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Synthesis of Cyclic β-Silylalkenyl Triflates via an Alkenyl Cation Intermediate

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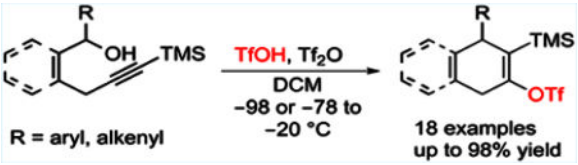
Abstract

Trimethylsilylalkyne derivatives are transformed into cyclic β-silylalkenyl triflates through cationic cyclization and subsequent trapping of the alkenyl cation by a triflate anion. β-Silylcyclohexenyl triflates and 3-trimethylsilyl-1,4-dihydronaphth-2-yl triflates are generated efficiently using this methodology. These products provide ready access to substituted cyclohexynes, exemplified by a concise total synthesis of β-apopicropodophyllin.

Abstract



Because of their high reactivities, small strained organic molecules, including arynes[1] and cycloalkynes,[2] have garnered much attention recently. Nevertheless, the modes through which cyclohexynes and related strained cyclic alkynes can be synthesized and reacted remain limited. Compounding this shortcoming, the majority of the reported syntheses and reactions of cyclohexynes have involved only the simple unsubstituted parent compound. The synthesis of cyclohexyne generally involves harshly basic conditions. Wittig and Roberts reported that cyclohexyne could be produced through dehydrohalogenation and elimination from the corresponding vinyl halide (Scheme 1).[3] Recently, Okano disclosed a simple method for the generation of substituted cyclohexynes through the direct elimination of cyclic enol trifluoromethanesulfonates (triflates, TfOs) using magnesium bisamides.[4] Although somewhat limited in substrate scope, several cyclohexynes were generated and subsequently trapped in moderate to good yields. The photochemical activation of a triazole to give cyclohexyne was developed by Willey and co-workers,[5] and the thermal or photochemical decomposition of a bis(diazirine) to generate cyclohexyne was elucidated by

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ASSOCIATED CONTENT
Supporting Information
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Detailed procedures and NMR spectroscopic data (PDF)

Banert.[6] By far, the most commonly adopted methods to obtain cyclohexynes are the desilylation/elimination of β-silylcyclohexenyl triflates[7] and the decomposition of cyclohexenyl iodonium salts.[8] These methods have proven amenable in the synthesis of complex molecules, although most examples have been limited to the generation of unsubstituted cyclohexynes.[2d-f,7d,9]

An understanding of reactive intermediates is essential to the study of many chemical reactions. Among the most exhaustively studied reactive intermediates in organic chemistry are those derived from formerly tetracoordinated carbon: carbocations, carbanions, carbon-centered radicals, and carbenes. In contrast, the unsaturated variants of these species have garnered significantly less attention.[10] In particular, vinyl cations, the unsaturated variants of carbocations (probably the most thoroughly investigated carbon-based reactive intermediates), have been studied the least. This stark gap in knowledge has been forged by the general belief that vinyl cations are high-energy intermediates and that simple alkylvinyl cations cannot be produced readily through solvolysis. Despite the fact that hydration of propyne or allene in aqueous sulfuric acid has been known since the 1870s,[11] vinyl cations were not proposed as viable reaction intermediates until Jacobs and Searles did so in 1944.[12] In 1964, Grob and Cseh reported the first formation of vinyl cations through the solvolysis of arylvinyl halides.[13] The use of superior leaving groups, such as the triflate anion, soon allowed for direct solvolytic formation of simple vinyl cations. The ability to readily generate and investigate a multitude of unique vinyl cations led many to pursue these reactive intermediates.[14] It is now well established that these intermediates can function as excellent electrophiles toward both n- and π-donors with reactivities higher than those of their saturated counterparts.

Recently, Fañanás and Rodriguez reported the simple generation of cyclic vinyl fluorides and triflates from enynes or alkynols upon activation with tetrafluoroboric acid or triflic acid (Scheme 2).[15] Inspired by this simple yet elegant method, we suspected that we could adapt it to the synthesis of substituted β-silylalkenyl triflates—the most common precursors to cyclohexynes. Treatment of silylalkynols with triflic acid, a Brønsted superacid, would liberate water to generate the cation **A**, which would undergo cationic cyclization to give the highly reactive alkenyl cation **B**. Trapping of this cation by a triflate anion would provide the cyclic β-silylalkenyl triflate product.

