Organic LETTERS

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Functionalization of Silyldienol Ethers at the γ-Position via 2-Silyloxypentadienyl Cations

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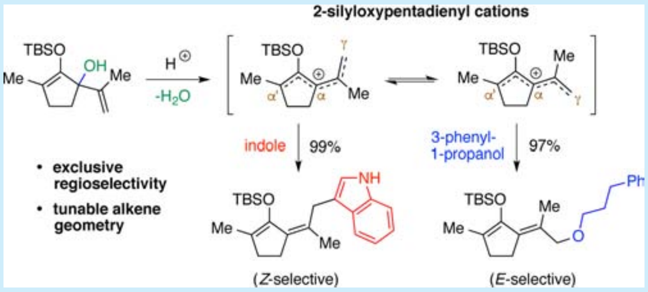
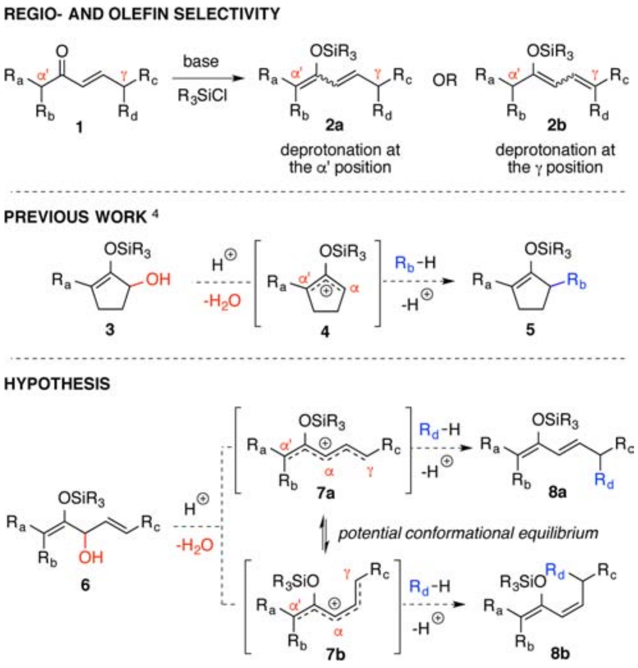
Ⓢ *Supporting Information*

ABSTRACT: This report describes Brønsted acid catalyzed *de novo* synthesis of silyldienol ethers bearing tetrasubstituted double bonds via an intermediacy of 2-silyloxypentadienyl cations. The reactivity of these novel cationic intermediates could be modulated and harnessed toward direct nucleophilic additions regioselectively at the γ-position to produce highly functionalized silyldienol ethers with tunable control of the resulting double bond geometry.



Silyldienol ethers are isolable synthetic intermediates that have found significant applications in the construction of complex molecules. These compounds commonly serve as a convenient source of four carbon atoms in various carbon–carbon bond forming processes, such as [4 + 2] cycloaddition reactions[1] and vinylogous Mukaiyama aldol reactions.[2] Silyldienol ethers are generally prepared via deprotonation of α,β-unsaturated ketones, *viz* **1**, in the presence of a base, followed by the capture of the forming dienolate anions with trialkylsilyl chloride. Nevertheless, due to the comparable acidity of hydrogen atoms at the α'- and γ-positions, this classical enolization strategy could potentially produce a mixture of isomeric products **2a** and **2b**. Hypothetically, this regioselectivity issue could be further convoluted by the lack of control in the stereochemistry of the forming alkenes (Scheme 1).[3]

Scheme 1. Synthesis of Silyldienol Ethers



Our group recently reported a new tactic that rapidly functionalized silylenol ethers at the α-position via an intermediacy of unsymmetrical silyloxyallyl cations, *viz* **4**.[4] These reactive species were generated upon ionization of α-hydroxy silylenol ether precursors **3** promoted by a Brønsted acid and readily underwent direct nucleophilic addition, regioselectively at the less substituted α-carbon, to produce the corresponding α-functionalized silylenol ethers **5**. Encouraged by this work and others,[5] we envisioned that the regioselective synthesis of silyldienol ethers, with an opportunity to control the double bond stereochemistry, could be potentially accomplished via an analogous approach. More specifically, we intended to exploit the utility of 2-silyloxypentadienyl cation intermediates in this process.

