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Traceless Acetal-Directed Catalytic Hydrosilylation of Propargyl Acetates Harnessing the π-Acidic Catalyst

Udaya Sree Dakarapu,† Yao Chung Chang,† Thirupataiah Avullala, Suman Das Adhikary, Hiep H. Nguyen, and Junha Jeon*

Cite This: ACS Catal. 2024, 14, 14696−14702 Read Online

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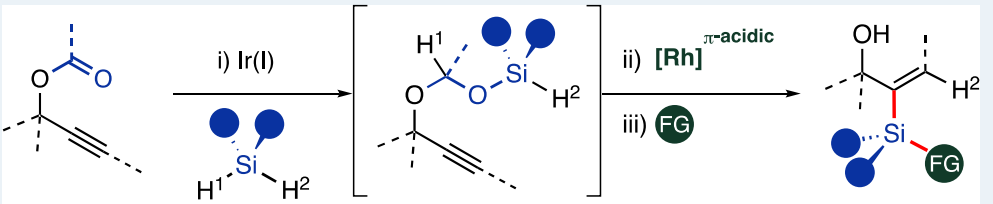


ABSTRACT: Traceless acetal-directed, α-specific *syn*-hydrosilylation of propargyl alcohols has been developed, enabling a synthesis of β-silyl allylic alcohols. An introduction of inexpensive, readily accessible acetal as a traceless, two-atom tether directing group (DG), along with a π-acidic catalyst, facilitates the proximal, α-selective *syn*-hydrosilylation of a broad spectrum of primary to tertiary propargyl alcohols. Notably, the utilization of a highly fluorinated, π-acidic Rh(I)/P(C_6F_5)$_3$ catalyst allows rapid cyclizing *syn*-addition of a silicon−metal species across a C−C triple bond via a strong M-π interaction. A postmodification of the resulting cyclic silyl acetal not only removes the DG, rendering it traceless, but also introduces a functional group to the silicon moiety, enhancing the versatility and utility of the products.

KEYWORDS: *hydrosilylation, alkyne, acetal, vinylsilane, transition metal catalysis*

INTRODUCTION

Vinylsilanes are stable and virtually nontoxic.[1−4] Their significance lies in their role as crucial building blocks for the synthesis of bioactive molecules and functional materials.[1,2,4] The versatile nature of vinylsilanes allows for either independent or simultaneous conversion of both the alkene and silyl moieties into several important functional groups. These functional group (FG) transformations encompass a wide range of reactions, including stereoselective electrophilic substitution,[5,6] cycloaddition,[7] ene reaction,[8] oxidation,[9−11] sigmatropic rearrangement,[12,13] and a variety of organometallic reactions (e.g., Heck reaction,[14] Denmark−Hiyama cross-coupling,[4,15] Murai reductive *ortho*-alkylation,[16] hydroesterification,[17] and olefin metathesis[18−20]). In particular, β-silyl allylic alcohols (i.e., proximal hydroxy vinylsilanes) have served as important latent α-hydroxy ketones and multisubstituted olefins through oxidation[9−11] and cross-coupling[4,15] stereoselective electrophilic substitution reactions,[5,6] respectively.

Despite significant advancements in transition-metal-catalyzed alkyne hydrosilylation to access such synthetic building blocks, alkyne hydrosilylation performed on unsymmetrical alkynes often results in formation of an inseparable mixture of regio- and stereoisomers. In particular, intramolecular α-regioselective hydrosilylation of propargylic hydrosilyl ethers **1** remains challenging. It simply arises from the instability of putative oxasilacyclobutanes **2** via 4-*exo*-*dig* cyclization instead of giving 5-*endo*-*dig* cyclization product **3** (Figure 1a).[16,21] To address this issue, Fürstner achieved innovative Ru-catalyzed, intermolecular α-selective *anti*-hydrosilylation of propargylic alcohols **4** to give α-hydroxy vinylsilanes **5** (α/β = 60:40 to 100:1) through the interligand interactions (Figure 1b).[22] Tomooka and Denmark independently reported Pt-catalyzed, α-selective *syn*-hydrosilylation of propargylic alcohol derivatives by introducing a dimethylvinylsilyl and siloxane-directing group (DG) to the substrate, respectively, to improve the