Our investigation of the feasibility of this process began with reacting ynol **1a**[16] under the conditions developed by Fañanás and Rodŕiguez (Table 1). Interestingly, their conditions led only to complete decomposition of the starting material, with no identifiable products (entry 1). We believe that the decomposition occurred because of the ready formation of vinyl cation **B**, which is likely more stable than its TMS-free counterpart, due to the β-silyl effect.[17] Not to be discouraged, we performed the transformation at a lower temperature (−78 °C), followed by slow warming to room temperature using dichloromethane (DCM) as the solvent (entry 2). Gratifyingly, we obtained the desired cyclization product **2a**, albeit as a 1:1 mixture with the desilylated product **3**. When adding triflic acid as a solution in DCM to increase its solubility at low temperature, we lowered the amount of desilylated product formed, but obtained a rearranged ketone (**4**) in its place (entry 3). Further dilution of the reaction almost completely eliminated the formation of **3**, but with a stark increase in the

yield of **4** (entries 4–9). Believing that this ketone was the byproduct of hydration of the alkyne, we devised a strategy to eliminate the water produced in the reaction. Fañanás and Rodriguez noted that hexane was the preferred solvent for preventing side reactions with water. By adding triflic anhydride (Tf_2O) to the reaction mixture, so that it would react with the water formed from the dehydration process, the amount of the ketone byproduct **4** decreased dramatically (entry 10). Superstoichiometric amounts of Tf_2O improved the chemoselectivity further, generating **2a** as the sole product (entry 12). Warming the reaction to −20 °C, rather than room temperature, allowed the use of a stoichiometric amount of Tf_2O (entry 14).

With several alkynols in hand, we explored the scope of this cationic cyclization (Scheme 3). Treatment of the alcohol **1a** under the established conditions provided the desired *β*-silylalkenyl triflate product **2a** cleanly in 97% yield. Progressing to more electron-rich substrates bearing 4-methoxy- and 4-methyl-phenyl substituents, we obtained the desired products **2b** and **2c** in yields of 94 and 91%, respectively. Even an electron-withdrawing fluorophenyl group was tolerated well under the conditions, providing the product **2d** in 85% yield.

Both 3-ffiryl and 2-naphthyl substitutions gave their cyclohexenyl products **2e** and **2f**, respectively, in great yields. Several allylic alcohols also furnished their *β*-silylvinyl triflate products in good yields. A cinnamyl alcohol derivative provided its corresponding cyclohexene **2g** cleanly in 91% yield, while an allylic alcohol counterpart gave its cyclic alkenyl triflate **2h** in good yield. Interestingly, both *E*- and *Z*-double bond isomers converged to a single product, **2i**, when reacted under the standard conditions. A cyclic alkene was also tolerated, giving the cyclopentenyl-substituted cyclohexene **2k** in excellent yield.

Next, we explored the preparation of a different molecular scaffold using this methodology: the 1,4-dihydronaphthalene core (Scheme 4). We observed improved efficiencies when performing the reaction at −98 °C, presumably because the initial alkyl cation was formed more readily with the greater stability imparted by the bis-benzyl moieties. The alcohol **5a** underwent cationic cyclization/vinyl cation formation/triflate ion trapping cleanly, but **6a** was isolated in only moderate yield. Progressing to substituted bis-benzyl alcohols, we obtained good yields from substrates presenting electron-rich moieties, exemplified by the 4-methoxy-, 4-methyl-, and 4-phenyl-substituted derivatives (**6b-d**, respectively). The presence of an ortho-substituted phenyl group had a profound effect on the reaction, providing **6e** in only moderate yield.[18] Both 2-naphthyl- and 3-thienyl-substituted 1,4-dihydronaphthalenes (**6f** and **6g**, respectively) were isolated in good yields.

