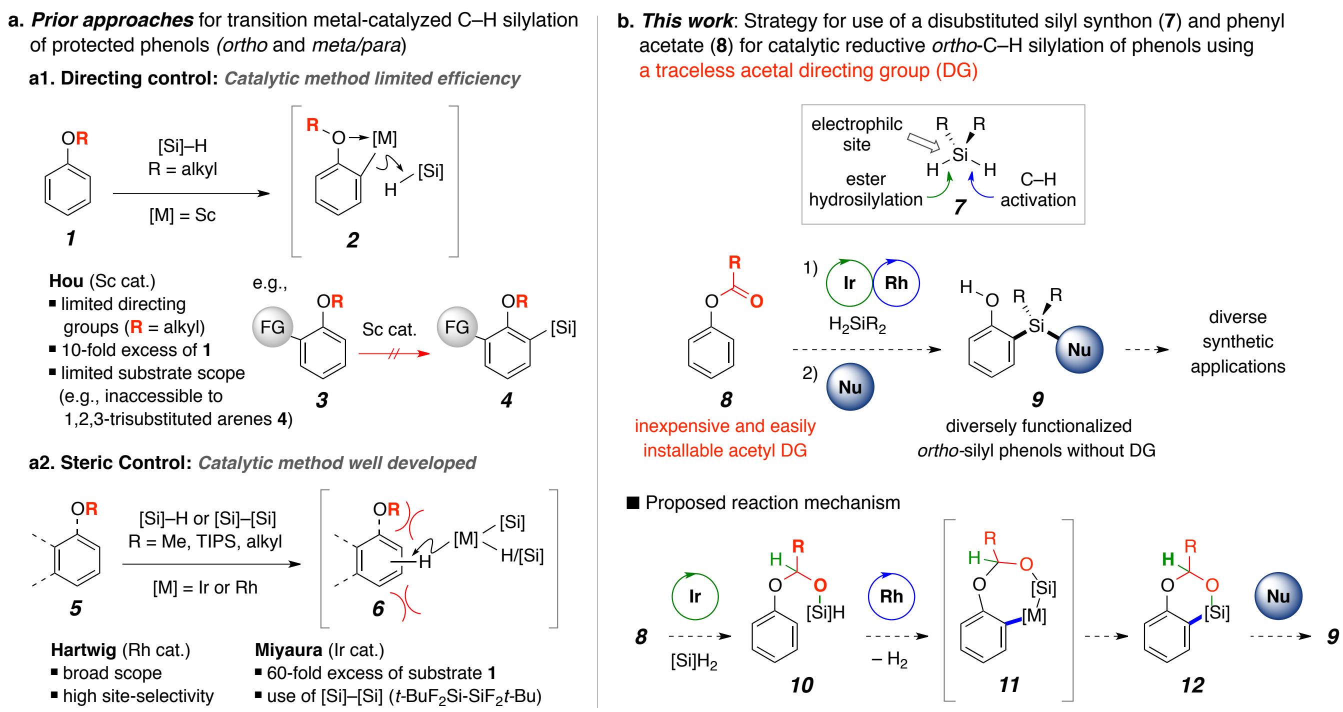
KEYWORDS: *phenol, C–H activation, silylation, silyl acetal, traceless directing group*

INTRODUCTION

Interest in organosilane chemistry has increased rapidly in recent years,[1] including development of silicon-based materials[2] and many biomedically relevant agents.[1a, 3] The recent expanding use of these compounds has included their participation in a wide variety of chemical transformations. Such synthetic activities include silicon-based cross-coupling reactions,[4] oxidations,[5] silanol hydrogen bond donor catalysts,[6] and as directing groups for C–H functionalization.[7] In particular, selective silylative functionalization of phenols is important because many bioactive natural products and unnatural congeners, including medicinally important molecules, contain phenolic moieties that contribute to their biological activities.[8] In light of this fact, there is a fundamental need for development of more efficient catalytic strategies that provide site-selective access to this motif from readily available precursors. Thus far, several very useful phenol silylation methods have been developed: 1) a sequence of (non-)selective bromination, *O*-silylation, and lithium-halogen exchange followed by retro-Brook reactions,[9] 2) metal-catalyzed silylation of prefunctionalized, protected halopheonls,[10] 3) directed *ortho*-metalation (D*o*M)/silylation of phenols,[11] and 4) KO*t*-Bu-catalyzed silylation of aromatic heterocycles.[12] These methods offer excellent site-selectivity. However, limitations in these systems exist as they generally require a (sub-)stoichiometric amount of basic reagents, thereby displaying modest functional group compatibility, or involve a limited substrate scope and/or moderate yields.

Significant advances to transition metal-catalyzed selective C–H bond functionalizations for preparing structurally diverse, bioactive molecules.[13] have been made through directing group-assisted[13a, 13g, 13h, 13j, 13k, 13p, 14] or direct[13d, 13f] C–H bond activation strategies. Although directing group-assisted C–H bond functionalization strategies can achieve the desired transformation with high reactivity and selectivity, directing groups are often difficult to install and manipulate after processes are completed. Additional functional group interconversions, typically involving redox adjustment, are usually carried out under harsh reaction conditions, if indeed removal of the directing group is at all possible. To resolve these limitations, strategies for traceless directing group-assisted C–H functionalization have been developed.[7a-d, 15] For instance, Gevorgyan[7a, 7b, 16] and Ge[7c] reported remarkable C–H *ortho*-alkenylation, oxygenation, and carboxylation of phenols with silanol traceless directing groups. However, a traceless directing group approach for *ortho*-C–H silylation has not been reported to date.

Scheme 1. Catalytic, Site-Selective C–H Silylation of Phenols and Phenol Derivatives



Although diverse catalytic arene dehydrogenative silylations have been developed to prepare valuable organosilanes,[17] surprisingly, only one example of catalytic *ortho*-C–H silylation of phenol derivatives has been developed (Hou group, 2011)[17h] as depicted in Scheme 1.a1. While this Hou's pioneering work associated with scandium metallocene-catalyzed directed *ortho*-silylation of anisoles exhibited excellent site-selectivity, despite requiring a highly strained, four-membered metallacycle **2**, it requires excess anisole substrates (10-fold) and has somewhat limited substrate scope (inaccessible to 1,2,3-trisubstituted arenes, **3** to **4**). Furthermore, the removal of alkyl masking groups in the presence of silanes is not trivial. Miyaura[18] and Hartwig[19] have reported Rh and Ir-catalyzed steric-controlled *meta- or para*-silylation of anisoles, respectively (Scheme 1.a2). While Miyaura's Ir-catalyzed silylation required 60-fold excess of anisole substrates **5**, the method developed by Hartwig showed broad substrate scope and high site-selectivity, yet the removal of a hydroxyl masking group in the presence of silanes is again questionable.

