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Dual Role of Silanol Groups in Cyclopropanation and Hiyama−Denmark Cross-Coupling Reactions

Louis-Philippe B. Beaulieu, Lukas B. Delvos, and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box. 6138,
Station Downtown Montréal, Québec, Canada H3C 3J7

andre.charette@umontreal.ca

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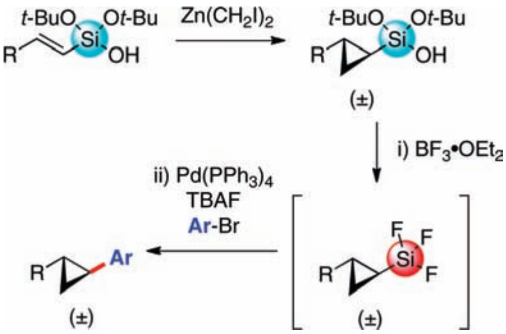
ABSTRACT



Di-*tert*-butoxy(alkenyl)silanols serve as substrates in the Simmons−Smith cyclopropanation reaction furnishing the corresponding di-*tert*-butoxy(cyclopropyl)silanols, which may be included in a Hiyama−Denmark cross-coupling reaction. The silanol group bears two distinct roles as it provides a directing group during the cyclopropanation and mediates the transmetalation event in the cross-coupling. The nature of the ligands on the silicon atom had a profound effect on reactivity in the cross-coupling, whereby substituting the alkoxide groups for fluorides allowed for efficient cross-coupling.

The cyclopropane unit continues to generate interest through its unique bonding properties and its numerous applications in diverse chemical transformations.[1] These motifs are present in several bioactive natural products as well as synthetic drugs,[2] which has prompted the development of methodologies for their synthesis. The Simmons−Smith reaction is one of the most important methods to form cyclopropanes.[3] Over the years, many variations of the seminal reaction[4] with zinc−copper couple and diiodomethane were disclosed, thereby increasing its synthetic utility. Notable among these is the protocol devised by Furukawa,[5] which allows the preparation of the zinc carbenoid from diethylzinc via an alkyl exchange with diiodomethane in various solvents. This landmark led to the development of other carbenoids, namely $Zn(CH_2Cl)_2$,[6] $CF_3CO_2ZnCH_2I$,[7] and 2,4,6-$Cl_3C_6H_2OZnCH_2I$,[8] which display either increased reactivity or stability, thus making the cyclopropanation of relatively unreactive unfunctionalized olefins feasible. Another strategy to access unfunctionalized cyclopropanes relies

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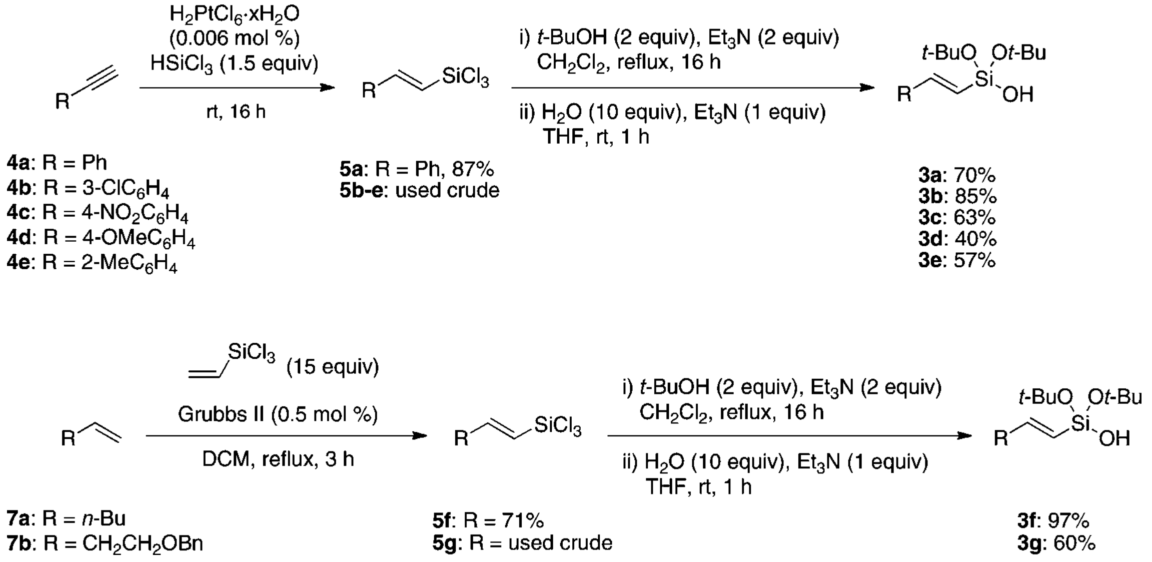
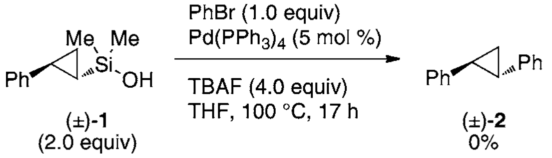
10.1021/ol1002863