Our hypothesis is as follows: ionization of α-hydroxy silylenol ether derived starting materials **6**, promoted by a Brønsted acid catalyst, should readily generate the corresponding 2-silyloxypentadienyl cations, viz. **7a**. The ensuing attack by nucleophiles to these reactive intermediates should occur at the less substituted electrophilic carbon, i.e. the γ-position, thus producing conjugated γ-functionalized silyldienol ether **8a** in a regioselective manner. Nonetheless, we must also consider the possibility that 2-silyloxypentadienyl cations **7a** could participate in conformational equilibrium with **7b**. This alternative configuration, upon nucleophilic addition also at the γ-position,

Received: January 20, 2016
Published: February 11, 2016

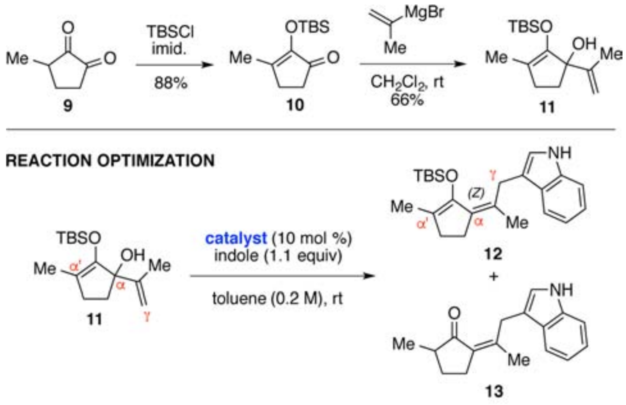
ACS Publications

DOI: 10.1021/acs.orglett.6b00196
Org. Lett. 2016, 18, 1084–1087

would generate silyldienol ether adduct **8b**, bearing the opposite olefin geometry. As opposed to 3-oxypentadienyl cations, which have been subjected to extensive studies due to their facile participation in the Nazarov electrocyclization,[6] synthetic utilities of 2-oxypentadienyl cations and their structurally related species are essentially underexplored.[7] In fact, to the best of our knowledge, there are no accounts on the reactivity of these cationic intermediates toward regioselective addition by nucleophiles.

Scheme 2 describes our proof-of-concept study, in which divinyl alcohol derived compound **11** was employed as a model substrate. We reasoned that the cyclic nature of this material would help simplify the forming diene geometry. Moreover, compound **11** was easily synthesized in just two steps from commercially available 1,2-dione **9**, which was subjected to regioselective silylation with a mixture of TBSCl and imidazole, followed by addition of 2-propenylmagnesium bromide to the resulting ketone **10**. We initially screened several Lewis and Brønsted acids to ionize starting material **11**. As indicated in entry 4, we discovered that the use of catalytic pyridinium triflate and indole in toluene at room temperature cleanly produced the corresponding γ-functionalized silyldienol ether **12** in a quantitative yield.

Scheme 2. Proof of Concept Studies



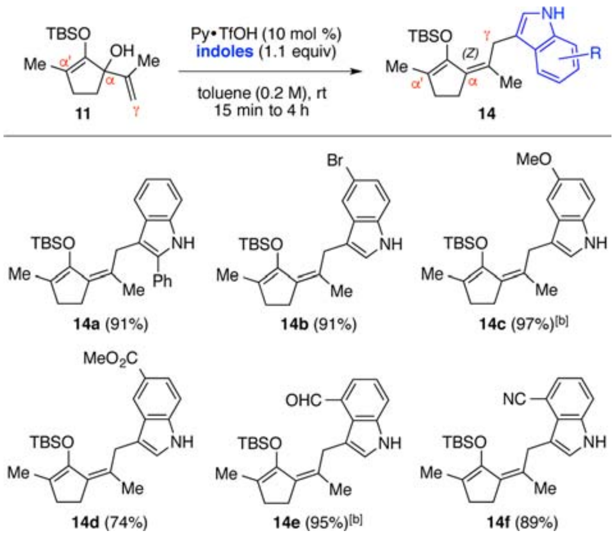
entry	catalyst	time (h)	yield of **12** (%) [a]
1	$La(OTf)_3$	23	20
2	AcOH	18	42
3	Py•TsOH	2	68
4	Py•TfOH	2.5	99
5	TfOH	0.2	45 [b]

[a]The double bond geometry was determined by NOE. [b]Protodesilylation product **13** was isolated in 48% yield.