We recently demonstrated the design and application of a single-pot, catalytic (exhaustive) reductive C_{sp2}–H and C_{sp3}–H silylation and silanolization of aromatic carboxylic acid derivatives.[20] In these studies, we established the mechanism for the hydridosilyl *O,O*-silyl acetal–directed catalytic C–H silylation, where the turnover-determining step is an irreversible substrate-metal coordination that proceeds to C–H bond cleavage.[1a, 21] To develop a more general, catalytic method to improve arene *ortho*-C–H silylation of phenols, we have designed a novel approach to sequential catalytic reductive C–H silylation. This process centers on post-installation of other useful moieties on a silicon center that includes spontaneous removal of directing groups by employing versatile silyl acetal directing groups. Hence, we specifically address the aforementioned challenges and limitations in synthesis of diversely functionalized silyl phenols and significantly expand the versatility of C–H functionalization (Scheme 1.b). Herein, we report a single-pot sequential metal-catalyzed reductive *ortho*-C–H silylation of phenols, with traceless mixed acetal directing groups, utilizing inexpensive and easily installable acetyl formal directing group and readily available catalyst and silane. This strategy involves the relay of Ir-catalyzed hydrosilylation of phenyl acetates **8**[22] exploiting disubstituted silyl synthons **7** to afford silyl acetals **10** and Rh-catalyzed C–H silylation[17b, 17c, 17e, 17n, 17q, 17r] to provide dioxasilines **12**. A subsequent nucleophilic addition to silicon removes the acetal directing groups and provides unmasked phenol products **9** in a single vessel. Importantly, the resulting *ortho*-silyl phenols **9** are useful synthetic vehicles for direct applications to many other important transformations, examples of which include: harnessing aryne chemistry;[23] Au-catalyzed oxidative cross-coupling;[4d, 4e] synthesis of dibenzosiloles;[24] and catalytic synthesis of a chiral BINOL[25] scaffold.

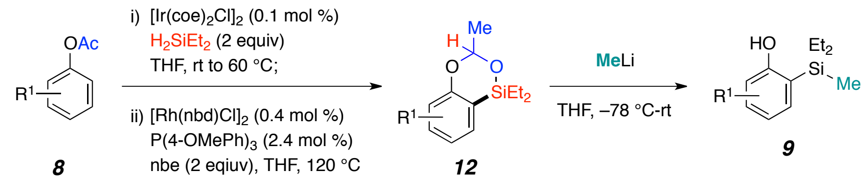
RESULTS AND DISCUSSION

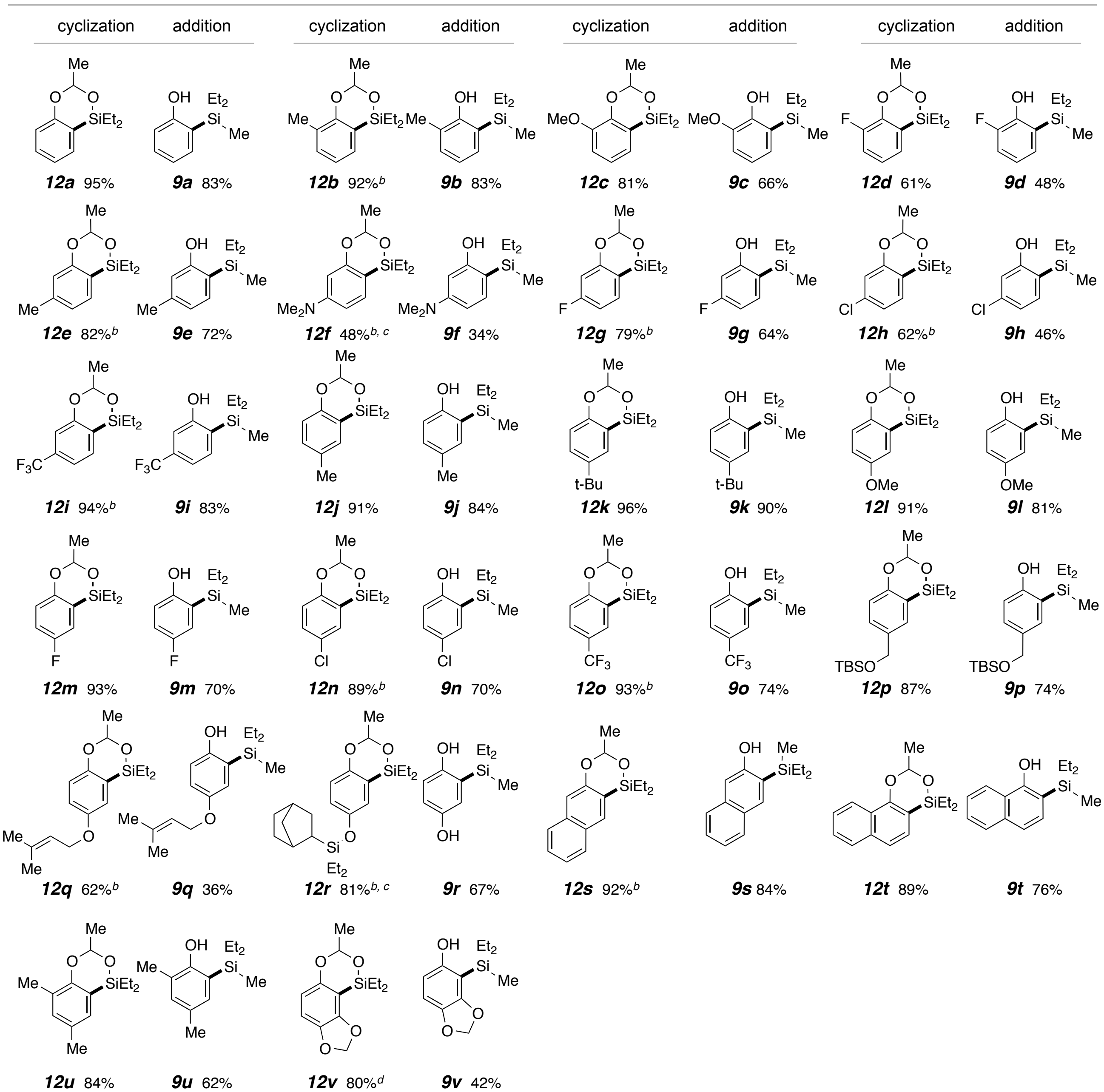
A Single-Pot Catalytic Reductive *ortho*-C–H Silylation of Phenols with Traceless Mixed *O,O*-Acetal Directing group. Prevalent directed C–H bond functionalizations proceed through five- or six-membered cyclometallated intermediates.[4a] However, our initial concern was that our proposed process conceivably requires a rather unfavorable rhodacycloheptane intermediate **11** (Scheme 1.b). To address this concern, we demonstrated the strategy for traceless, formal acetate directing group-assisted *ortho*-silylation of phenols (Table 1). Gratifyingly, the single-pot, two-step strategy involving Ir-catalyzed ester hydrosilylation (0.1 mol % of $[Ir(coe)Cl]_2$]) and Rh-catalyzed C–H bond silylation using $[Rh(nbd)Cl]_2$ (0.4 mol %) and monodentate phosphine P(4-

MeOPh)$_3$)[17e] (2.4 mol %) directly produced benzodioxasiline **12a** in excellent yield (95%). A distinctive feature of this mixed *O,O*-acetal directed Rh-catalyzed C–H silylation was essentially complete reaction within 15 min, despite the fact that a putative cyclometallated rhodacycloheptane intermediate might be involved.