Scheme 1. Synthesis of Di-*tert*-butoxy(alkenyl)silanols



on the use of a directing group that could later participate in a cross-coupling reaction. Alkenylboronic esters have been cyclopropanated with use of this approach,[9,10] and the resulting cyclopropylboronic esters have either been directly reacted in a cross-coupling reaction[11] or previously converted to the corresponding boronic acids[12] or trifluoroborates.[13] Despite the recent advances[14] for the cross-coupling of readily available, stable, nontoxic, and environmentally benign organosilanols with various electrophilic partners, little attention has been devoted to the Simmons−Smith cyclopropanation of alkenylsilanols. Hiyama and co-workers have reported the synthesis of dimethyl(alkenyl)silanols, the Simmons−Smith cyclopropanation of these substrates, and the subsequent Tamao−Flemming oxidation of the resulting dimethyl(cyclopropyl)silanols.[15]Mori and collaborators later performed the diastereoselective Simmons−Smith cyclopropanation of vinylsilanols bearing a chiral silicon atom, affording the corresponding enantiomerically enriched cyclopropylsilanols after a Tamao−Flemming oxidation.[16] Herein we report our efforts toward the Hiyama−Denmark cross-coupling of (cyclopropyl)silanols, whereby the bifunctional silanol moiety both serves as a directing group in the cyclopropanation step and mediates the transmetalation event during the cross-coupling.

We started our investigation by attempting the cross-coupling of (±)-(dimethyl((1*S*,2*R*)-2-phenylcyclopropyl)silanol (**1**) with bromobenzene using the conditions developed by Hiyama for alkyltrifluorosilanes (eq 1).[17]



(1)

Unfortunately, no (±)-(1*S*,2*S*)-1,2-diphenylcyclopropane (**2**) was formed at the outset of the cross-coupling reaction with either Hiyama's conditions or those developed recently by Denmark.[13] This led us to consider modulating the nature of the ligands on the silicon atom, such as to facilitate the rate-limiting transmetalation step in the cross-coupling.[18] DeShong[19] and Denmark[20] have reported an improved efficiency of the cross-coupling of aryl- and alkenylsilanes respectively upon increasing the electron-withdrawing character of the ligands directly bound to the silicon atom. They argue that this operates through the facilitated formation of the hypervalent pentacoordinated siliconate intermediate with TBAF, since the more electrophilic substituents are better able to stabilize the negative charge of the siliconate complex. We thus elected to incorporate two alkoxide functionalities onto the silicon instead of the methyl groups. Di-*tert*-butoxy(alkenyl)silanols (**3a**−**h**) were readily synthesized from the corresponding trichloro(alkenyl)silanes by using a modified procedure developed by Kojima (Scheme 1).[21] Di-*tert*-butoxy(styryl)silanols (**3a**−**e**) may be accessed through

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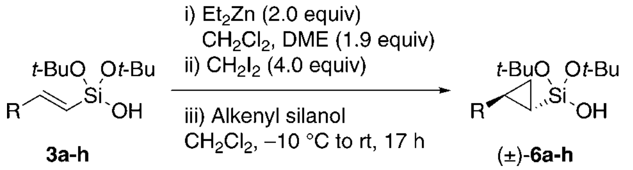
the hydrosilylation of a phenylacetylene derivative (**4a**−**e**) followed by the alcoholysis/hydrolysis of either the isolated (**5a**) or crude (**5b**−**e**) trichlorosilane. The (alkenyl)trichlorosilanes (**5f**, **5g**) are synthesized with use of a cross-metathesis methodology developed by Fischer and collaborators.[22] The di-*tert*-butoxy(alkenyl)silanols (**3f**, **3g**) may be generated by using the same alcoholysis/hydrolysis procedure.

The Simmons−Smith cyclopropanation of di-*tert*-butoxy(alkenyl)silanols (**3a**−**h**) with 2.0 equiv of the preformed zinc carbenoid bis(iodomethyl)zinc [$Zn(CH_2I)_2$] proceeded smoothly, providing the corresponding di-*tert*-butoxy(cyclopropyl)silanols (**6a**−**h**) in excellent isolated yields (Table 1). The (alkenyl)- and (cyclopropyl)silanols may be purified by filtration over a pad of silica gel and stored for several months without significant degradation, making them convenient substrates for cross-coupling reactions.

