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# Cyclic vinylogous triflate hemiacetals as new surrogates for alkynyl aldehydes

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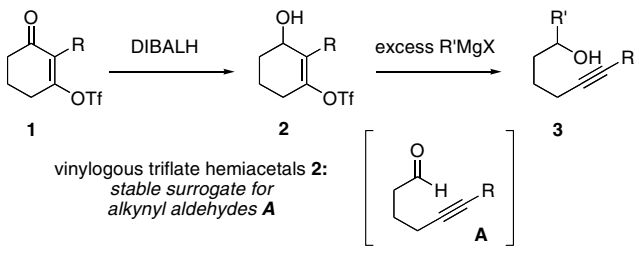
**Abstract**—Cyclic vinylogous triflate hemiacetals can serve as 'synthetic equivalents' for alkynyl aldehydes: treatment of a vinylogous triflate hemiacetal with excess amounts of Grignard reagents produces acyclic alkynyl alcohols in good to high yields. This transformation likely involves the Grob-type C–C bond cleaving fragmentation to form the alkynyl aldehyde in situ. Subsequent nucleophilic attack of the Grignard reagent furnishes secondary alkynols. Vinylogous triflate hemiacetals are easily prepared by DIBALH reduction of vinylogous acyl triflates, which are derived from cyclic 1,3-diketones.


Carbonyl moieties are ubiquitous components of important molecules in a wide range of areas in chemistry.[1] The diverse reactivity of carbonyl compounds presents many options in organic synthesis, but the high reactivity of those compounds usually needs to be managed effectively to achieve the desired transformations. Aldehydes, being generally more reactive than ketones and esters, pose particular problems related to the myriad reaction pathways in which aldehydes participate.

Protecting group strategies are often employed to control the reactivity of C=O bonds, with acetals of various types being perhaps the most popular.[2] Under a range of mild hydrolytic conditions, acetals may be reversibly converted into hemiacetals, which generally collapse to reveal the underlying carbonyl group. Protecting groups enable one to shuttle sensitive functionality through harsh reaction sequences before the deprotection at the appropriate stage.

Alternatively, masked carbonyls may be employed to reveal the reactive ketone or aldehyde substrate during the course of the desired reaction, rather than in a previously mentioned protecting group manipulation. For example, olefination conditions have been applied to convert cyclic hemiacetals (lactols, usually prepared by reduction of lactones) into hydroxy alkenes via in situ-generated aldehydes.[3] Due to the stability of many cyclic hemiacetals, their emergence as masked aldehydes was almost inevitable. This convenient approach obviates the need to prepare and handle the labile aldehyde prior to the desired reaction.

This letter describes a new class of stable alkynyl aldehyde surrogate: cyclic vinylogous triflate hemiacetal **2**. Vinylogous hemiacetals **2** arise from DIBALH reduction of cyclic vinylogous ester derivatives **1**, which in turn are prepared from the corresponding 1,3-diketone (Eq. 1).[4] Subsequent treatment of **2** with excess amounts of Grignard reagents directly affords alkynyl alcohols **3**, presumably through in situ generation of alkynyl aldehyde intermediate **A**. In contrast to ordinary cyclic hemiacetals (lactols), vinylogous triflate hemiacetals **2** are not subject to reversible masking and unmasking of the reactive aldehyde.




(1)

*Keywords*: Alkynyl aldehyde surrogate; C–C bond cleavage; Grignard reagent; Vinylogous acyl triflate; Vinylogous triflate hemiacetal.
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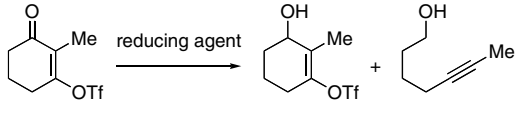
The tandem fragmentation/addition process (**2** → **3**) illustrated in Eq. 1 is made possible by the nucleofugacity of the triflate group, which activates the σ-bond framework of **2** for the Grob-type fragmentation. We have been studying the related tandem addition/fragmentation process that converts cyclic vinylogous acyl triflates (**1**) into acyclic alkynyl ketones, amides, and related compounds using various carbon and nitrogen nucleophiles.[5] The synthesis of acyclic alkynyl aldehydes by the reaction of **1** with an equimolar amount of hydride agent, however, could not bring about the desired aldehydes in acceptable yield and purity, despite strong evidence that they are generated efficiently in the reaction mixture (vide infra). We concluded that the problem stems from the high lability of alkynyl aldehydes under the reaction conditions, which prompted the current efforts.