We then investigated the scope of the single-pot sequential catalytic reductive *ortho*-C–H silylation of phenyl acetates (Table 1). Phenyl acetates bearing a substituent at the *ortho* position (i.e., methyl, methoxy, fluoro) underwent the C–H silylation to provide benzodioxasilines (**12b**-**12d**) in good yields. The reaction of phenyl acetates possessing a *meta* substituent (**12e**-**12i**) exhibited high site selectivity favoring silylation at less congested C–H bonds (>20:1 regioselectivity). *para*-Substituted phenyl acetates holding methyl, *t*-butyl, methoxy, halogens (F and Cl), trifluoromethyl, silyl blocking group (TBS), and trisubstituted alkene groups were tolerated by the reaction conditions to afford benzodioxasilines (**12j**-**12q**). Interestingly, 4-hydroxyphenyl acetate initially afforded C–H silylation product **12r**, wherein unprotected hydroxy group efficiently underwent dehydrogenative silylation with excess diethylsilane, followed by hydrosilylation with norbornene (hydrogen acceptor). Reductive C–H silylation of both 1- and 2-naphthyl acetates provided single regioisomers (**12s** and **12t**, respectively) with excellent yields. Disubstituted 2,4-dimethylphenyl acetate also generated product **12u** via selective activation of C(sp^2)–H bond over C(sp^3)–H bond, with good yield (84%). C–H silylation of sesamol acetate afforded the major product **12v** (4-Si:6-Si = 3:1) at the more sterically hindered position. The subsequent nucleophilic ring-opening reactions of the resulting **12** with MeLi in the same vessel afforded *ortho*-silyl phenols, which allow concomitant removal of acetal directing group, thereby revealing hydroxy groups. These results clearly establish that the sequence of Ir and Rh-catalyzed reactions, followed by the ring-opening process, provides a viable catalytic synthesis of *ortho*-silyl phenols.

Table 1. Catalytic Reductive *ortho*-C–H Silylation of Phenyl Acetates with a Traceless Acetal Directing Group[a]

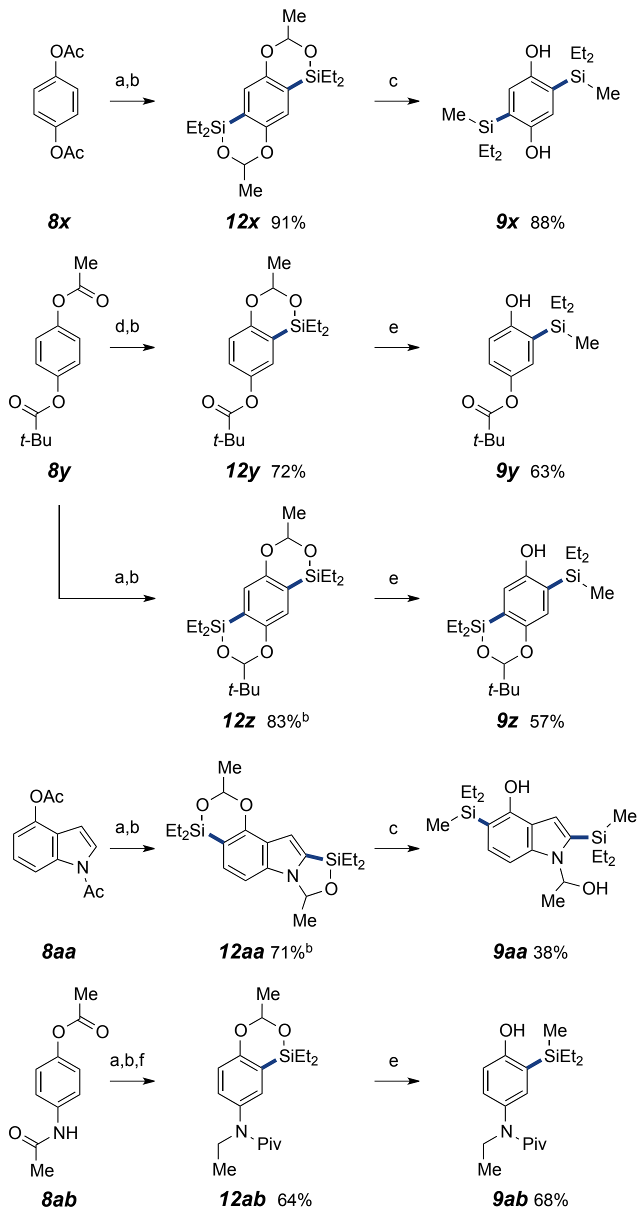




[a]Conditions: phenol acetates **8** (1 mmol), $[Ir(coe)_2Cl]_2$ (0.1 mol %), THF (3.3 M); $[Rh(nbd)Cl]_2$ (0.4 mol %), $P(4\text{-}OMePh)_3$ (2.4 mol %), norbornene (2 equiv), THF (1M), 120 °C, 15 min; MeLi (3 equiv), THF (0.5 M), –78 °C. [b]Determined by ^1H NMR spectroscopy utilizing an internal standard (CH_2Br_2). [c]$[Ir(coe)_2Cl]_2$ (0.5 mol %), H_2SiEt_2 (4 equiv); $[Rh(nbd)Cl]_2$ (1 mol %), $P(4\text{-}OMePh)_3$ (6 mol %), 120 °C. 60 min; MeLi (6 equiv). [d]3:1 regioisomeric ratio of **12v**.

Synthesis of Multi-Substituted Arenes. Catalytic transformation of diacetates or *N*-acetyl acetates into multi-substituted arenes, were examined with this C–H bond silylation strategy using traceless mixed *O,O*- and *N,O*-acetal directing groups (Scheme 2). Dual catalytic reductive C–H silylation of 1,4-phenylene diacetate **8x**, followed by the double-fold ring-opening with MeLi furnished tetra-substituted arene (**9x**) in excellent yield (88%). Furthermore, highly chemoselective reductive C–H silylation/ring-opening of 4-acetoxyphenyl pivolate **8y** to afford tri-substituted arene (**9y**) in 72% yield was observed, as achieved by selective hydrosilylation of acetate

Scheme 2. Synthesis of Multi-Substituted Arenes via Dual Catalytic Reductive *ortho*-C–H Silylation of Aromatic Acetates with Traceless Acetal Directing Groups[a]