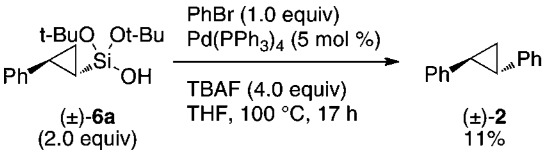
Table 1. Cyclopropanation Scope



entry	R	yield of **6** (%)[a]
1	Ph	93 (**6a**)
2	$3\text{-}ClC_6H_4$	91 (**6b**)
3	$4\text{-}NO_2C_6H_4$	92 (**6c**)
4	$4\text{-}OMeC_6H_4$	89 (**6d**)
5	$2\text{-}MeC_6H_4$	95 (**6e**)
6	*n*-Bu	81 (**6f**)
7	$BnO(CH_2)_2$	96 (**6g**)
8	H	88 (**6h**)

[a] Isolated yields.

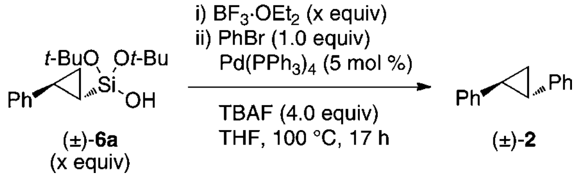
(±)-Di-*tert*-butoxy((1*S*,2*R*)-2-phenylcyclopropyl)silanol (**6a**) was shown to be moderately reactive in the Hiyama−Denmark cross-coupling, with 11% isolated yield of coupling product (**2**) (eq 2).



(2)

This result, despite being encouraging, still underlined the insufficient reactivity of the organosilane in the cross-coupling. To further increase the electrophilic nature of the silicon atom, **6a** was treated with $BF_3{\cdot}OEt_2$ prior to the cross-coupling reaction, such as to generate the trifluorosilane in situ.[23] Gratifyingly, this led to the isolation of **2** in 75% yield when the silanol was used as the limiting reagent (Table 2). Increasing the amout of silanol also led to improved yields with 1.5:1 (silanol:bromoarene) being optimal in this case.

Table 2. Effect of the Stoichiometry of the Reactants in the Hiyama−Denmark Coupling

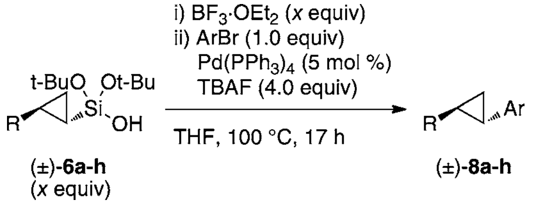


entry	*x* equiv	yield (%)[a]
1	0.8	75
2	1.2	79
3	1.5	91
4	2.0	90

[a] Isolated yields.

The scope of the Hiyama−Denmark cross-coupling (Table 3) tolerated electron withdrawing (**8b**, **8c**, **8f**) and donating (**8h**) groups on the aryl bromides. The reaction was compatible with a variety of functional groups on both coupling partners, namely an ester group (**8b**) and a ketone functionality (**8c**), and proceeded smoothly with 3-bromopyridine (**8g**). Whereas the coupling of styryl-substituted (cyclopropyl)silanols could be performed with 1.5 equiv of these compounds, the coupling of (cyclopropyl)silanols **6c**, **6d**, and **6h** required a larger excess of the silanol relative to the aryl bromide to achieve good yields.

Table 3. Hiyama−Denmark Cross-Coupling Scope



entry	*x*	R	Ar	yield of **8** (%)[a]
1	1.5	Ph	$2\text{-}MeC_6H_4$	89 (**8a**)
2	1.5	$3\text{-}ClC_6H_4$	$4\text{-}EtOC(O)C_6H_4$	70 (**8b**)
3	1.5	$4\text{-}NO_2C_6H_4$	$3\text{-}FC_6H_4$	85 (**8c**)
4	1.5	$4\text{-}OMeC_6H_4$	$4\text{-}CF_3C_6H_4$	92 (**8d**)
5	1.5	$2\text{-}MeC_6H_4$	3-Py	79 (**8e**)
6	2.0	*n*-Bu	$4\text{-}MeC(O)C_6H_4$	63 (**8f**)
7	2.0	$BnO(CH_2)_2$	$3\text{-}ClC_6H_4$	80 (**8g**)
8	2.0	H	$4\text{-}OMeC_6H_4$	80 (**8h**)

[a] Isolated yields.

In conclusion we have reported the synthesis of di-*tert*-butoxy(vinyl)silanols, which serve as substrates in the

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Simmons−Smith cyclopropanation reaction furnishing the corresponding di-*tert*-butoxy(cyclopropyl)silanols. These compounds are the first (cyclopropyl)silanes to be reacted in a Hiyama−Denmark cross-coupling. The silanol group bears two distinct functions as it provides a directing group during the cyclopropanation and mediates the transmetalation event in the cross-coupling. The nature of the ligands on the silicon atom had a profound effect on reactivity in the cross-coupling, whereby substituting the alkoxide groups for fluorides allowed for efficient cross-coupling. This contribution underlines the synthetic utility of silanol groups in organic chemistry. The development of asymmetric cyclopropanation conditions is ongoing and will be reported in due course.

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Supporting Information Available: Full experimental details and NMR spectral data for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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