Received: July 11, 2024
Revised: September 4, 2024
Accepted: September 6, 2024

https://doi.org/10.1021/acscatal.4c04132
ACS Catal. 2024, 14, 14696−14702

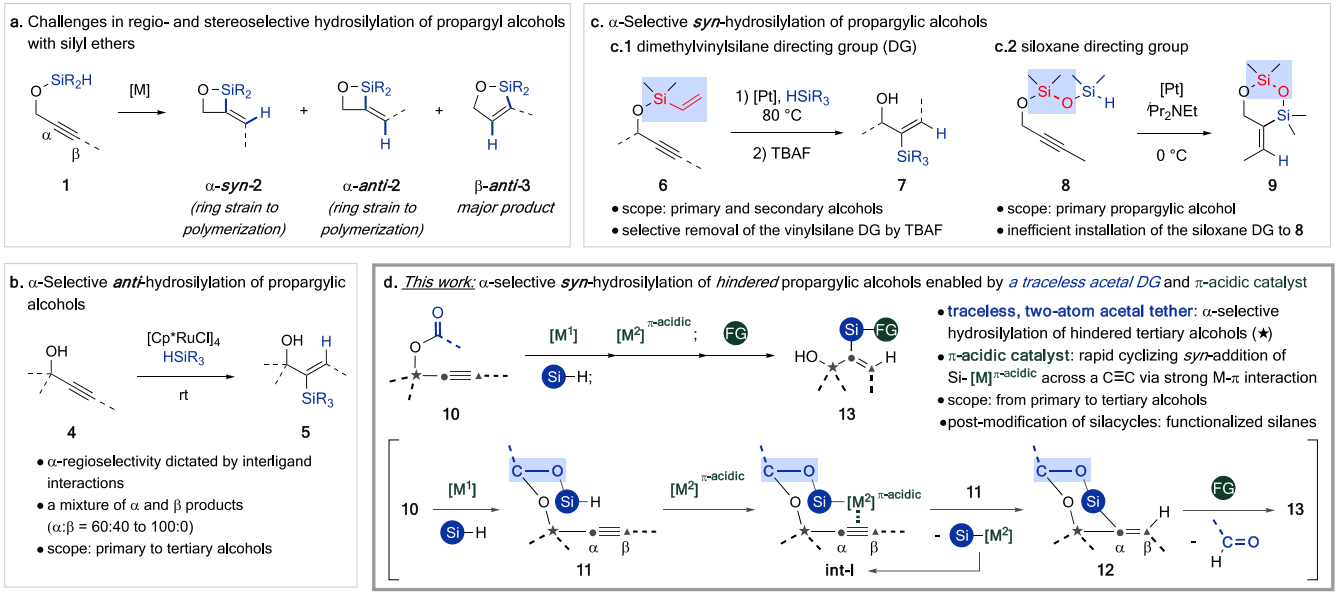
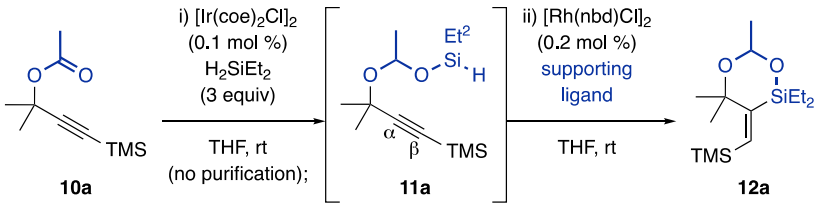


Figure 1. Hydrosilylation of propargyl alcohols. FG = functional group, DG = directing group. FG = functional group.

Table 1. Evaluation of the Alkyne Hydrosilylation Catalyst[a]



entry	supporting ligand	yield (%)[b]	α/β[c]	E/Z[d]
1	PPh_3	81	only α	only E
2	$P(4\text{-}MeOPh)_3$	84	only α	only E
3	PPh_2Et	83	only α	only E
4	JohnPhos	84	only α	only E
5	PCy_3	78	only α	only E
6	$P(C_6F_5)_3$	92	only α	only E
7	$P(OPh)_3$	77	only α	only E
8	Cp^{*-}[e]	90	only α	only E
9	$Tp^{(CH3)2}K$	82	only α	only E
10	$Tp^{CF3,Ph}Na(THF)$	88	only α	only E
11	$Tp^{(CF3)2}Na(THF)$	85	only α	only E

[a]Conditions: (i) **10a** (0.20 mmol), THF (1 M); (ii) supporting ligand (1.2 mol % for phosphine ligands, 0.4 mol % for Cp^{*-} and Tp ligands), THF (0.4 M). [b]Determined by ^1H NMR spectroscopy utilizing an internal standard (mesitylene). [c]Determined by GC/MS analysis and ^1H NMR spectroscopy. [d]Determined by NOE experiments. [e]$[RhCp^*Cl_2]_2$ was used. TMS = trimethylsilyl.

proximal α-selectivity,[23,24] in contrast to the preferential distal functionalization in most intermolecular hydrosilylation (Figure 1c).[25] The former approach employs elevated temperature conditions for primary and secondary propargyl alcohols, while the latter experiences inefficient installation of the siloxane DG, which is mainly associated with the use of a large excess of tetramethyldisiloxane reagent, a requisite purification step, and a limited scope (primary propargylic alcohol).

