Synthetic Methods

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Brønsted Acid Catalyzed α′-Functionalization of Silylenol Ethers with Indoles**

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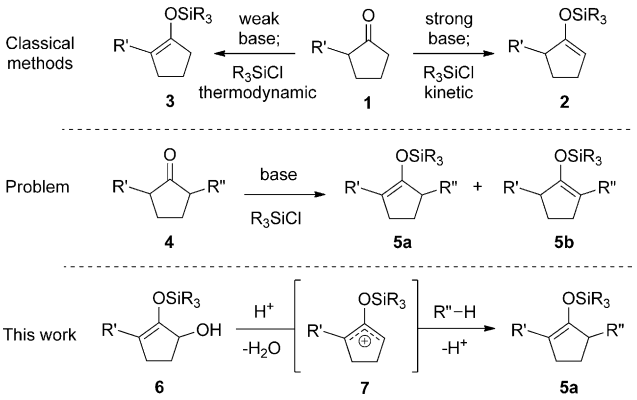
Dedicated to Professor Richard E. Taylor on the occasion of his 50th birthday

Abstract: *A new method which enables carbon–carbon bond formation at the α′-position of silylenol ethers by using catalytic amounts of pyridinium triflate is reported. This chemistry successfully produces, structurally challenging, highly substituted indole-containing silylenol ethers in excellent yields with complete regiocontrol, presumably through silyloxyallyl cation intermediates. Despite the use of Brønsted acid, the silylenol ether moiety does not undergo protodesilylation, thus underscoring the very mild reaction conditions.*

Silylenol ethers are useful, isolable intermediates in organic synthesis. They are convenient to handle, and their harnessed reactivity has enabled broad synthetic utilization.[1] Classical methods to prepare silylenol ethers typically involve treatment of ketones with a base and trialkylsilyl chloride, in which the regioselectivity of the enolization is controlled by the reaction conditions.[2] For example, the use of strong bulky bases, such as LDA, at cryogenic temperatures deprotonate the less-sterically hindered α-hydrogen atom and generate the kinetic enolate en route to less-substituted silylenol ethers (**1**→**2**; Scheme 1). Alternatively, enolization methods with a weak base in the presence of trialkylsilyl chlorides under equilibration conditions will favor removal of the more sterically congested proton and yield the thermodynamically driven, more-substituted silylenol ethers (**1**→**3**). While these strategies have proven effective in differentiating enolization at the α- versus α′-position of monosubstituted ketones, for example **1**, regioselective formation of a silylenol ether from α,α′-disubstituted ketones, such as **4**, is problematic, as subjection of such substrates to either of these reaction conditions could lead to a mixture of the silylenol ethers **5a** and **5b**. Although discrimination in the enolization at the α- versus α′-positions in disubstituted ketones could be influenced by the inherent steric and electronic bias from the substituents,[2,3] regioselective methods to access silylenol ethers without relying on these effects are lacking.[4]



Scheme 1. Preparation of silylenol ethers.

Herein we describe our contribution to this longstanding problem through the development of a synthetic strategy involving cationic processes. We envisioned that a structural motif, such as the α′-hydroxy silylenol ether **6**, could be ionized to yield the putative oxyallyl cation **7**, which could then undergo direct addition with a carbon nucleophile at the sterically less-congested α′-carbon atom to provide the silylenol ether **5a** exclusively as a single regioisomer (Scheme 1). The overall success of this chemistry is critically dependent on the ionization of the α′-hydroxy group. We propose that this should be readily promoted by a Brønsted acid. Although Brønsted acids are known to promote protodesilylation of silylenol ethers in polar, nucleophilic solvents,[5] we believe that in a nonpolar, non-nucleophilic medium, protonation of the α′-hydroxy group, thus leading to ionization, should be kinetically competitive.