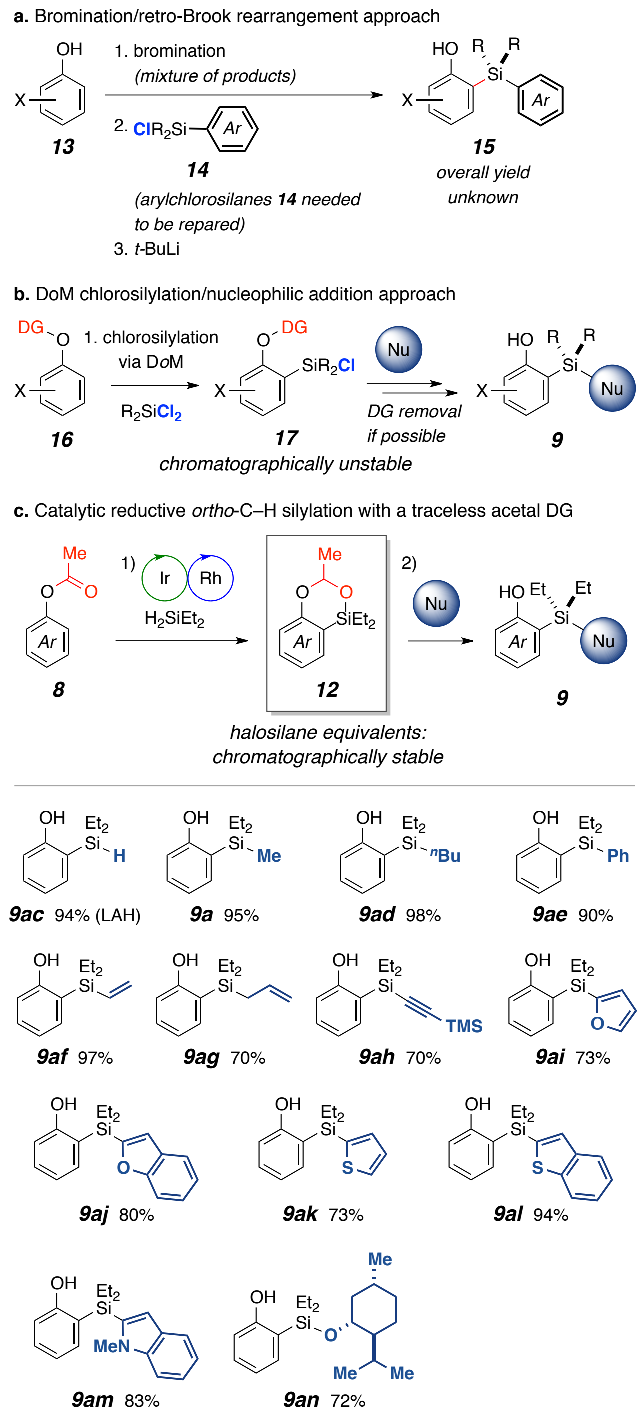


[a]Conditions: (a) $[Ir(coe)Cl]_2$ (0.5 mol %), H_2SiEt_2 (4 equiv), THF (2 M), 60 °C, 10 h. (b) $[Rh(nbd)Cl]_2$ (1 mol %), $P(4\text{-}OMePh)_3$ (6 mol %), nbe (4 equiv), THF (1 M), 120 °C, 30 min. (c) MeLi (6 equiv), THF, –78 °C. (d) $[Ir(coe)Cl]_2$ (0.5 mol %), H_2SiEt_2 (2 equiv), THF (2 M), rt, 10 h. (e) MeLi (3 equiv), THF, –78 °C. (f) PivCl (1.5 equiv), Et_3N (2 equiv), CH_2Cl_2, rt.

over pivolate (2 equiv of H_2SiEt_2 at rt). However, under dual hydrosilylation conditions (4 equiv of H_2SiEt_2 at 60 °C) dual C–H silylation of **8y** provided tetra-substituted arene (**12z**) (83% yield), which underwent ring-opening reaction with MeLi to give **9z**. *N*-Acetyl-4-indolyl acetate **8aa** also tolerated the reaction conditions to provide dual C–H silylation product **12aa,** via formation of the intermediate containing mixed *O,O*- and *N,O*-silyl acetals (not shown). Upon treatment with MeLi, **9aa** was generated in 38% yield over three steps. Several conditions were employed in attempts to remove the hemiaminal group; however protodesilylation (at C-5) was observed under most reaction conditions studied. Notably, when *para*-acetamide substituted phenyl acetate (i.e., *O*-acetyl acetaminophen) was subjected to the hydrosilylation conditions mixed *O,O*-silyl acetal, with concomitant reduction of amide to secondary silyl amine, initially formed which subsequently underwent C–H silylation to provide **12ab,** after pivalation of the amine. Subsequent treatment with MeLi afforded trisubstituted arene **9ab**.

Dioxasilines as Halosilane Equivalents for Synthesis of Functionalized Silanes. Organosilanes and organosilanols have been utilized for their unique biological functions and biomedically relevant agents.[3, 26] Although advances have been achieved, syntheses of diverse silanes by catalytic means remain significantly limited. For example, Brookhart reported only two synthetically useful silanes (Et_2SiH_2 and $PhMeSiH_2$) for Ir-catalyzed ester hydrosilylation.[22f] Furthermore, a stoichiometric method for synthesis of functionalized phenolic silanes **15,** involving (non-)selective bromination/retro-Brook reactions, requires substantial effort (i.e., preparation of chloroarylsilanes **14** bearing various aryl moieties) and the overall yield is unknown (Scheme 3.a).[9b] Alternatively, directed *ortho*-metalation (D*o*M)/silylation of phenols[11] also has limitations imposed by generation of chromatographically unstable chlorosilanes **17** and a difficult directing group removal step, associated with facile protodesilylation (Scheme 3.b). To improve this limited silane scope, and thereby prepare diversely functionalized silanes, we investigated sequential catalytic C–H silylation, coupled with nucleophilic ring-opening reactions of "dioxasilines as stable halosilane equivalents" that readily incorporate a variety of motifs (Scheme 3.c). Advantages of this method would be two-fold; first, it provides a post-introduction of silyl substituents containing useful functional groups, which may be not compatible with an Ir/Rh-catalytic cascade; second, it eliminates the need to prepare a variety of the not readily available dihydrosilanes for hydrosilylation. Therefore, we explored an array of nucleophiles; hydride (lithium aluminum hydride) (to **9ac**), carbon nucleophiles [MeLi (or MeMgBr) (to **9a**), *n*-BuLi (to **9ad**), PhLi (or PhMgBr) (to **9ae**), vinyl magnesium chloride (to **9af**), allyl magnesium chloride (to **9ag**), lithium trimethylsilyl acetylide (to **9ah**), heteroaryl lithium reagents (to 2-silyl furan **9ai**, 2-silyl benzofuran **9aj**, 2-thiofuran **9ak**, 2-silyl benzothiofuran **9al**, and 2-silyl indole **9am**], and oxygen nucleophiles (lithium mentholate) (to **9an**). All these nucleophiles afforded excellent to good yields of corresponding silyl phenols.