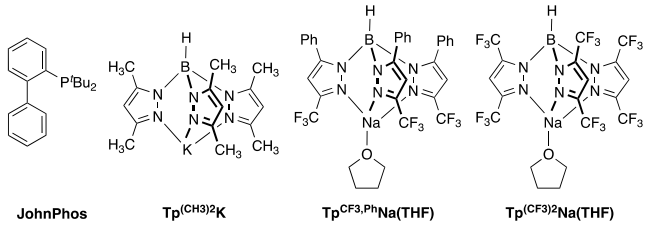
Herein, we report our approach to α-selective *syn*-hydrosilylation of propargyl alcohols using a traceless acetal DG and a π-acidic $Rh(I)/P(C_6F_5)_3$ catalytic system to provide β-silyl allylic alcohols **13** (Figure 1d). The design aspects of our traceless DG strategy are 4-fold: (1) an efficient preparation of an acetal DG from inexpensive and readily accessible esters via Ir-catalyzed ester hydrosilylation without the need for purification, (2) the development of a two-atom, acetal DG [cf., siloxane (Si−O) in **8**] which conceptually delivers hydrogen and a silicon moiety to unsymmetrical alkyne in a regio- and stereoselective manner via 6-*exo*-*dig* cyclization (cf., 4-*exo*-*dig* cyclization with propargylic hydrosilyl ethers **1**),[26−33] (3) the use of a π-acidic catalyst for establishing a strong M-π interaction which enables rapid *syn*-silyl metalation (**int-I**), leading to an expansion of the scope of propargylic alcohols by encompassing all substrate classes—primary, secondary, and tertiary propargylic alcohols and heterocycle-containing alkynes, and (4) postmodification of the resulting silacycles for the facile removal of the acetal DG along with the concomitant diversification of the silyl group in a single reaction vessel.

https://doi.org/10.1021/acscatal.4c04132
ACS Catal. 2024, 14, 14696−14702

RESULTS AND DISCUSSION

Given the limited literature on the α-hydrosilylation of tertiary alcohols vis-à-vis primary and secondary alcohols, we selected a model substrate to investigate the potential impact of steric hindrance on α-versus β-hydrosilylation. Hydrosilyl acetal **11a** holding the two-atom tether was conveniently prepared through chemoselective Ir-catalyzed ester hydrosilylation over alkyne hydrosilylation within **10a** in near quantitative yield without requiring purification (Table 1).[26] Specifically, under the catalytic conditions developed, the internal alkyne adjacent to the ester remained intact. With **11a** in hand, we set off to survey the catalytic conditions to effect α-selective alkyne hydrosilylation. Unfortunately, the various Ir catalysts that we examined gave lower yields. Next, a range of supporting ligands, including phosphines, phosphite, pentamethylcyclopentadienyl (Cp*), and tris(pyrazolyl)borates (Tp), were examined with variations in their electronic and steric capabilities in the presence of a rhodium precatalyst (Table 1). This study showed that the use of a rhodium catalyst, assembled through the combination of the Rh^{I} precatalyst and highly fluorinated phosphine ligand $P(C_6F_5)_3$, resulted in an excellent yield (92%) of **12a** with excellent regio- and stereoselectivity (entry 6).

To gain a better understanding of the high efficiency observed in the reaction with the highly fluorinated phosphine



$P(C_6F_5)_3$, in situ ^1H NMR spectroscopy was employed to monitor the progress of the hydrosilylation reactions of **11a** with the ligands listed in Table 1. As shown in Figure 2a, the rate of hydrosilylation was largely correlated with the electronic nature of the ligands, with electron-poor ligands showing faster reaction kinetics than their electron-rich counterparts. Generally, the rate order followed the trend: triaryl phosphine > monoalkyldiaryl phosphines > dialkylmonoaryl phosphines > triaryl phosphite > trialkyl phosphines. A similar trend was observed for the electronic properties of the Tp ligand series: $[Tp(CF_3)_2]^-$ > $[TpCF_3,Ph]^-$ > $[Tp(CH_3)_2]^-$. In particular, the electron-poor, highly fluorinated phosphine ligand $P(C_6F_5)_3$ exhibited a substantially faster kinetic profile. First-order kinetic plots of ln ($[M_0]/[M_t]$) versus time for the hydrosilylation showed that the reaction with $P(C_6F_5)_3$ proceeded nearly 5 times faster than with tris(pentaprotiophenyl)phosphine $P(C_6H_5)_3$ (Figure 2b).[32] The results suggest that the electron-withdrawing nature of the highly fluorinated $P(C_6F_5)_3$ ligand enhances the Lewis acidity of the rhodium center. Consequently, the π-acidic rhodium center augments the Rh-π interaction, which in turn facilitates rapid silyl-rhodation and ultimately accelerates catalytic turnover. Overall, a π-acidic $Rh(I)/P(C_6F_5)_3$ catalyst is synthetically advantageous for acetal-directed, α-specific *syn*-hydrosilylation of propargyl acetates, enabling shorter reaction times and higher yields.