During our research on the direct reductive ring opening reaction of vinylogous acyl triflate **1a** (derived from 2-methyl-1,3-cyclohexanedione) to form the corresponding acyclic primary alkynol **4a** using a variety of reducing agents,[5] we observed the formation of cyclic vinylogous hemiacetal **2a** along with the desired product, **4a** (Eq. 2, Table 1). The products ratios depended on the sources of hydride species. Strong reducing agents, such as $LiBHEt_3$ (super hydride), furnished **4a** as the sole product (entry 1). Reduction using milder borohydrides (e.g., $LiBH_4$) predominantly afforded **2a** along with small amounts of **4a** (entry 2). When the reduction of **1a** was conducted with $(i\text{-Bu})_2AlH$ (DIBALH; 2.2 equiv) as the hydride source in THF between −78 and 60 °C within 80 min, vinylogous hemiacetal **2a** was formed selectively in almost quantitative yield (entry 3).[6] Optimization of these reaction conditions revealed that the excess DIBALH and mild heating were unnecessary. Thus, vinylogous ester derivative **1a** was treated with an approximately equimolar amount of DIBALH (1.1 equiv) at −78 °C to rt (within 50 min), giving **2a** in excellent yield (entry 4).[7] Surprisingly, the treatment of **1a** with *i*-BuMgCl (2.2 equiv) furnished acyclic secondary alkynol **3a** in 59% isolated yield as the sole product (entry 5). This result implies that half of the Grignard reagent behaved as a hydride source and the other half reacted as a carbon nucleophile.[8] The DIBALH reduction of triflate **1b** (derived from 1,3-cyclohexanedione) provided vinylogous hemiacetal **2b** in 95% yield (Eq. 3).




(2)

**1a** **2a** **4a**

**Table 1.** Reduction of vinylogous acyl triflate **1a** using various reducing agents[a,b]

| Entry | Reducing agent | Yield[c] (%) | |
|---|---|---|---|
| | | **2a** | **4a** |
| 1 | $LiBHEt_3$ | 0 | 65[d] |
| 2 | $LiBH_4$ | 62 | 9 |
| 3 | $(i\text{-Bu})_2AlH$ | 99[d] | 0 |
| 4 | $(i\text{-Bu})_2AlH$[e] | 97[d] | 0 |
| 5[f] | *i*-BuMgCl | 0 | 0 |

[a] Standard reaction conditions: vinylogous acyl triflate **1a** (0.5 mmol) was treated with reducing agent (1.1 mmol) in 2 mL of THF at −78 to 60 °C within 80 min.

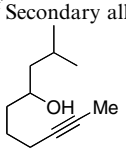
[b] Experiments described in entries 1–3 were originally conducted enroute to an optimized procedure for the preparation of **4a** (see Ref. 5). Aldehyde **A** (R = Me) was never isolated in acceptable yield or purity.

[c] Estimated yield based on $^1H$ NMR otherwise noted.

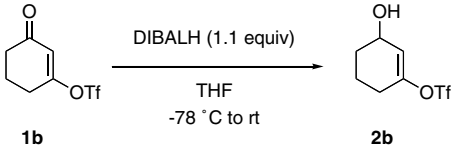
[d] Isolated yield.

[e] Vinylogous acyl triflate **1a** (0.5 mmol) was treated with 0.55 mmol of DIBALH at −78 °C to rt within 50 min.

[f] Secondary alkynol **3a** was obtained in 59% isolated yield.