The formation of the 1,4-dihydronaphthalene skeleton granted us access to a variety of aryltetralin lactones. To demonstrate the utility of this reaction, we report a concise synthesis of the cytotoxic lignin *β*-apopicropodophyllin (Scheme 5).[19] Isolated from the Jamaican plant *Hyptis verticillata, β*-apopicropodophyllin, which was initially assigned with the isomeric structure belonging to hyptinin,[19b] has displayed inhibitory effects on S1T, an adult T-cell leukemia cell line.[20] The addition of an aryllithium, derived from the known bromide 7,[21] into 3,4,5-trimethoxybenzaldehyde quickly produced the alkynol **8** required for cyclization. Applying our new methodology provided the *β*-silylalkenyl triflate **9** efficiently

and in excellent yield. Notably, this reaction was run on a gram scale, producing 1.06 g of the β-silylalkenyl triflate 9. The corresponding cyclohexyne, formed after treatment with tetrabutylammonium fluoride (TBAF), was trapped through a reaction with a known oxazole in a Diels-Alder/retro Diels-Alder sequence. Subsequent treatment with aqueous HCl provided the synthetic target β-apopicropodophyllin.[22]

In conclusion, we have developed a simple and efficient method for the formation of cyclic β-silylalkenyl triflates through a sequence involving cationic cyclization and trapping of the resulting alkenyl cation. The highly reactive nature of vinyl cations allowed trapping by the weakly nucleophilic triflate anion. The straightforward transformations of the resulting cyclic β-silylalkenyl triflates provided strained cyclohexynes that could serve as prime dienophiles. This strategy allowed the succinct total synthesis of β-apopicropodophyllin in two steps from the silyl triflate **9**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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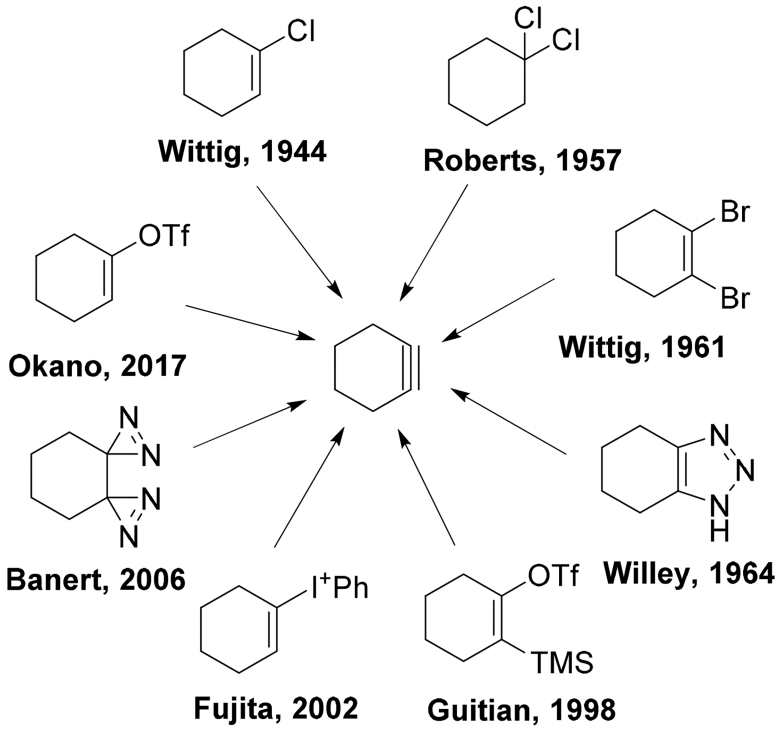
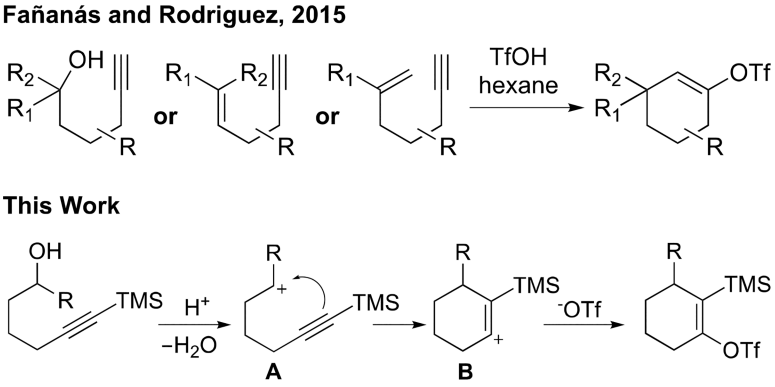
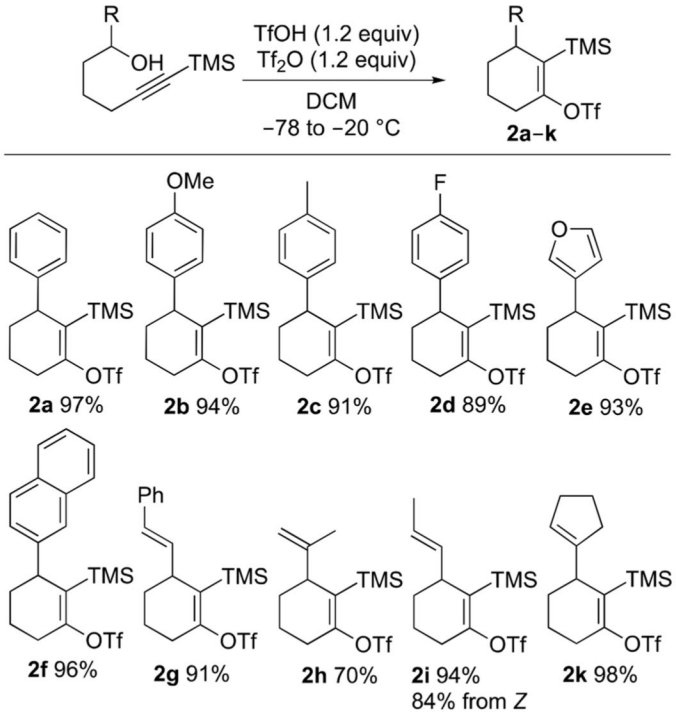