Based on our preliminary kinetic studies along with literature precedents,[32,33] the plausible overall mechanisms for the three-step sequence involving (i) Ir-catalyzed hydrosilylation of

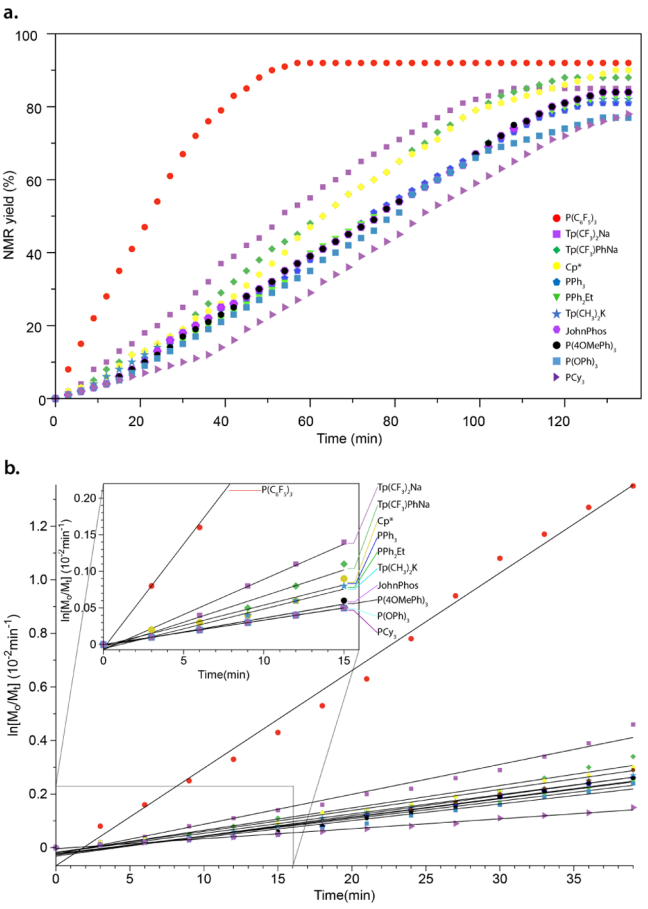


Figure 2. (a) Kinetic profiles of the alkyne hydrosilylation of **11a** with ligands. The data sets were obtained by in situ ^1H NMR spectroscopy in C_6D_6 at 20 °C using an internal standard (mesitylene). **11a** (0.20 mmol), supporting ligand (1.2 mol % for phosphine ligands, 0.4 mol % for Cp^{*-} and Tp ligands), THF (0.4 M). $[RhCp^*Cl_2]_2$ (0.2 mol %) used. (b) First-order kinetic plots of ln ($[M_0]/[M_t]$) versus time at 25 °C with different ligands. M_0: initial concentration, M_t: concentration at a given time.

esters, (ii) alkyne hydrosilylation harnessing the π-acidic Rh catalyst, and (iii) the activation−functionalization of silacycle **12** are depicted in Figure 3. First, Brookhart's a binuclear silylene-bridged iridium dimer enables chemoselective hydrosilylation of esters **10**, affording hydrosilyl acetals **11**.[26] While a modified Chalk−Harrods mechanism is generally accepted in alkene/alkyne hydrosilylation chemistry, our preliminary mechanistic investigations failed to identify a Rh−H species using extensive ^1H NMR spectroscopy. Instead, we propose an oxidative addition of a Si−H bond in hydrosilyl acetals **11** to the Wilkinson-type, electron-poor rhodium catalyst, followed by reductive elimination of HCl, generating the requisite π-acidic Rh^{I}−silane **int-I**. The establishment of a strong rhodium-π interaction between a Rh^{I}−Si moiety and a C−C triple bond within **int-I**, coupled with rapid silyl rhodation, is key to the successful rapid cyclizing, 6-*exo*-*syn* alkyne hydrosilylation to produce the vinylsilyl rhodium species **int-II**. A subsequent bimolecular rhodium-π interaction, followed by σ-bond metathesis within **int-II**, gives the product (*E*)-dioxasilinanes **12** and regenerates **int-I**, completing the catalyst cycle. To assess the potential protonation of int-2 by HCl, we introduced a stoichiometric amount of base, such as Hünig's base or $NaHCO_3$, to the hydrosilylation reaction mixture.

https://doi.org/10.1021/acscatal.4c04132
ACS Catal. 2024, 14, 14696−14702

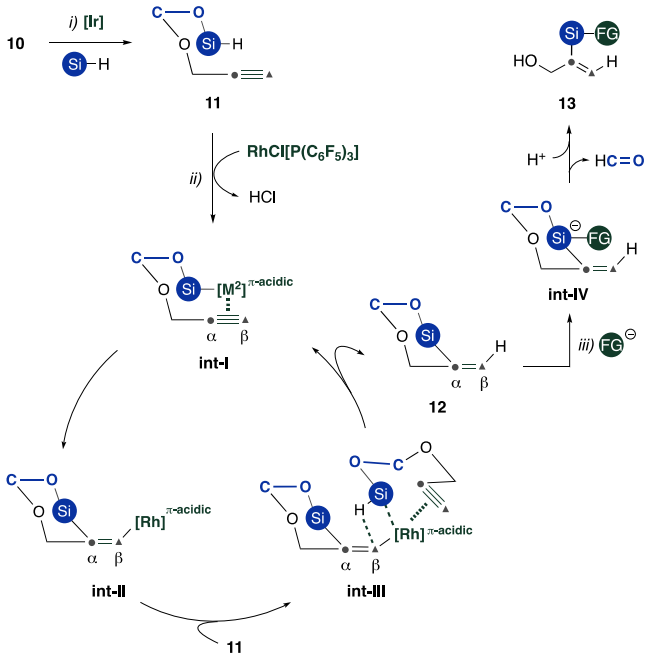


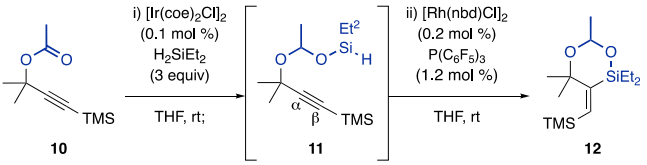
Figure 3. Proposed mechanisms for traceless acetal-directed, proximal, α-selective *syn*-hydrosilylation of propargyl alcohols harnessing the π-acidic Rh catalyst.