There were two notable observations from these experiments: (1) as hypothesized, the addition of indole occurred solely at the γ-position; (2) surprisingly, the newly formed tetrasubstituted double bond in silyldienol ether **12** was produced exclusively as the *Z* isomer. This result is particularly intriguing, as the construction of tetrasubstituted alkenes in stereoselective manner is a formidable synthetic challenge.[8] The exquisite control of selectivity in this reaction did not originate from the free pyridine liberated upon proton transfer. As indicated in entry 5, a control experiment using catalytic triflic acid afforded silyldienol ether **12** also as a single isomer, along with the protodesilylated α,β-unsaturated ketone byproduct **13**, presumably generated due to the strongly acidic reaction conditions.

As shown in Scheme 3, the high regioselectivity in the γ-functionalization of divinyl alcohol **11** with catalytic pyridinium triflate appeared to be universal across various substituted indoles that were subjected to our studies. For example, sterically encumbered 2-phenylindole, halogen-containing 5-bromoindole, and electron-rich 5-methoxyindole generated silyldienol ethers **14a**−**14c** in excellent yields. Electron-deficient indoles, such as those containing methyl-5-carboxylate, 4-carbonitrile, and 4-carboxaldehyde groups, cleanly produced the corresponding adducts **14d**−**14f** in excellent yields. The tetrasubstituted alkenes in all of these products were produced exclusively with *Z* geometry.

Scheme 3. Scope of Indoles[a]

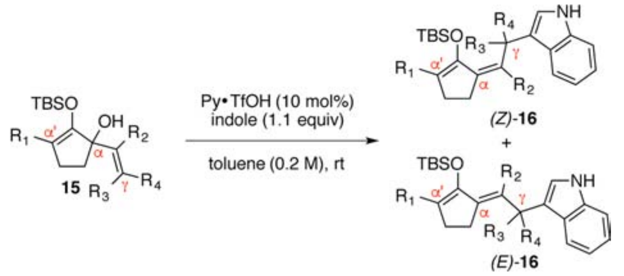


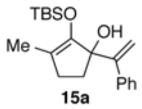
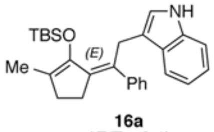
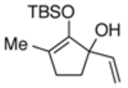
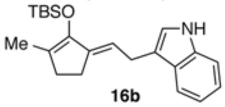
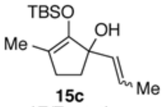
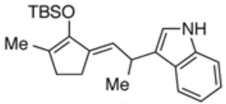
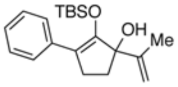
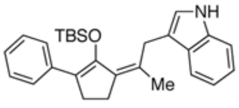
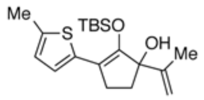
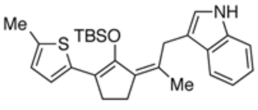
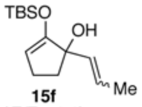
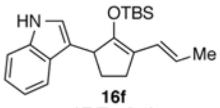
[a]The double bond geometry was determined by NOE. [b]The structural assignment of these products was confirmed by X-ray crystallography.[9]

To identify the controlling elements for the observed regioselectivity and alkene geometry in the above nucleophilic addition reactions, we prepared a series of starting materials **15** with various substitution patterns at the α'-, β-, and γ-positions and exposed them to our standard indoylation conditions (Table 1). As shown in entries 1−3, we began by modulating the β-position via substituted divinyl alcohols **15a**−**15c** and discovered its importance in dictating the forming alkene geometry. For instance, replacement of the β-methyl substituent with a sterically more demanding phenyl group in substrate **15a** afforded γ-indole adduct **16a** in 75% yield; however, we observed a significant erosion in the double bond selectivity (up to 3:1 when the reaction was carried out at −15 °C). Interestingly, removal of the β-substituent in starting materials **15b** and **15c** fully reversed the resulting olefin geometry, as these compounds produced their respective adducts **16b** and **16c** as the *E* isomer.