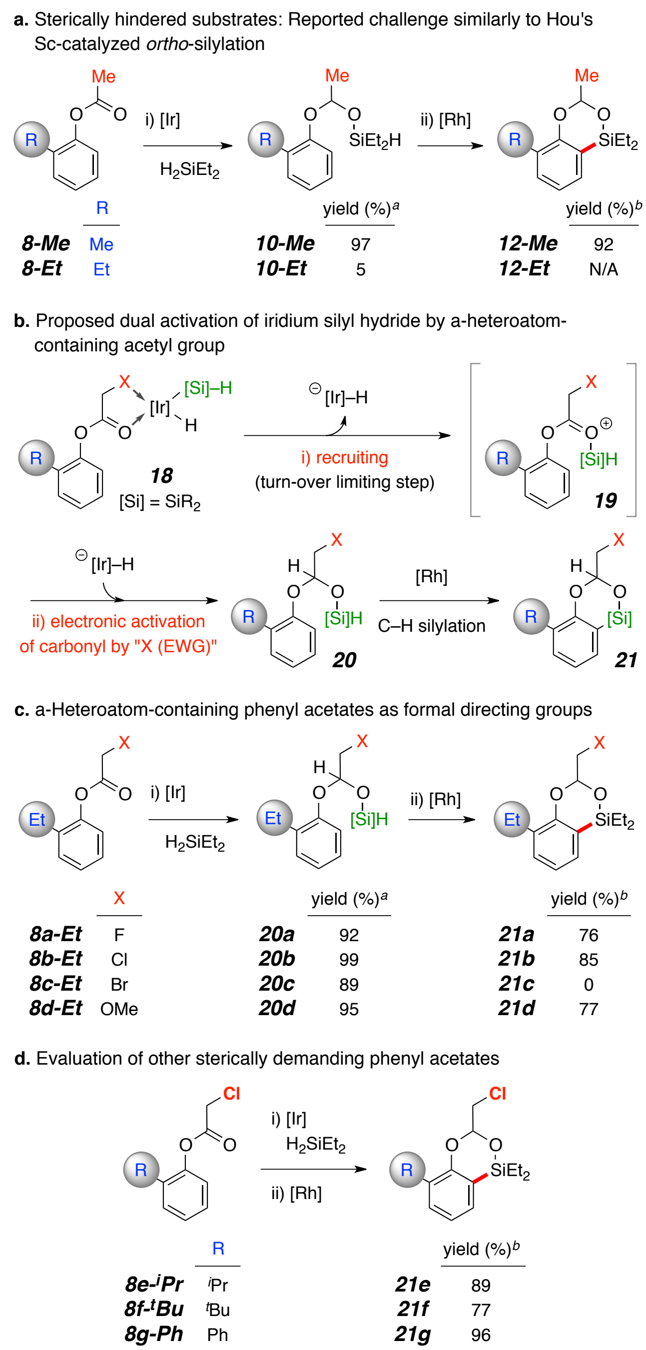
Scheme 3. Dioxasilines as Halosilane Equivalents for Synthesis of Functionalized Silanes[a]



[a]Isolation yield from either **12** or **18**.

Synthesis of 1,2,3-Trisubstituted Arenes via Catalytic Reductive C–H Silylation. Based on the wide substrate scope presented in Table 1, we investigated the potential of catalytic reductive *ortho*-C–H silylation of phenols directed by silyl acetal. However, we encountered a problem during our investigation of the substrate scope of *ortho*-C–H silylation of sterically hindered phenols. Surprisingly, minor steric variation on a substrate, such as **8-Et** (cf., **8-Me**), drastically hindered the hydrosilylation (Scheme 4.a). The Hou group also observed similar reactivity, in fact even more sensitive to the sterics, with Sc-catalyzed arene *ortho*-silylation, where even *ortho*-methyl anisole did not react (see **3** to **4** in Scheme 1.a1).[17h] Of note, efficient catalytic synthesis of 1,2,3-trisubtituted arenes are not trivial owing to the necessity of high reactivity over

Scheme 4. Synthesis of 1,2,3-Trisubstituted Arenes via Catalytic Reductive C–H Silylation of Sterically Hindered Phenyl Acetates: Dual Activation of Iridium Silyl Hydride by α-chloroacetyl directing group[a]

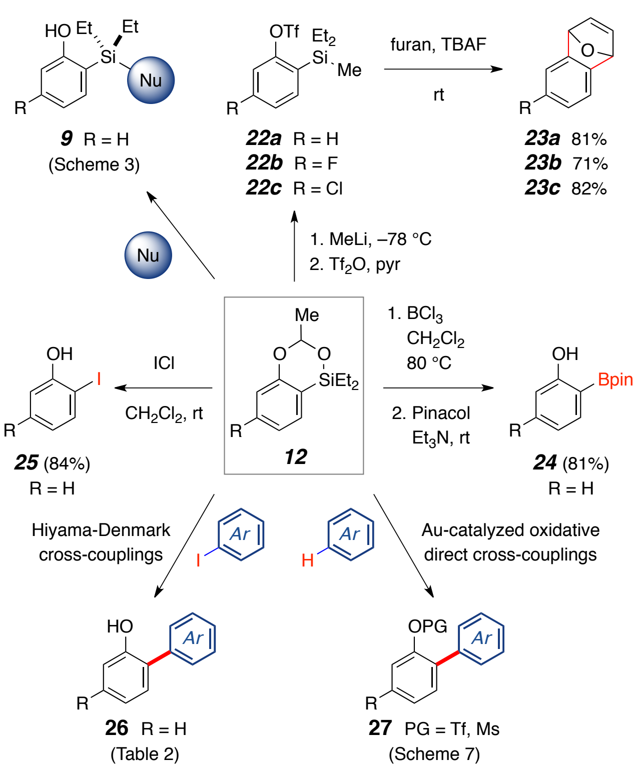


[a]Determined by ^{1}H NMR spectroscopy utilizing an internal standard (CH_2Br_2). [b]Isolation yield (two steps from the corresponding phenyl acetate).

steric hindrance and high regioselectivity. Although A-values of methyl and ethyl are fairly similar (1.7 vs. 1.75 kcal/mol, respectively),[27] it is speculated that the population of reactive conformers by rotation perhaps dictates this unusual reactivity difference. To overcome this obstacle, we explored a development of other efficient traceless directing groups (Scheme 4.b). Brookhart proposed that the turnover-limiting step of Ir-catalyzed hydrosilylation would be transfer of silylium ions (R_2HSi^+) to the carbonyl oxygen of esters.[22f, 28] We speculated that effective recruiting of iridium silyl hydride species to esters could be a crucial factor for hindered esters (**18** to **19**). In addition, the electron withdrawing X atom (group) could facilitate Ir-mediated hydride transfer to carbonyl (**19** to **20**). Therefore, to transfer the silylium ions to carbonyl and succeeding iridium hydride more easily, we designed and examined an α-heteroatom-containing acetyl formal directing group as a bidentate chelating moiety (e.g., an α-fluoro, chloro, bromo, methoxy acetyl) to metal (Scheme 4.c). We found that α-chloroacetate was among the most effective formal directing groups. This method was expanded to more sterically demanding *ortho*-substituted substrates. Remarkably, the phenyl α-chloroacetate smoothly underwent sequential hydrosilylation/C–H silylation of substrates bearing *ortho*-isopropyl, *tert*-butyl, and phenyl moieties (Scheme 4.d). These are surprising results because only a few successful chelation-controlled nucleophilic addition to α-halo carbonyl or imino electrophiles have been reported, owing to the relatively low basicity of halogens and all these prior examples utilized α-fluoro carbonyl derivatives.[29] Although the Walsh group demonstrated diastereoselective chelation-controlled addition of carbon nucleophiles to α-chloro aldimines, transition metal-catalyzed chelation-controlled hydrosilylation of α-chloroesters has not previously been described.[30]

Synthetic Applications of Benzodioxasilines: A major aspect of this work is to introduce a novel strategy to catalytic *ortho*-C–H silylation via sequential C–H silylation post-installation of other useful moieties on a silicon center. This approach permits spontaneous removal of a directing group and simultaneously addresses the challenges of synthesis of diversely functionalized unmasked *ortho*-silyl phenols **9** (Scheme 3). We further explored the powerful synthetic utilities of catalytically generated *ortho*-silyl phenols to other important transformations (Scheme 5).