**3a**




(3)

**1b** **2b**

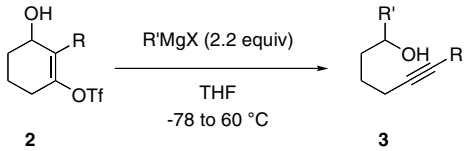
95%

Despite considerable efforts, we were unable to obtain the corresponding alkynyl aldehyde (**A**, R = Me) in satisfactory yield. We treated vinylogous hemiacetal **2a** with equimolar amounts of bases, such as $LiBHEt_3$,[9] *n*-BuLi,[10] PhMgBr, LiHMDS, NaH, and NaOEt; in most cases, a complex mixture of compounds was formed, which included a small amount of aldehydes as determined by $^1H$ NMR analysis of the crude mixtures. These observations—including the reaction of **1a** with excess amounts of *i*-BuMgCl to form secondary alkynol **3a** (entry 5 of Table 1)—prompted us to investigate **2a** as a novel alkynyl aldehyde surrogate; vinylogous triflate hemiacetal **2a** was isolable (and in nearly quantitative yield).

We conducted a series of reactions between vinylogous triflate hemiacetal **2a** and excess amounts of diverse Grignard reagents (Eq. 4, Table 2). Indeed, the reaction of **2a** with PhMgBr (2.2 equiv) in THF between −78 and 60 °C within 80 min furnished benzylic alcohol **3b** in 84% yield (entry 1).[11] The tandem fragmentation/addition reaction also took place using isopropenylmagnesium bromide to afford allylic alcohol **3c** in high yield (entry 2). Alkyl and allyl Grignard reagents gave rise to the corresponding alcohols (**3d** and **3e**, respectively) in good yields (entries 3 and 4). Addition of the alkynylmagnesium chloride[12] to the in situ-generated aldehyde proceeded smoothly to furnish propargyl alcohol **3f** in high yield (entry 5). The reaction of vinylogous hemiacetal **2b** with PhMgBr, however, afforded **3g** in only 15% yield with a significant amount of recovered starting material **2b** under the same reaction conditions (entry 6).

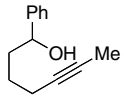
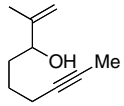
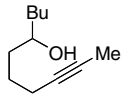
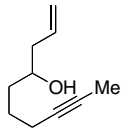
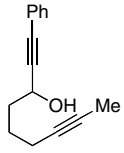
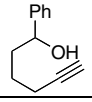
The mechanistic pathway for the present stepwise ring opening reaction of vinylogous acyl triflates **1**—

**Table 2.** Tandem fragmentation/addition reaction of vinylogous triflate hemiacetals **2** using various Grignard reagents[a]

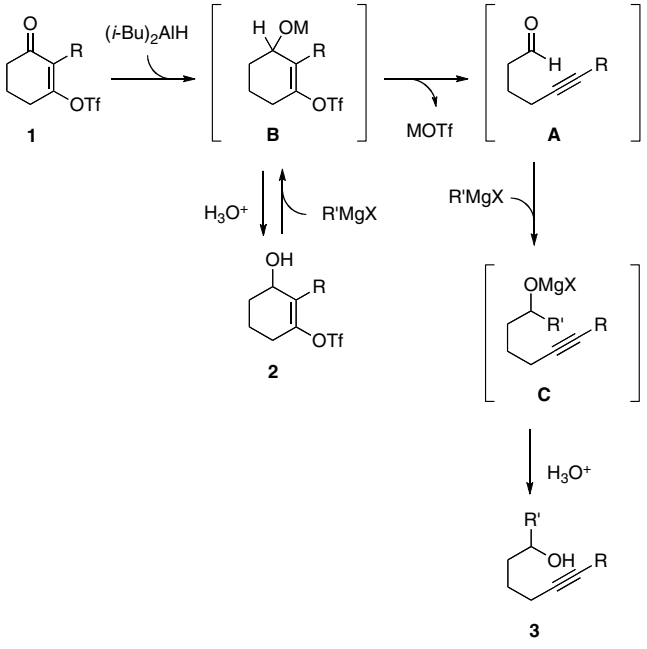



(4)