The synthetic application of oxyallyl cation intermediates is well documented in processes such as the Nazarov cyclization,[6] [4+3] cycloadditions,[7] and [3+2] cycloaddition.[8] However, examples on the intermolecular direct trapping of oxyallyl cations with nucleophiles remain scarce.[9] In fact, there are only a handful of contemporary examples which illustrate the use of carbon nucleophiles, in particular indoles, in this chemistry.[9f,g] This advancement is, however, significant, as such strategies have also empowered the concise syntheses of various biologically active indole-containing alkaloids, enabled by the crucial carbon(sp^2)–carbon(sp^3) bond formation at the α-position of carbonyl compounds.[10]

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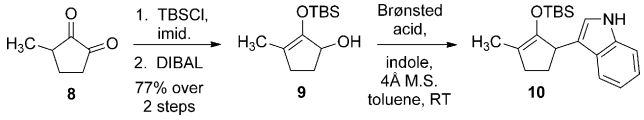
The initial investigation on our proposed method employed the α′-hydroxy silylenol ether **9** (see Table 1) as a model substrate. This compound was prepared in just two steps and 77% yield from commercially available 3-methylcyclopentane-1,2-dione (**8**) by enolization under thermodynamic conditions using TBSCl and imidazole, followed by reduction of the remaining ketone with DIBAL.

Our study then proceeded towards surveying the appropriate Brønsted acid. We began with pyridinium salts,[11a,b] and a hypothesis that the mild acidity of pyridinium ions in a nonpolar solvent, such as toluene, should not affect the integrity of the silylenol ether moiety. Driven by our interest towards developing synthetic strategies to access indole-alkaloid natural products, we decided to use indole to capture the putative silyloxyallyl cation intermediate. As shown in entries 1–3 of Table 1, pyridinium tosylate, pyridinium sulfate,

Table 1: Screening of Brønsted acid and optimization.



Entry	Brønsted acid (equiv)	Equiv of indole	*t* [h]	Yield [%][a]
1	Py·TsOH (2.0)	4.0	0.7	58
2	$Py_2{\cdot}H_2SO_4$ (2.0)	4.0	48	trace
3	Py·TfOH (2.0)	4.0	9	86
4	Py·TfOH (2.0)	2.0	32	84
5	Py·TfOH (2.0)	1.1	32	69
6	Py·TfOH (1.5)	2.0	24	84
7	Py·TfOH (1.0)	2.0	36	75
8	Py·TfOH (0.1)	2.0	66	91
9	TfOH (0.1)	2.0	6	67[b]

[a] Yield of product isolated after flash column chromatography.
[b] Protodesilylation product was isolated in 8% yield. DIBAL = diisobutylaluminum hydride, M.S. = molecular sieves, TBS = tert-butyldimethylsilyl.

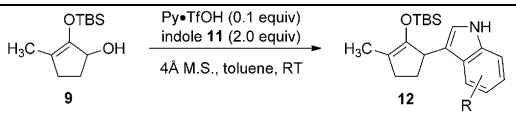
and pyridinium triflate were initially explored, and 4 Å molecular sieves were added to absorb water generated upon ionization of the starting material. Treatment of **9** with 2 equivalents of pyridinium tosylate and 4 equivalents of indole in toluene at room temperature consumed the starting material in less than an hour and afforded the α′-indole silylenol ether **10** in 58% yield as a single regioisomer. Interestingly, the reaction failed with pyridinium sulfate, and **9** was fully recovered. Pyridinium triflate proved to be the best Brønsted acid, thus leading to the production of the silylenol ether **10** in 86% yield. As expected, protodesilylation of either **9** or **10** did not occur under these mildly acidic conditions. In fact, the stability of both **9** and **10** enabled us to easily monitor the progress of reaction by simple TLC analyses and to isolate the product using silica-gel column chromatography.