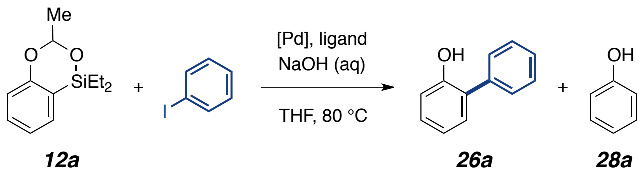
Scheme 5. Synthetic applications of Benzodioxasilines



Aryne Cycloaddition of *ortho*-Silyl triflates and Halo and Boro *ipso*-desilylations. 1,2-Silyl triflates are versatile motifs for a variety of areas in organic synthesis. Our catalytic *ortho*-silylation method permits access to 1,2-diethylmethylsilyl triflates **22** containing a variety of substituents in an extremely straightforward fashion. Some of such substrates were previously difficult to prepare owing to functional group incompatibility or electronic bias. We demonstrated aryne–furan cycloaddition which produced **23a-c** in good yields (Scheme 5).[23] In addition, benzodioxasiline **12** could easily undergo iodo and boro-induced *ipso*-desilylations to generate **24** and **25** in good yields, respectively (Scheme 5).

Pd-Catalyzed Hiyama-Denmark Cross-Coupling. The biaryl scaffold is prevalent in biologically active molecules and is an ubiquitous functional motif in medicines.[31] The Hiyama-Denmark cross-coupling, using non-toxic aryl silanes, is among the most versatile catalytic method for biaryl synthesis.[4a-c] Nonetheless, this strategy suffers from the requirements for aryl halide sources in the C–C bond-forming reaction and basic conditions for activating silanes. When attempting Pd-catalyzed Hiyama-Denmark cross-coupling of benzodisiloxane **12a**, we observed product **26a** in low to moderate yields (3-50%), along with significant protodesilylation byproduct **28a** (Table 2). Based upon our literature survey the efficiency of silicon-based cross-coupling of sterically encumbered *ortho*-substituted silanes (or siloxanes) with corresponding haloarene cross-coupling partners has been generally poor.[32]

Table 2. Pd-Catalyzed Hiyama-Denmark Cross-Couplings of Benzodioxasiline[a]

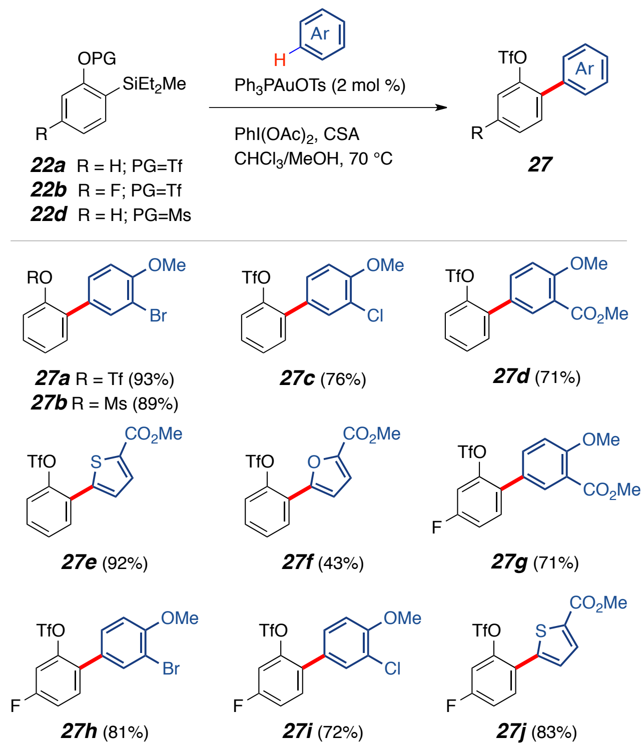


entry	PdL_n	ligand	yield of **26a** (%)[c]
1	$Pd(OAc)_2$	PCy_3	20
2	$Pd(OAc)_2$	P(*t*-Bu)$_3$	50
3	$Pd(OAc)_2$	RuPhos	5
4	$Pd(OAc)_2$	XPhos	5
5	$Pd(OAc)_2$	SPhos	11
6	$Pd(OAc)_2$	P(4-MeOPh)$_3$	6
7	$Pd(OAc)_2$	dcpe	3
8	$Pd(OAc)_2$	dppe	12
9	$Pd(OAc)_2$	dppp	9
10	$Pd(OAc)_2$	dppb	10
11	$Pd(OAc)_2$	dppf	12
12	$Pd(OAc)_2$	XantPhos	21
13	$Pd_2(dba)_3$	P(*t*-Bu)$_3$	5
14	$Pd(PPh_3)_2Cl_2$	P(*t*-Bu)$_3$	15
15	$[allylPdCl]_2$	P(*t*-Bu)$_3$	11
16	$PdCl_2$	P(*t*-Bu)$_3$	5
17	$Pd(CF_3CO_2)_2$	P(*t*-Bu)$_3$	23

[a]Conditions: silane **12a** (0.1 mmol), solvent (0.2 M) (details in Supporting Information). [b]Determined by GC/MS analysis. [c]Determined by ^{1}H NMR spectroscopy utilizing an internal standard (CH_2Br_2). RuPhos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, dcpe = 1,2-bis(dicyclohexylphosphino)ethane, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

Au-Catalyzed Oxidative Direct Arylation of Aryl Silanes. A direct alternative to the Hiyama-Denmark cross-coupling would be the oxidative direct cross-coupling of aryl silanes, with simple arenes as a partner,[13c, 13f, 13j, 33] as recently reported by Lloyd-Jones and Russel.[4d, 4e] This strategy is, however, underexploited in 2-silyl triflates derived from dioxasilines as oxidative direct coupling partners (Scheme 6). Our developed reductive C–H silylation strategy would enable the rapid preparation of such triflate-containing partners for the silane-based oxidative direct coupling. Gratifyingly, gold(I)-catalyzed oxidative cross-coupling of 1,2-silyl triflates **22** with non-prefunctionalized arenes afforded biaryls **27** in moderate to excellent yields (Scheme 6). With brief optimization, the Au-catalyzed silane-based oxidative cross-coupling directly provided biaryls **27a** to **27j**, holding useful