However, neither base significantly affected reaction rates or yields compared with the base-free reaction. While a protonation mechanism remains plausible, these results further support the proposed metathesis mechanism. Upon addition of an anionic external FG to **12**, a putative, penta-coordinated silicon species **int-IV** is formed. The succeeding irreversible ring-opening fragmentation of **int-IV** produces β-silyl allylic alcohols **13** upon protonation with acid, along with the elimination of a corresponding aldehyde which can further react with the anionic **FG**. This approach not only removes a DG but also diversifies the newly introduced silyl moiety in a single pot, improving the scope of organosilanes.

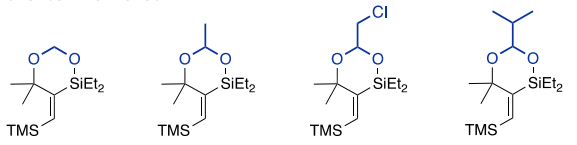
With the optimized conditions in hand, the impact of acetal tethers on cyclization was studied (Table 2). Sterically and electronically tuned hydrosilyl acetals (**11a**−**11f**) were accessed via Ir-catalyzed ester hydrosilylation and evaluated for alkyne hydrosilylation. Consistent with our findings in the context of arene C−H silylation,[28,30] the sterically more accessible esters **10a**−**10d** (R = H, Me, α-chloro, ^{i}Pr) smoothly underwent sequential Ir and Rh catalysis, involving ester and alkyne hydrosilylation, respectively, leading to the formation of (*E*)-dioxasilinanes **12a**−**12d**. Ester hydrosilylation of sterically demanding ester **10e** (R = ^{t}Bu) to afford **11e** exhibited slower kinetics (12 h), but the rate of alkyne hydrosilylation of **11e** was comparable to that of substrates **11a**−**11d** (ca. 0.5 h). While electron-deficient trifluoromethyl ester **10f** underwent ester hydrosilylation at significantly slower rates (48 h), alkyne hydrosilylation was achieved in 1 h, yielding **12f**. Together, the π-acidic Rh catalyst facilitated fast cyclization of all types of hydrosilyl acetals with excellent regio- and stereoselectivity.

Encouraged by the high regio- and stereoselectivity achieved with structurally diverse hydrosilyl acetals, we investigated the scope of traceless acetal-directed, α-selective hydrosilylation of propargyl alcohols to produce β-silyl allylic alcohols **13** via (*E*)-dioxasilinanes **12** (Table 3). Trimethylsilyl-substituted primary

Table 2. Scope of Hydrosilyl Acetals[a]

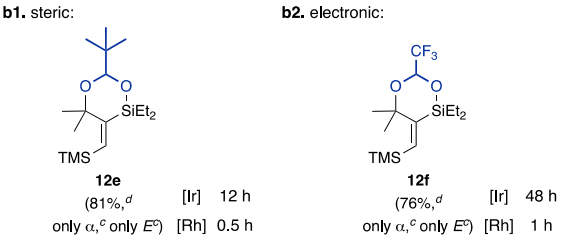


a. General substitutent effect



	12b	**12a**	**12c**	**12d**
	(88%,[b] only α,[c] only *E*[c])	(91%,[b] only α,[c] only *E*[c])	(83%,[b] only α,[c] only *E*[c])	(94%,[b] only α,[c] only *E*[c])
[Ir]	2 h	3 h	3 h	6 h
[Rh]	0.5 h	0.5 h	0.5 h	0.5 h

b. Steric and electronically varied acetals



[a]Conditions: (i) **10** (0.2 mmol), THF (1 M); (ii) THF (0.4 M). [b]Isolation yield. [c]Determined by GC/MS analysis and ^{1}H NMR and NOE spectroscopy. [d]Yield was determined by the reaction of **12e** and **12f** with MeLi.