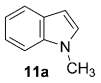
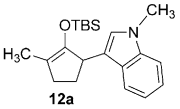
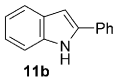
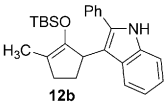
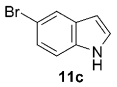
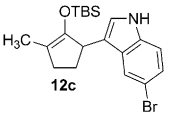
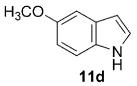
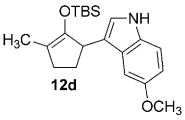
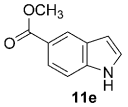
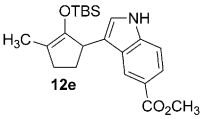
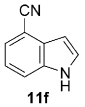
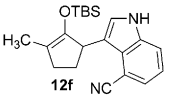
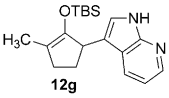
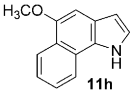
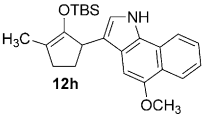
Our reaction optimization continued with a systematic screening on the molar equivalents of the nucleophile and the Brønsted acid. As shown in entries 3–5 (Table 1), reducing the amount of indole from 4 to 2 equivalents impeded the rate of reaction, but it did not affect the yield of the product. We established that 2 equivalents of indole were optimal, as further decrease to 1.1 equivalents eroded the yield to only 69%. Our efforts then shifted towards pyridinium triflate, and we found that the use of 1.5 and 1.0 equivalents of the Brønsted acid afforded **10** in 84 and 75% yields, respectively (entries 6 and 7). Remarkably, reducing the loading of pyridinium triflate to a catalytic range furnished the best result. As indicated in entry 8, activation of **9** with 0.1 equivalents of the Brønsted acid produced **10** in 91% yield upon isolation. Although the reaction took 66 hours to reach completion, the silylenol ether functionality remained intact, and strongly underscored the very mild nature of our reaction conditions. As shown in entry 9, the use of catalytic triflic acid readily produced **10** in 67% yield. Not surprisingly, these strongly acidic conditions also generated a small amount of the protodesilylation product. This critical experiment implied that pyridine did not play any role in controlling regioselectivity between the α- versus α′-positions with regard to the addition of indole. Instead, pyridine appeared to have served simply as a conjugate base spectator in this reaction.

With the optimized reaction conditions in hand, we then explored the functionalization of **9** with various indoles (Table 2). As depicted in entry 1, the use of *N*-methyl-indole (**11a**) afforded the coupling product **12a** in 72% yield. Placement of a phenyl substituent at the 2-position of the indole (**11b**) produced the silylenol ether **12b** in 83% yield, thus suggesting that an increase in the steric congestion neighboring the nucleophilic carbon center in indole did not affect the efficacy of the reaction. The electronic requirements of the nucleophile were also examined (entries 3–6). A halogen-containing indole, such as 5-bromoindole (**11c**), readily afforded the α′-functionalized silylenol ether **12c** in 84% yield. An electron-rich nucleophile, such as 5-methoxyindole (**11d**), was found to be robust in this chemistry, thus yielding product **12d** in 76%. Electron-deficient indoles, such as methyl indole-5-carboxylate (**11e**) and 4-cyanoindole (**11f**), were also tolerated to produce the silylenol ethers **12e** (67%) and **12f** (60%), respectively, although these reactions took a considerably longer time to complete. An attempt to accelerate the rate of reactions with electron-poor indoles by slightly raising the temperature up to 40 °C was not productive. Such reaction conditions resulted in decomposition materials and eroded product yields. The products **12a–f** were isolated as a single regioisomer with the enol functionality being generated exclusively at the kinetically and thermodynamically less-favorable site.[11a,c,12] The structural assignment was further supported by the 4-cyanoindole-containing silylenol ether **12f**, which exists as a crystalline material, and we were able to unambiguously confirm its structure using X-ray crystallography (see the Supporting Information).[13]

The azaindole **11g** was also subjected to the scope of indoles study, but **9** remained unreacted, presumably because of the neutralization of the Brønsted acid catalyst by the basicity of azaindole (Table 1, entry 7). Interestingly, an attempt to perform this reaction with 2 equivalents of pyridinium triflate still did not yield the product **12g**. In this case, we believe that protonation of azaindole by the Brønsted acid strongly deactivated its nucleophilicity, thus

Table 2: Scope with respect to indoles.



Entry	Indole	Product	*t* [hrs]	Yield [%][a]
1	 **11a**	 **12a**	41	72
2	 **11b**	 **12b**	41	83
3	 **11c**	 **12c**	53	84
4	 **11d**	 **12d**	40	76
5	 **11e**	 **12e**	74 21	67[b] 57[c]
6	 **11f**	 **12f**	147 21	60[b] 53[c]
7	 **11g**	 **12g**		n.r.[d]
8	 **11h**	 **12h**	47	57

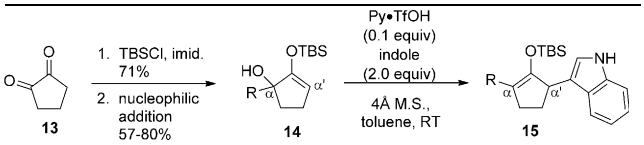
[a] Yield of product isolated after flash column chromatography. [b] The starting material **9** was not fully consumed. [c] Reactions were performed at 40 °C. [d] No reaction under the optimized conditions or at 40 °C. The reaction also failed with 2 equivalents of pyridinium triflate.