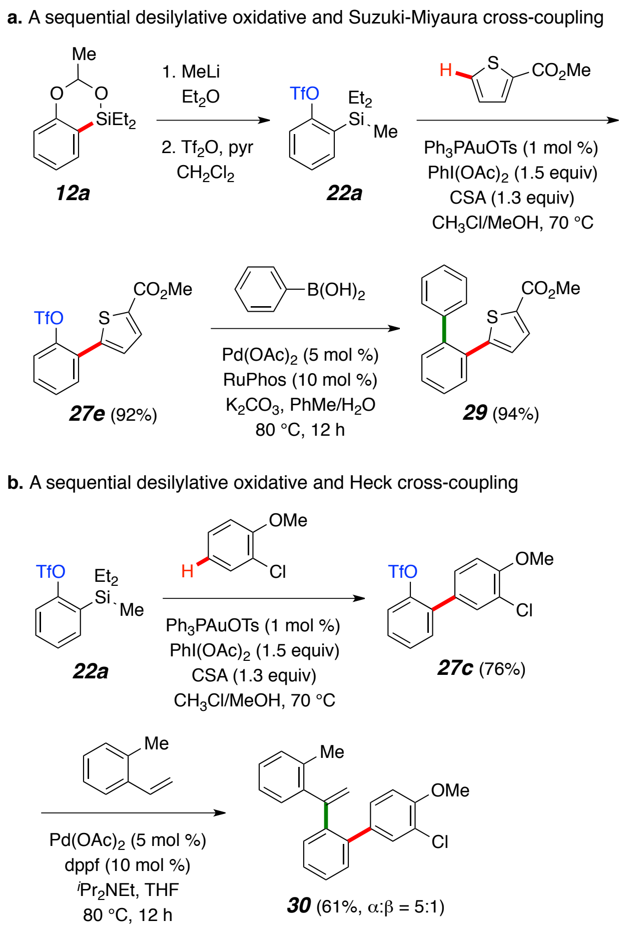
Scheme 6. Au-Catalyzed Oxidative Direct Cross-Coupling of *ortho*-Silyl Phenols with Arenes



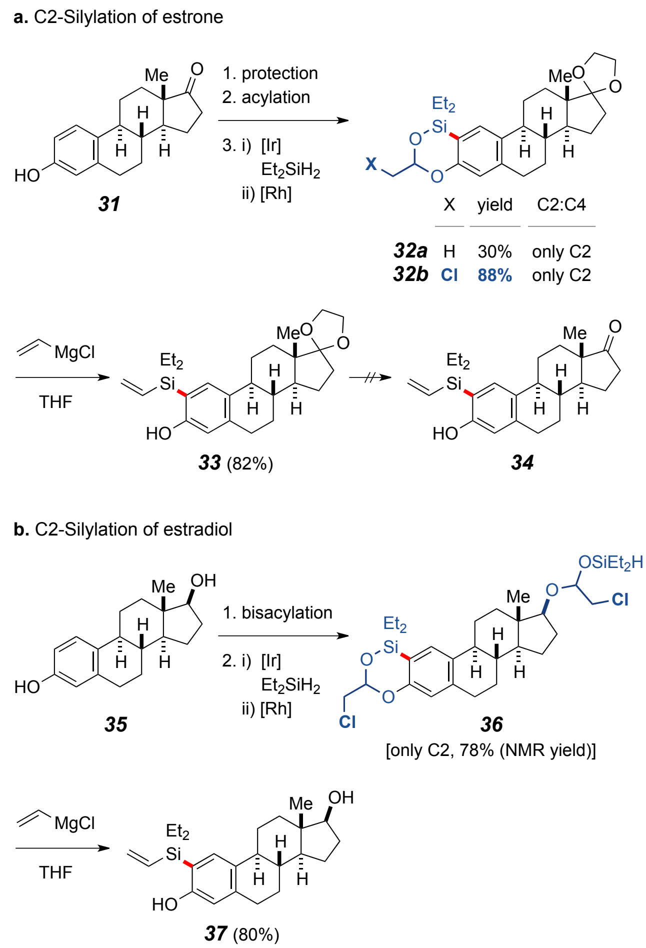
functional groups and moieties (e.g., triflate, mesylate, ester, bromide, chloride, fluoride, furan, and thiopene). These functional groups are useful for subsequent downstream reactions such as other metal-catalyzed cross-couplings.

Orthogonal Cross-Coupling. The Au-catalyzed oxidative cross-coupling of biaryls **27a**, **27c** to **27j**, bearing triflate groups, can be used for subsequent cross-coupling reactions. Examples include Suzuki cross-coupling of **27e** with phenyl boronic acid to generate 1,2-diaryl benzene **29** (94%) (Scheme 7a) and Heck reaction of **27c** with 2-methylstyrene to furnish 1,1-disubstituted alkene **30** (61%) (Scheme 7b).

Scheme 7. Sequential Orthogonal Cross-Couplings of Benzodioxasilines



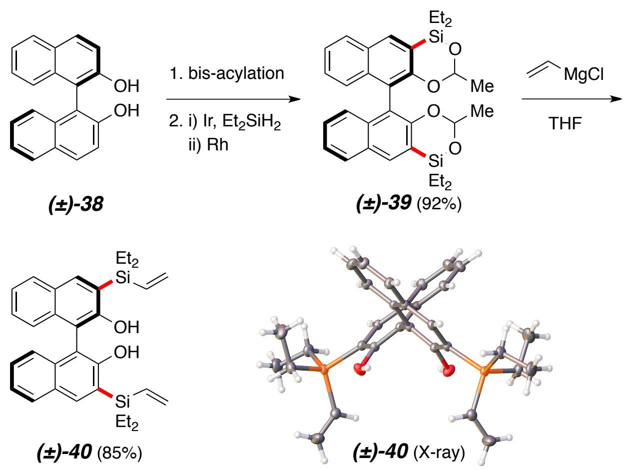
Scheme 8. Selective C–H Silylation and Ring-Opening Reactions of Estrone and Estradiol



Late-Stage Functionalization of Phenol-Containing Bioactive Molecules Estrone and Estradiol. We explored the synthetic utility of the catalytic reductive acetal directing group-assisted *ortho*-C–H silylation of phenols in known bioactive molecules (Scheme 8). We again exhibited that α-chloroacetyl-derived silyl acetal was crucial to afford ester hydrosilylation/C–H bond silylation (only C2 position) of estrone to provide **32b** (88% yield) (cf., the parent acetyl directing group only afforded **32a** in 30% yield), presumably due to remote steric influence (Scheme 8a). Ring-opening of **32b** by vinyl lithium furnished **33** (80% yield).[7a, 16, 34] Unfortunately, we were unable to remove the ketal protecting group within **33** under a variety of reaction conditions, due to concomitant protodesilylation of C2-silane.[34] We then studied a more direct method involving late-stage functionalization of estradiol **35** (Scheme 8b). A four-step sequence, involving bischloroacetylation, reductive C–H silylation, and vinyl addition, directly permits C2-silyl estradiol **37** (via **36**) without protecting group manipulation.