(**10g**), secondary (**10h**, **10i**), and tertiary propargyl acetates (**10a**) provided **12g**−**12i** and **12a** in good to excellent yields with excellent α-regio- and stereoselectivity. Notably, the primary propargyl acetate **10g** exhibited slower hydrosilylative cyclization kinetics and lower yield compared to secondary and tertiary propargyl acetates, presumably due to the absence of the Thorpe−Ingold effect. Cycloalkynol derivatives (**10j**−**10m**), ranging from three- to six-membered rings, tolerated the reaction conditions and generated **12j**−**12m**. Furthermore, alkyl-, phenyl-, and naphthyl-substituted propargyl acetates (**10n**−**10p**) uneventfully underwent, producing the corresponding (*E*)-dioxasilinanes (**12n**−**12p**) in good yields. Notably, the enyne substrate **10q**, containing a cyclohexenyl substituent, was compatible with the reaction conditions, leading to the formation of **12q** (79% yield). Heterocycle-substituted propargyl acetates were then examined. The reaction of benzofuran-substituted propargyl acetate **10r** afforded **12r** (77% yield). However, the reaction of pyridine-substituted propargylic acetate **10s** posed a significant challenge. Although a nearly quantitative conversion of **10s** to hydrosilyl acetal **11s** was observed under the conditions of Ir-catalyzed ester hydrosilylation, an additional extensive optimization was required for the Rh-catalyzed alkyne hydrosilylation step. Instability of both hydrosilyl acetal **11s** and cyclic acetal **12s** was observed under the standard Rh-catalyzed hydrosilylative cyclization conditions. However, we were pleased to discover that modifying the reaction conditions to a shorter reaction time (15 min) at higher temperature (100 °C) vis-à-vis 30 min at room temperature for

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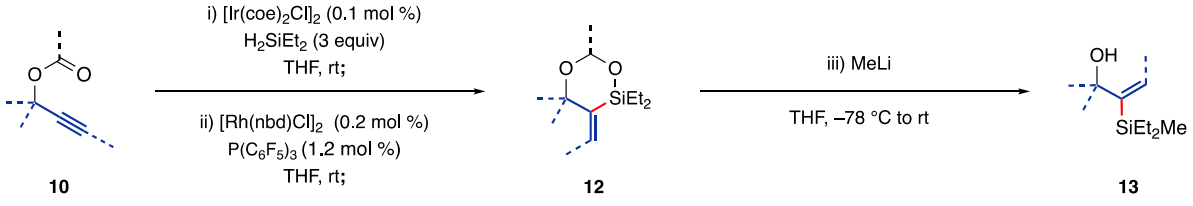
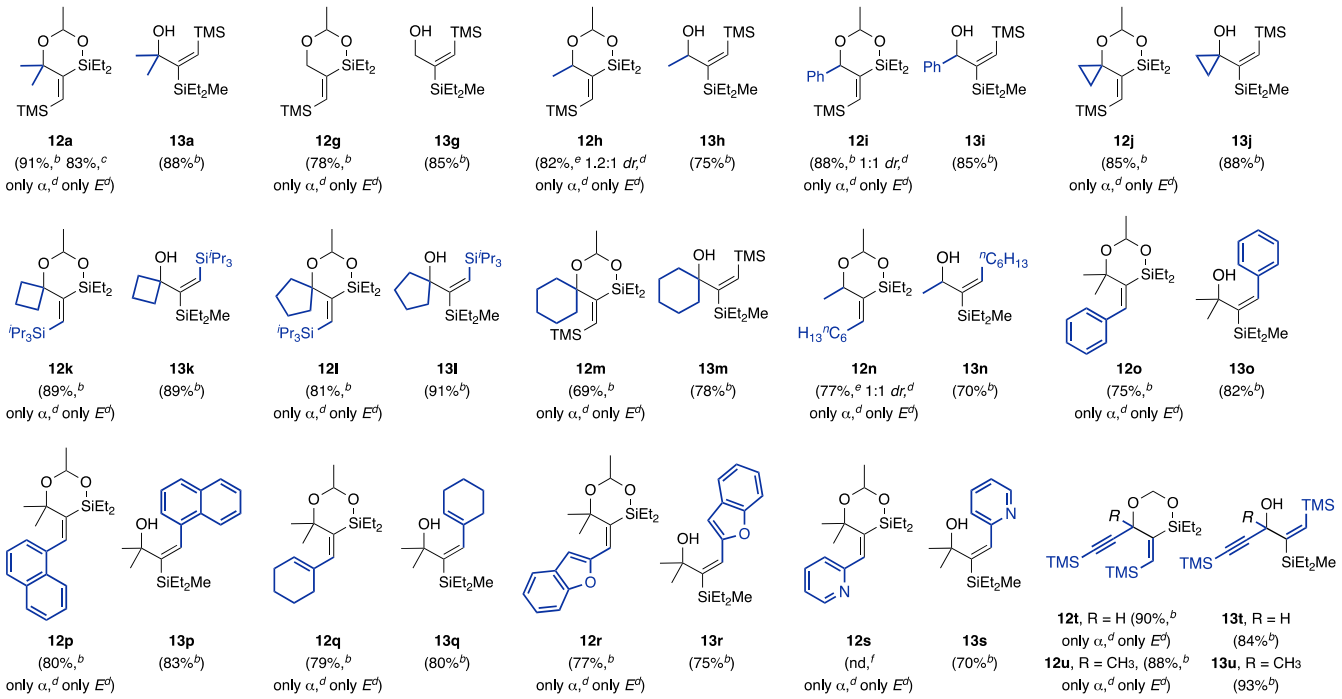
Table 3. Scope of Propargyl Acetates[a]