We then probed the role of α'-substituents. As shown in Table 1, entries 4−6, treatment of α'-phenyl and α'-thiophene substituted starting materials **15d** and **15e** with catalytic pyridinium triflate and indole produced their respective γ-functionalized silyldienol ethers **16d** and **16e** in good yields as a single regioisomer. These results supported our original hypothesis, in which nucleophilic additions to the putative 2-silyloxypentaldienyl cations would preferably occur at the least substituted electrophilic carbon. Nevertheless, we learned that nucleophilic addition at the α'-position, leading to formation of

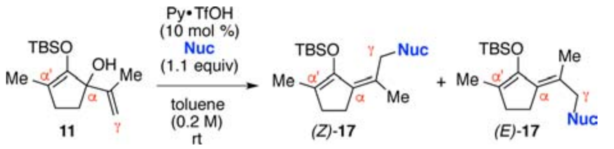
Table 1. Scope of Substrates

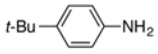
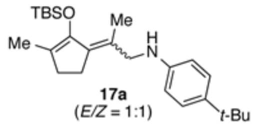
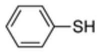
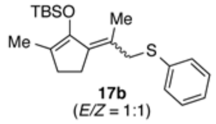
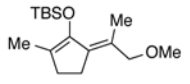
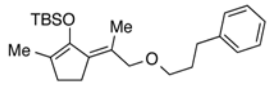
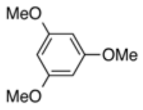
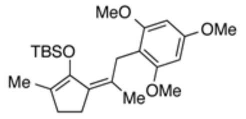
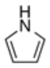
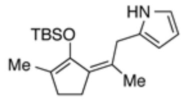


entry	starting material, **15**	product, **16**	yield of **16** (%) [a] (time)
1	 **15a**	 **16a** (*E*/*Z* = 3:1)	75 [b] (48 h, -15 °C)
2	 **15b**	 **16b**	64 (1 h)
3	 **15c** (*E*/*Z* = 1:1)	 **16c**	64 (14 h)
4	 **15d**	 **16d**	87 (22 h)
5	 **15e**	 **16e**	52 (14.5 h)
6	 **15f** (*E*/*Z* = 1:1)	 **16f** (*E*/*Z* = 3:1)	57 [c] (24 h)

[a]The double bond geometry was determined by NOE. [b]Product **16a** was isolated in 67% yield with *E*/*Z* ratio =1.7:1 when the reaction was performed at room temperature. [c]The product of indole addition at γ-position was isolated in 7% yield.

Table 2. Scope of Nucleophiles



entry	nucleophile	product, **17**	yield of **17** (%) [a] (time)
1		 **17a** (*E*/*Z* = 1:1)	73 (0.75 h)
2		 **17b** (*E*/*Z* = 1:1)	62 (5 h)
3	MeOH	 **17c**	59 (0.25 h)
4		 **17d**	97 (0.75 h)
5		 **17e**	60 (0.75 h)
6		 **17f**	89 (0.25 h)

[a]The double bond geometry was determined by NOE.

a presumed thermodynamically more favorable silyldienol ether isomer, became considerably much more competitive when the degree of substitution at both α′- and γ-positions was identical. For example, activation of substrate **15f** with our standard reaction conditions predominantly afforded α′-indole product **16f** in 57% yield.