Catalytic Synthesis of 3,3'-Bissilyl BINOL Using a Traceless Acetal Directing Group. Lastly, we examined whether this catalytic silylation method is applicable to preparation of a 3,3'-bis-silylation of binaphthol (BINOL), which has been extensively utilized for asymmetric catalysis. 3,3'-Bis-silyl BINOL **40** was synthesized from *rac*-BINOL, in high yield, in a four steps operation–of note, only one enantiomer of the BINOL racemic mixture is presented in Scheme 9. Overall, our development of a strategy for late-stage modification enables synthesis of structurally unique bioactive molecules and chiral scaffolds in a rapid and highly site-selective manner and obviates a stepwise, multi-step synthesis, which would be difficult through the existing catalytic *ortho*-C–H silylation.[17h]

Scheme 9. 3,3'-Bis-Silylation of BINOL



CONCLUSION

A new strategy, employing disubstituted silyl synthons and phenyl acetates, for a single-pot sequential metal-mediated, catalytic reductive C–H silylation of phenols with traceless acetal directing groups, has been successfully achieved. The relay of Ir-catalyzed hydrosilylation of phenyl acetates and Rh-catalyzed C–H silylation provides dioxasilines. A subsequent nucleophilic addition of diverse nucleophiles to dioxasilines serving halosilane equivalents not only readily incorporates a variety of functional moieties, but also concomitantly removes the acetal directing groups in a single vessel. To resolve synthetic challenges of 1,2,3-trisubstited, hindered arenes, we developed a new α-chloroacetyl formal directing group which allows catalytic reductive *ortho*-C–H silylation of sterically hindered phenols. We also demonstrated several important downstream reactions of the resulting 1,2-silyl phenols, including Au-catalyzed oxidative direct cross-coupling, aryne cycloaddition chemistry, and late-stage silylation of phenolic bioactive molecules and BINOL scaffold, exploiting the traceless acetal directing group strategy to afford C2-silyl estrone, C2-silyl estradiol, and 3,3'-bissilyl BINOL.

EXPERIMENTAL SECTION

General Experimental Information. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in flame- or oven-dried glassware. Anhydrous toluene and dichloromethane (DCM) were distilled from CaH_2. Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone. Triethylamine and pyridine were distilled from KOH. DMF and DMSO were stored over 4Å molecular sieves. All other solvents and reagents from the commercial sources were used as received. NMR spectra were recorded on a 500 or 300 MHz NMR spectrometer. ^{1}H NMR chemical shifts are referenced to chloroform (7.26 ppm)and DMSO-d_6 (2.50 ppm). ^{13}C NMR chemical shifts are referenced to $^{13}CDCl_3$ (77.23 ppm), and DMSO-d_6 (39.52 ppm). The following abbreviations are used to describe multiplets: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), nfom (non-first-order multiplet), and br (broad). The following format was used to report peaks: chemical shift in ppm [multiplicity, coupling constant(s) in Hz, integral, and assignment]. ^{1}H NMR assignments are indicated by structure environment, e.g., CH_aH$_b$. ^{1}H NMR and ^{13}C NMR were processed with iNMR software program. Infrared (IR) spectra were recorded using neat (for liquid compound) or a thin film from a concentrated DCM solution. Absorptions are reported in cm^{-1}. Only the most intense and/or diagnostic peaks are reported. MPLC refers to medium pressure liquid chromatography (25-200 psi) using hand-packed columns of silica gel (20-45 μm, spherical, 70 Å pore size), an HPLC pump, and a differential refractive index detector. High-resolution mass spectra (HRMS) were recorded in Electrospray ionization time-of-flight (ESI-TOF) mode. Samples were introduced as mixed solutions of methanol and methylene chloride (DCM). GC-MS experiments using electron impact ionization (EI) were performed at 70 eV using a mass-selective detector. Analytical TLC experiments were performed on F254 plate, 250 μm thickness. Detection was performed by UV light or potassium phosphomolybdic acid, permanganate, *p*-anisaldehyde staining.

General Procedure for Ir-catalyzed Reductive Ester Silylation–Preparation of Silyl Acetals (10): $[Ir(coe)_2Cl]_2$ (0.9 mg, 0.1 mol %) and aryl acetates **8** (1 mmol) were added to a flame-dried, nitrogen-purged septum-capped vial. The mixture was dissolved with THF (0.3 mL, 3.3 M), and diethylsilane (0.26 mL, 2 mmol) was added to the mixture. The septum on the vial was replaced by a screw cap with a Teflon liner under a N_2 atmosphere [note: diethylsilane (bp 56 °C and density 0.686 g/mL) is volatile]. The reaction mixture was stirred for 3-12 h at 60 °C. Volatiles were removed *in vacuo* to afford silyl acetals **10**, which were directly used for subsequent reactions without further purification.

General Procedure for Rh-catalyzed Arene *ortho*-C–H Silylation of Hydridodiethylsilyl Acetals –Preparation of Benzodioxasilines (12): $[Rh(nbd)Cl]_2$ (1.84 mg, 0.4 mol %), *tris*(4-methoxyphenyl)phosphine (8.45 mg, 2.4 mol %), norbornene (188 mg, 2 mmol), and THF (1 mL, 1 M) were added to the crude silyl acetals **10** (1 mmol). The septum on the vial was replaced by a screw cap with a Teflon liner, and the mixture was stirred at 120 °C for 15 min (unless otherwise mentioned in Table 1). Reaction progress was monitored by GC/MS spectrometry. The resulting benzodioxasilines **12** were directly used for a subsequent reaction without further purification. For an analytical purpose, volatiles were removed *in vacuo*, and the resulting mixture was dissolved with pentane, filtered through a pad of Celite®, and concentrated in vacuo. The crude product was purified by MPLC (hexanes/EtOAc = 80:1, 5 mL/min, retention time 5-15 min).

General Procedure for Nucleophile Opening of Benzodioxasiline–Preparation of 2-Silylphenol (9): The crude benzodioxasilines **12** (1 mmol in THF, 1 M) were diluted with THF (1 mL, 0.5 M) and cooled to –78 °C, then nucleophiles (3 equiv) were added into the reaction mixture and stirred at –78 °C for 30 min. The reaction was quenched at –78 °C by adding saturated aqueous ammonium chloride solution, then the mixture was acidified to ca. pH 4-5 with aqueous HCl (1 M). The mixture was extracted with diethyl ether. The combined organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. Volatiles were removed *in vacuo,* and the crude mixture was purified by MPLC to afford 2-silyl phenols **9** (hexanes/EtOAc = 20:1, 5 mL/min, retention time 6-20 min).

ASSOCIATED CONTENT

The following file is available free of charge on the ACS Publications website at http://pubs.acs.org.
Experimental details and spectroscopic characterization data for all compounds.

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§Y.H and P.A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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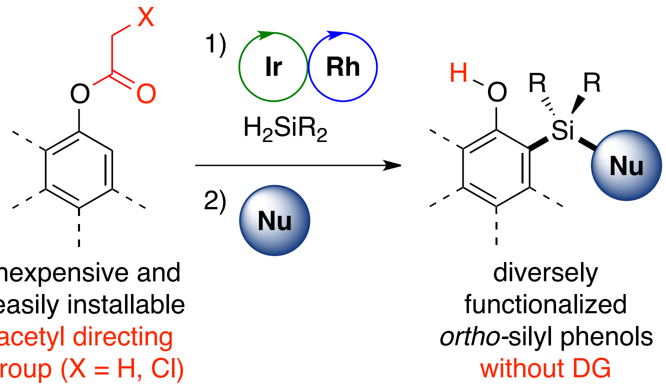
TOC graphic



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