Scheme 1.
Methods To Generate Cyclohexyne



Scheme 2.

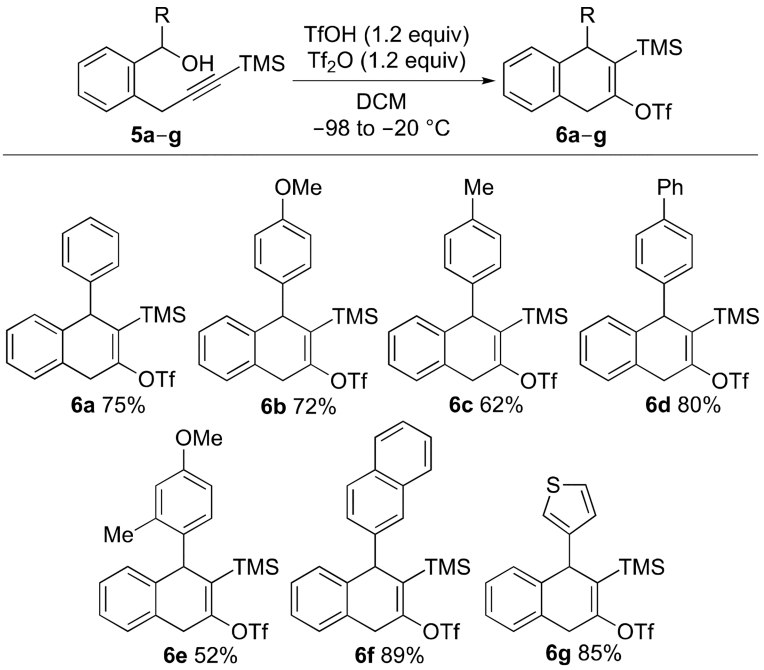
Forming Cyclohexenyl Triflates via Alkenyl Cations



[a]A solution of TfOH and Tf_2O in DCM (0.5 mL) was added dropwise to a solution of the corresponding alcohol (0.1 mmol) in DCM (1 mL) at −78 °C, and then the mixture was warmed to −20 °C. [b]Yields reported for isolated products.

Scheme 3.