**2** **3**

| Entry | R′MgX | 2 | Product | 3 | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | PhMgBr | **2a** (R = Me) |  | **3b** | 84 |
| 2 |  | **2a** (R = Me) |  | **3c** | 81 |
| 3 | *n*-BuMgCl | **2a** (R = Me) |  | **3d** | 76[c] |
| 4 |  | **2a** (R = Me) |  | **3e** | 79 |
| 5 | Ph–C≡C–MgCl[d] | **2a** (R = Me) |  | **3f** | 90 |
| 6 | PhMgBr | **2b** (R = H) |  | **3g** | 15[e] |

[a] Vinylogous hemiacetal **2** (0.5 mmol) was treated with Grignard reagent (1.1 mmol) in 2 mL of THF at −78 to 60 °C within 80 min.
[b] Isolated yield.
[c] **2a** was recovered in 19% yield.
[d] The alkynyl Grignard reagent was prepared from phenylacetylene (3 equiv) and *n*-BuMgCl (2.2 equiv) in THF at 60 °C for 30 min.
[e] **2b** was recovered in 81% yield.




**Scheme 1.** Proposed mechanistic pathway for the stepwise ring opening reaction of vinylogous acyl triflates **1** through vinylogous triflate hemiacetals **2**.

DIBALH reduction of **1** and subsequent treatment of vinylogous triflate hemiacetals **2** with excess amounts of Grignard reagents—is proposed as shown in Scheme 1. The alkoxyaluminum intermediate (**B**-*Al*) is formed by 1,2-reduction of **1** with $(i\text{-Bu})_2$AlH (DIBALH). This species is apparently more stable with respect to fragmentation than the alkoxyboronate intermediate (**B**-*B*) generated by $LiBHEt_3$ reduction, and vinylogous hemiacetals **2** were formed upon aqueous workup. The Grob-type C–C bond cleaving fragmentation[13,14] occurs upon treatment of **2** with excess Grignard reagents, presumably via the alkoxymagnesium intermediate (**B**-*Mg*).[15] In situ-generated alkynyl aldehydes **A** would then react with the remaining Grignard reagent to furnish intermediate **C**, and aqueous workup yields secondary alkynols **3**. This stepwise procedure to reach **3** demonstrates the utility of isolable vinylogous triflate hemiacetals **2** as alkynyl aldehyde surrogates.

In conclusion, treatment of vinylogous hemiacetal **2a** with excess amounts of Grignard reagents produced acyclic alkynols **3** in good to high yields. This transformation likely involves the Grob-type C–C bond cleaving fragmentation to form alkynyl aldehyde **A** in situ, and subsequent nucleophilic attack of the Grignard

reagent furnishes secondary alkynols **3**. The vinylogous triflate hemiacetals **2** are prepared by DIBALH reduction of vinylogous acyl triflates **1**, derived from cyclic 1,3-diketones, and serve as surrogates for alkynyl aldehydes.