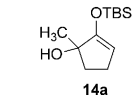
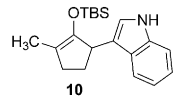
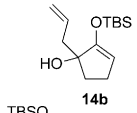
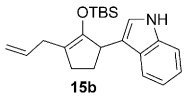
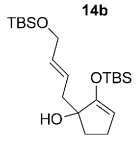
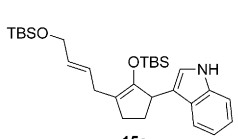
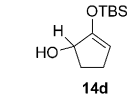
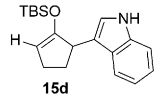
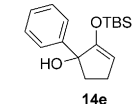
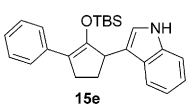
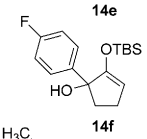
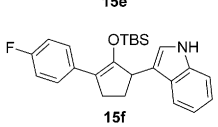
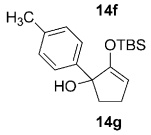
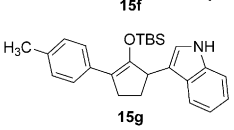
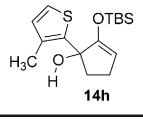
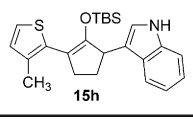
rendering it inactive towards nucleophilic addition to the putative oxyallyl cation intermediate. As shown in entry 8, the functionalized benzindole **11h** was found to be suitable in this chemistry. This carbon nucleophile readily led to structurally complex silylenol ether **12h** in 57% yield as a single regioisomer.

The steric and electronic requirements exhibited by the substituent at the α-position in the starting material towards α′-functionalization were also investigated. As a result of very limited commercial availability of the 1,2-diketone precursors required for the preparation of substrates analogous to compound **9**, the tertiary α-hydroxy silylenol ether **14** (see Table 3) was employed as a starting material in this study. This compound was readily synthesized in just two steps from cyclopentane-1,2-dione (**13**). Upon monosilylation with TBSCl and imidazole, treatment of the resulting ketone with a variety of organometallic reagents readily introduced structural diversification at the α-position. We proposed that ionization of starting material **14** with catalytic pyridinium triflate should readily generate the putative silyloxyallyl cation and react with indole to give α,α′-disubstituted silylenol ether **15**.

As shown in Table 3, we initially incorporated a methyl group to form the silylenol ether **14a** as a control experiment (entry 1). Exposure of this substrate to the activation protocols afforded the α′-indole substituted product **10** in 75% yield, thus validating our hypothesis. Aliphatic chains in the starting materials **14b** and **14c** cleanly produced **15b** (60%) and **15c** (93%), respectively. The survival of the primary TBS ether in **15c** again highlighted the very mild reaction

Table 3: Diversification of silylenol ether substrates.



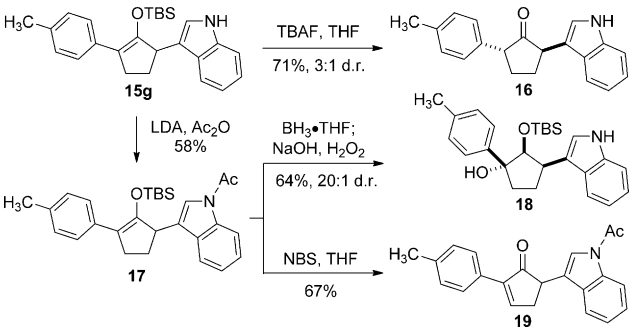
Entry	Starting material	Product	*t* [h]	Yield[%][a]
1	 **14a**	 **10**	10	75
2	 **14b**	 **15b**	138	60
3	 **14c**	 **15c**	96	93
4	 **14d**	 **15d**		n.r.[b]
5	 **14e**	 **15e**	30	86
6	 **14f**	 **15f**	17	91
7	 **14g**	 **15g**	60 22	92 91[c]
8	 **14h**	 **15h**	46	86