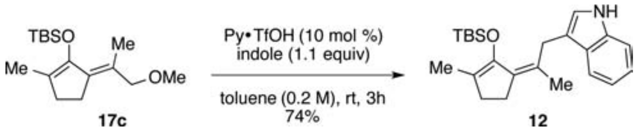
Table 2 depicts our exploration in the compatibility of various nucleophiles in this methodology beyond substituted indoles. We commenced by employing heteroatom-centered nucleophiles (Table 2, entries 1−4). Attempts to functionalize starting material **11** with *tert*-butylaniline and thiophenol under catalytic pyridinium triflate afforded the corresponding silyldienol ethers **17a** and **17b** in good yields, however as a 1:1 mixture of double bond isomers. Surprisingly, the use of methanol and 3-phenyl-1-propanol produced the respective products **17c** and **17d** with a complete reversal of selectivity, in which the tetrasubstituted alkene geometry was observed exclusively as the *E* isomer. We also examined the utility of other aromatic nucleophiles. For instance, 1,3,5-trimethoxybenzene and pyrrole afforded the corresponding γ-functionalized silyldienol ethers **17e** and **17f** in high yields. As anticipated, these products were isolated as the *Z*-isomer (Table 2, entries 5−6).

The exact mechanism by which heteroatom nucleophiles eroded or even reversed the double bond selectivity from *Z* to *E* geometry is currently under investigation. However, at this stage, we speculated that stereoselective formation of the (*E*) double bond in products **17c** and **17d** was perhaps driven by thermodynamics, as the generation of these compounds from their corresponding 2-silyloxypentadienyl cation intermediates should be reversible under the reaction conditions. The hypothesis was readily supported by an experiment depicted in Scheme 2, in which activation of compound **17c**, as an *E*-isomer, with catalytic pyridinium triflate and indole generated γ-indole silyldienol ether **12** with a complete inversion of the tetrasubstituted double bond to the *Z* geometry (Scheme 4).[10]

In summary, we have developed a rational design to generate 2-silyloxypentadienyl cations under mild Brønsted acid catalysis and uncovered their unprecedented reactivity toward direct nucleophilic additions. Furthermore, our ability to control regioselectivity between the α′- and the γ-positions has enabled

DOI: 10.1021/acs.orglett.6b00196
Org. Lett. 2016, 18, 1084−1087

Scheme 4. Reversal of Double Bond Geometry



us to exploit their useful synthetic utility toward the construction of highly functionalized silyldienol ethers bearing geometrically defined tetrasubstituted alkenes. We are currently pursuing detailed mechanistic studies and further applications of these chemistries.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00196.

Experimental procedures and spectral data of new compounds (PDF)
Crystallographic data for compound **14c** (CIF)
Crystallographic data for compound **14e** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under CHE-1464788. We gratefully acknowledge generous financial support from Louisiana State University and the Louisiana Board of Regents through the PFUND Award (LEQSF-EPS(2015)-PFUND-395). C.E.A. and J.R.S. thank the Louisiana Board of Regents for the Graduate Fellowship (LEQSF(2011-16)-GF-03 and LEQSF(2014-19)-GF-02). We thank Profs. George Stanley and Revati Kumar at LSU for their assistance with the DFT calculations. J.L.H. is an Undergraduate Research Participant.

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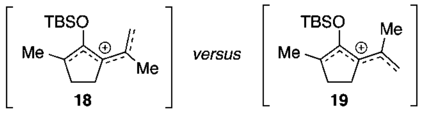
(9) The crystal of **14c** was a nonmerohedral twin, and refinement vs data detwinned using TWINABS resulted in a rather poor fit to the data, $R = 0.086$. However, the structure determination confirms the atom connectivity. See Supporting Information. (CCDC 1430091 and 1430092 contain crystallographic data for compounds **14c** and **14e**, respectively, which can be obtained free of charge from The Cambridge Crystallographic Data Centre).

(10) Silyldienol ether **12** appeared to be a kinetic product. We examined the ground state conformation of the putative 2-silyloxypentadienyl cations in the form of configurations **18** and **19**. Results obtained from DFT calculation (6-311g** basis set) indicated that the Gibbs energy of **18**, leading to the observed Z double bond in product **12**, is 2.5 kcal/mol more favorable than that of **19**.



favorable by 2.5 kcal/mol