## Acknowledgments

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## References and notes

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3. Representative example, see: Lawrence, N. J. In *Preparation of Alkenes*; Williams, J. M. J., Ed.; Oxford: Oxford, 1996; pp 31–32.
4. For preparation, see: (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028; (b) Hori, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 1480.
5. Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499, and references cited therein.
6. Similar reductions have been reported, see: (a) Yamano, Y.; Mimuro, M.; Ito, M. *J. Chem. Soc., Perkin. Trans. 1* **1997**, 2713; (b) von Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem. Eur. J.* **2001**, *7*, 4035–4046; (c) Martínez, A. G.; Alvarez, R. M.; Casado, M. M.; Subramanian, L. R.; Hanack, M. *Tetrahedron* **1987**, *43*, 275.
7. Standard experimental procedures for DIBALH reduction of vinylogous acyl triflates **1**. To a THF solution (20 mL) of 2-methyl-3-(trifluoromethanesulfonyloxy)-2-cyclohexenone (**1a**) (1.29 g, 5.0 mmol) was slowly added DIBALH (5.5 mL, 5.5 mmol; 1.0 M solution in heptane) at −78 °C under an Ar atmosphere. The mixture was stirred at −78 °C for 10 min, at 0 °C for 10 min, and then at rt for 30 min. Saturated aqueous $NH_4Cl$ solution was added to quench the reaction, and the mixture was then treated with aqueous NaOH solution (1 M) and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a silica gel column (hexanes/AcOEt = 20/1 to 2/1) to give 2-methyl-3-(trifluoromethanesulfonyloxy)-2-cyclohexen-1-ol (**2a**) in 97% yield (1.26 g). Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.60 (1H, t, $J = 7.5$ Hz), 1.71–1.90 (4H, m), 1.88 (3H, t, $J = 2.1$ Hz), 2.34 (2H, m), 4.22 (1H, m); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.7, 18.4, 27.7, 30.9, 69.2, 118.2 ($^1J(C,F) = 317$ Hz), 128.0, 146.4; IR (neat) 3365 (br), 1703, 1415, 1208, 1140, 1034 $cm^{-1}$; HRMS (FAB) Calcd for $C_8H_{11}O_4SF_3Na$ ($[M+Na]^+$) 283.0228. Found 283.0230.
8. (a) Wakefield, B. J. In *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; pp 111–130; (b) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.
9. The treatment of **2a** with 2.2 equiv of $LiBHEt_3$ gave the corresponding primary alkynol, 5-heptynol (**4a**), in good yield, see: Ref 5.
10. The reaction of **2a** with 2.2 equiv of organolithium reagents, such as *n*-BuLi or PhLi, gave a complex mixture of compounds.
11. Standard experimental procedures for the tandem fragmentation/addition reaction of vinylogous hemiacetals **2** using Grignard reagents. To a THF solution (2.0 mL) of 2-methyl-3-(trifluoromethanesulfonyloxy)-2-cyclohexen-1-ol (**2a**) (130.1 mg, 0.50 mmol) was slowly added PhMgBr (0.37 mL, 1.1 mmol; 3.0 M solution in ether) at −78 °C under an Ar atmosphere. The mixture was stirred at −78 °C for 10 min, at 0 °C for 10 min, at rt for 30 min, and then at 60 °C for 30 min. Saturated aqueous $NH_4Cl$ solution was added to quench the reaction and the mixture was extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a silica gel column (hexanes/ether = 50/1 to 3/1) to give 1-phenyl-5-heptyn-1-ol (**3b**) in 84% yield (79.5 mg). Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.33–1.60 (3H, m), 1.67 (3H, t, $J = 2.4$ Hz), 1.72–1.87 (2H, m), 2.07 (2H, tq, $J = 6.9$, 2.4 Hz), 4.61 (1H, m), 7.16–7.23 (3H, m), 7.26–7.27 (2H, m); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 3.3, 18.5, 25.1, 38.0, 74.1, 75.8, 78.8, 125.8, 127.4, 128.3, 144.6; IR (neat) 3368 (br), 1603, 1493, 1453, 1331, 1205, 1065, 1025, 760, 700 $cm^{-1}$; HRMS (CI) Calcd for $C_{13}H_{17}O$ ($[M+H]^+$) 189.1279. Found 189.1281.
12. The alkynyl Grignard reagent was prepared from phenylacetylene and *n*-BuMgCl by mixing in THF at 60 °C for 30 min, see: Ref. 8a, pp. 46–48.
13. (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1; (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535; Other reviews on the Grob-type fragmentations, see: (c) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 1041–1070; (d) Hesse, M. In *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991; pp 163–198.
14. Similar type of C–C bond cleavage reaction is observed in Eschenmoser–Tanabe fragmentation, see: (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708; (b) Felix, D.; Shreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896; (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943; (d) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739.
15. Fragmentation (**B** → **A**) should be accelerated by destabilizing steric interactions in **B**. Increased $A_{1,2}$-strain may explain why **2a** (R = Me) is a better substrate than **2b** (R = H). See Ref. 5 for more examples of fragmentations that are consistent with this observation.