[a]Conditions: (i) **10** (0.2 mmol), THF (1 M), rt; (ii) THF (0.4 M), rt; (iii) MeLi (2.2 equiv), THF, −78 °C to rt. [b]Isolation yield. [c]5 mmol of **10a** was used. [d]Determined by GC/MS analysis and ^{1}H NMR spectroscopy. [e]Determined by ^{1}H NMR spectroscopy utilizing an internal standard (mesitylene). [f]Yields of **12s** were not determined due to their partial instability. Conditions for **12s**: (i) **10s** (0.2 mmol), THF (1 M), rt; (ii) THF (0.4 M), 100 °C, 15 min nd: not determined.

all other substrates provided **12s**. The yield of **12s** was determined after the nucleophilic addition reaction with MeLi to produce β-silyl allylic alcohols **13s** (70% yield, three steps from **10s**). Finally, under identical conditions, secondary and tertiary bis-propargylic acetates **10t** and **10u** delivered **13t** and **13u** via (*E*)-dioxasilinanes **12t** and **12u** in good yields, respectively. The traceless nature of this reaction sequence was demonstrated by the addition of nucleophile (MeLi) to (*E*)-dioxasilinanes,[30,34] which removed the acetal-directing group, uncovered α-hydroxy group, and modified the silyl moiety in the same vessel to provide β-silyl allylic alcohols (**13a**, **13g**–**13u**).

Having demonstrated the scope of nucleophiles that add to cyclic silanes in our earlier work,[30,34] we next sought to examine the traceless acetal-directed, α-selective dual hydrosilylative cyclization of diyne **14** to generate bis-silyl diene (Scheme 1a). A three-step sequence involving consecutive ester and alkyne hydrosilylations of propargyl bisacetate **14**, followed by MeLi addition, furnished functionalized 1,6-dihydroxy bis-silyl diene **15** (71% yield). Dioxasilinane **12n**, prepared from the sequential Ir and Rh hydrosilylations of **10n**, was capable of directly engaging in stereoretentive Pd-catalyzed cross-coupling to afford vinylarene **16** (Scheme 1b).[4,15]

To demonstrate the versatility of this strategy, we investigated the late-stage hydrosilylative modification of bioactive phenyl-substituted-17α-ethinylestradiol (EE) derivative **17** (Scheme 2). Under the reaction conditions developed, **17** underwent two consecutive Ir- and Rh-catalyzed hydrosilylation to give (*E*)-dioxasilinanes **20** via **19**. Upon the addition of MeLi to **20**, vinylsilane estradiol **18** was directly synthesized (overall 78% yield, 3 steps).

CONCLUSIONS

In summary, we have demonstrated the design and synthesis of a traceless two-atom tether acetal DG for the highly regio- and stereoselective catalytic α-selective *syn*-hydrosilylation of propargyl alcohols, leading to β-silyl allylic alcohols. The acetal DG was conveniently prepared via Ir-catalyzed ester hydrosilylation with excellent FG tolerance and a high yield. A π-acidic rhodium catalyst enabled the proximal, α-selective *syn*-hydrosilylation of a broad spectrum of primary to tertiary propargyl alcohols, resulting in (*E*)-dioxasilinanes with excellent regio- and stereoselectivity. The steric and electronic impacts of the hydrosilyl acetal structure on the α-selective, *syn*-hydrosilylative cyclization were investigated, where the π-acidic Rh catalyst facilitated fast cyclization of all types of hydrosilyl acetals with excellent regio- and stereoselectivity, presumably due to the establishment of a strong Rh-π

https://doi.org/10.1021/acscatal.4c04132
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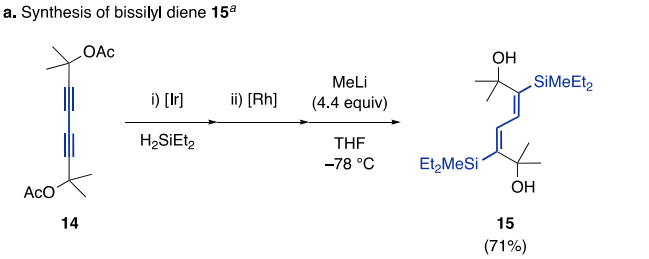
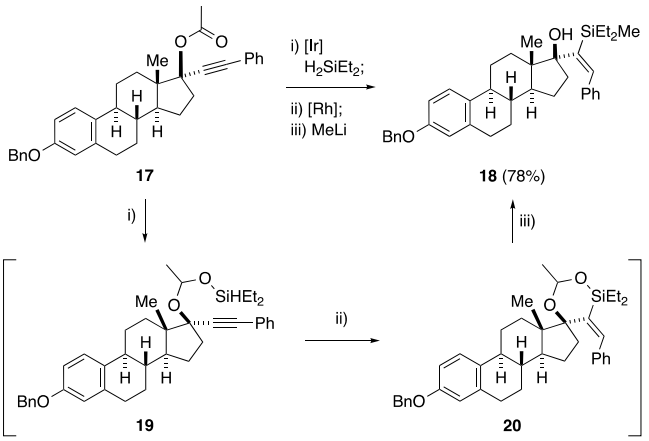
Scheme 1. Synthesis of Bis-Silyl Diene and Cross-Coupling of Vinylsilane[a]