[a] Yield of product isoalted after flash column chromatography. [b] No reaction under the reaction conditions. [c] The reaction was performed in a gram-scale setting. See the Supporting Information for reaction conditions.

conditions. Entries 1–3 revealed that increasing the steric bulk at the α-position profoundly impeded the rate of reaction. Interestingly, the unsubstituted α′-hydroxy silylenol ether **14d** failed to undergo reaction with indole under the reaction conditions, thus suggesting the requirement for a substituent at the α-position to help stabilize the participating cationic intermediates. Entries 5–8 signified that substrates bearing aromatic rings were found highly suitable in this chemistry. For instance, the phenyl-substituted starting material **14e** generated the α-phenyl-α′-indole silylenol ether **15e** in 86% yield. Weakly deactivated and weakly activated aromatic substituents in **14f** and **14g** furnished silylenol ethers **15f** and **15g**, respectively, in near quantitative yields. This method was suitable for scale-up, as demonstrated by the gram-scale preparation of the compound **15g**. Furthermore, the starting material **14h** produced the α-thiophene-α′-indole product **15h** in 86% yield, thus indicating that aromatic heterocycles were also compatible.

Similarly, these α′-functionalization products were obtained as a single structural isomer. In fact, regioselective synthesis of these high-value α,α′-disubstituted silylenol ethers by classical enolization methods from α,α′-disubstituted ketones would be impractical. Not only would such reaction conditions require protection of the indole ring, but complete discrimination of the two similarly acidic and sterically hindered hydrogen atoms at the α- versus α′-positions towards selective deprotonation would be very difficult. Equally as important, our chemistry also successfully addressed the challenging issue concerning the control of regioselectivity in the direct nucleophilic addition to unsymmetrical oxyallyl cations.[9f,g] We discovered that an introduction of a silyl ether group to the oxyallyl cation moiety enabled the capture of this putative cationic species by indole with complete control of regioselectivity, predictably at the less substituted carbon center. In fact, every example presented herein involved the generation of unsymmetrical silyloxyallyl cations with substituents having various steric and electronic features, and we were able to generate the corresponding α,α′-disubtituted silylenol ether products in excellent yields, and more importantly, as a single regioisomer.

Moreover, the construction of unsymmetrical silylenol ethers, as depicted in Tables 1–3, presented unique opportunities for us to synthesize other structurally demanding molecular architectures, such as those depicted in Scheme 2. For example, protodesilylation of the silylenol ether **15g** with TBAF readily produced the synthetically challenging α,α′-diaryl ketone **16** in 71% yield as a 3:1 mixture of diastereomers favoring the *anti* relative stereochemistry (see the Supporting Information for X-ray structure).[13] We also observed that the indole ring in **15g** could be safely protected using LDA and acetic anhydride without compromising the silylenol ether moiety. The resulting acetylated product **17** could then be subjected to a diastereoselective synthesis of a complex 1,3-diaryl cyclopentane-1,2-diol derivative by treatment with BH_3·THF, followed oxidative workup. These reaction conditions produced the corresponding monosilylated 1,2-*anti*-diol **18** in a good yield as a single diastereomer. The relative stereochemistry of the product was deduced through X-ray structure analysis (see the Supporting Information).[13,14] We also discovered that **17** could be cleanly oxidized with NBS. In fact, this interesting protocol readily generated α,α′-diaryl cyclopentenone **19** in 67% yield.



Scheme 2. Examples of synthetic utility of α,α′-diaryl silylenol ethers. LDA = lithium diisopropylamide, NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

In conclusion, we have described a new synthetic method for the functionalization of silylenol ethers at the α′-position with indole. To the best of our knowledge, our results constitute an original example for direct nucleophilic addition to putative silylenol-ether-bearing oxyallyl cations, and it occurs exclusively at the less substituted carbon center, under mild Brønsted acid catalysis. This chemistry enables robust production of synthetically valuable and versatile α,α′-disubstituted silylenol ethers in high yields with complete regiocontrol. We are now undertaking complete investigations to further explore this unprecedented reactivity of silyloxyallyl cations, including the origin of this remarkable control of regioselectivity. Our results will be reported in due course.

Keywords: Brønsted acid · heterocycles · nucleophilic substitution · oxyallyl cations · silylenol ethers

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[13] See Supporting Information. CCDC 1018597 (**12 f**), 1043447 (**16**), 1044752 (**18**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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