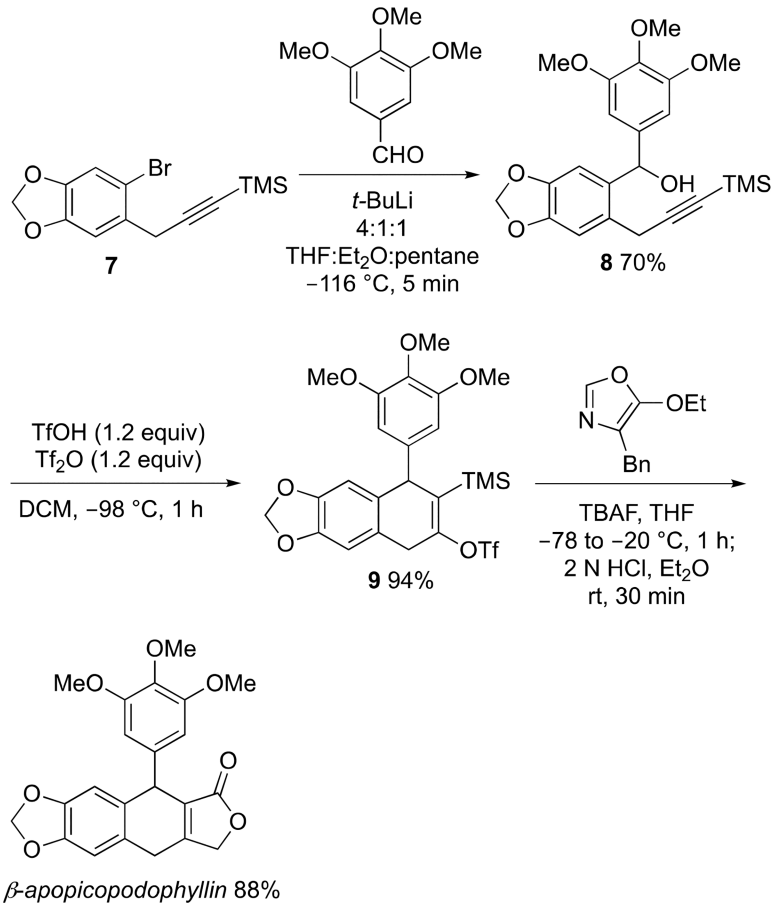
Generation of β-Silylcyclohexenyl Triflates[a,b]



[a]A solution of TfOH and Tf_2O in DCM was added dropwise to a solution of the corresponding alcohol in DCM at −98 °C, and then the mixture was warmed to −20 °C. [b]Yields reported for isolated products.

Scheme 4.

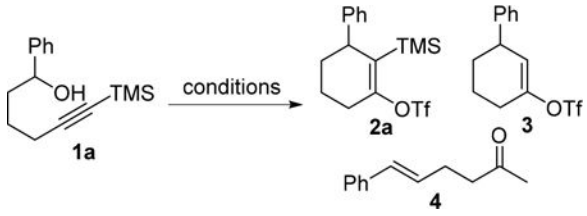
Synthesis of 1,4-Dihydronaphthalene Derivatives[a,b]



Scheme 5.
Synthesis of β-Apopicropodophyllin

Table 1.

Optimization of the Cationic Cyclization[a]



entry	concn (M)	Tf_2O (equiv)	ratio 2a:3:4[b]	conversion (%)[c]
1[d,e,f]	0.1	-	-	0
2[f]	0.1	-	1:1:0	100
3	0.1	-	1:0.6:0.1	100
4	0.075	-	1:0.3:0.1	100
5	0.063	-	1:0.3:0.15	100
6	0.05	-	1:0.26:0.13	100
7	0.038	-	1:0.23:0.23	100
8	0.025	-	1:0.16:0.29	100
9	0.013	-	1:0.06:0.46	99
10	0.0063	0.5	1:0.04:0.28	99
11	0.01	2	1:0:0.18	100
12	0.01	5	1:0:0	100
14[g]	0.067	1.2	1:0:0	100

[a] A solution of TfOH (1.2 equiv) and Tf_2O in DCM was added dropwise to a solution of 1a in DCM at −78 °C, and then the mixture was warmed to room temperature over 2 h.

[b] Ratios determined through crude ^1H NMR spectroscopic analysis.

[c] Conversion determined through crude ^1H NMR spectroscopic analysis.

[d] Hexanes used as solvent.

[e] Reaction run at rt.

[f] Neat TfOH was added directly to the reaction mixture.

[g] Reaction warmed to -220 °C