[a]Conditions: (i) **14** (0.2 mmol), (ii) $[Ir(coe)_2Cl]_2$ (0.1 mol %), H_2SiEt_2 (3 equiv), THF (1 M), rt; (ii) $[Rh(nbd)Cl]_2$ (0.2 mol %), $P(C_6F_5)_3$ (1.2 mol %), THF (0.4 M); (iii) MeLi (4.4 equiv), THF, −78 °C to rt. [b]Conditions: **10n** (0.2 mmol), (ii) $[Ir(coe)_2Cl]_2$ (0.1 mol %), H_2SiEt_2 (3 equiv), THF (1 M), rt; (ii) $[Rh(nbd)Cl]_2$ (0.2 mol %), $P(C_6F_5)_3$ (1.2 mol %), THF (0.4 M); PhI (2 equiv), $Pd_2(dba)_3$ (2.5 mol %), TBAF (4 equiv), THF, rt to 40 °C.

Scheme 2. Late-Stage Hydrosilylative Modification of the 17α-Ethinylestradiol (EE) Derivative[a]



[a]Conditions: (i) **17** (0.2 mmol), (ii) $[Ir(coe)_2Cl]_2$ (0.1 mol %), H_2SiEt_2 (3 equiv), THF (1 M), rt; (ii) $[Rh(nbd)Cl]_2$ (0.2 mol %), $P(C_6F_5)_3$ (1.2 mol %), THF (0.4 M); (iii) MeLi (2.2 equiv), THF, −78 °C to rt.

interaction. This catalytic protocol demonstrated reasonably broad FG compatibility and scope, including the pyridine-substituted propargylic acetate. The scope of the resulting silyl moiety was expanded by postmodification of the resulting cyclic silyl acetal, introducing a new FG to the silicon moiety. This protocol was applied to a synthesis of conjugated bis-silyl 1,3-diene and stereoretentive Pd-catalyzed cross-coupling of dioxasilinanes to afford vinylarene. Finally, the versatility of this method was demonstrated in a late-stage hydrosilylative modification of a bioactive, complex molecular framework of a 17α-ethinylestradiol (EE) derivative.

METHODS

General Procedure for Traceless Acetal-Directed Catalytic Hydrosilylation of Propargyl Acetates. $[Ir(coe)_2Cl]_2$ (0.1 mol %) and propargyl acetates **10** (1 equiv) were dissolved with THF (1 M) in a flame-dried vial. Dihydrosilane (3 equiv) was added to the mixture. The septum on the vial was replaced by a screw cap with a Teflon liner. The reaction mixture was stirred for 12 h at rt. The volatiles were removed in vacuo to afford hydrosilyl acetals **11**, which were directly used for a subsequent reaction without further purification. $[Rh(nbd)Cl]_2$ (0.2 mol %) and $P(C_6F_5)_3$ (1.2 mol %) were dissolved in THF (0.4 M). The crude hydrosilyl acetals **11** were added to the mixture in one portion. The septum on the vial was replaced by a screw cap with a Teflon liner, and the mixture was stirred at rt. The reaction progress was monitored via GC−MS spectrometry. The volatiles were removed in vacuo, and the resulting mixture was dissolved with pentane, filtered through a pad of Celite, and concentrated in vacuo to afford crude dioxasilinanes **12**, which were purified by MPLC (hexanes/EtOAc). To a flame-dried vial was added a solution of dioxasilinanes **12** (1 equiv) in THF (0.2 M), and the mixture was cooled to −78 °C. MeLi (1.6 M in Et_2O, 2.2 equiv) was added slowly to the reaction mixture. After being stirred for 30 min at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The volatiles were removed to afford crude material, which was purified by MPLC (hexanes/EtOAc) to afford β-silyl allylic alcohols **13** as a colorless oil.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c04132.

Experimental details and spectroscopic characterization data for all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Junha Jeon − *Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States;* orcid.org/0000-0001-8632-8098; Email: jjeon@uta.edu

Authors

Udaya Sree Dakarapu − *Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States*

Yao Chung Chang − *Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States*

Thirupataiah Avullala − *Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States*

Suman Das Adhikary − *Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States;* orcid.org/0000-0002-0570-9794

Hiep H. Nguyen − *Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.4c04132

https://doi.org/10.1021/acscatal.4c04132
ACS Catal. 2024, 14, 14696−14702

Author Contributions

†U.S.D and Y.C.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the National Institutes of Health (GM116031), the National Science Foundation (CHE2102712), and the Welch Foundation (Y-2196-20240404) for financial support. The NSF (CHE-0234811 and CHE-0840509) is acknowledged for partial funding of the purchases of the NMR spectrometers used in this work. T.A. thanks The University of Texas at Arlington for dissertation fellowship.

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https://doi.org/10.1021/acscatal.4c04132
ACS Catal. 2024, 14, 14696−14702