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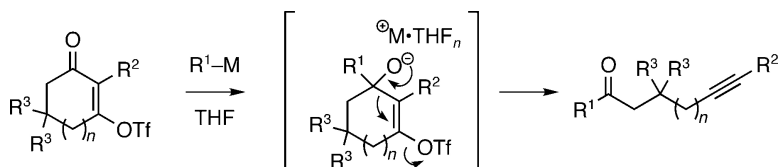- Copyright permission to reproduce figures and/or text from this article

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A Tandem Carbanion Addition/Carbon–Carbon Bond Cleavage Yields Alkynyl Ketones

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Carbon–carbon bonds are the foundation of organic chemistry. Tools for making such bonds are indispensable for the construction of complex molecules, and intense efforts are continually directed toward developing novel and selective bond-forming reactions. In contrast, C–C bond cleavage reactions receive less attention. Oxidative cleavage,[1] sigmatropic rearrangement,[2] and alkene metathesis[3] are key examples on a short list of synthetic methods that involve C–C bond cleavage. Chemists justifiably focus on bond-forming reactions; however, judicious use of bond cleavage can reveal frameworks that are otherwise difficult to prepare.

The Eschenmoser–Tanabe fragmentation (Scheme 1)[4,5] is a fundamental bond cleavage reaction, important from both a pedagogical and synthetic standpoint, although it is often overlooked in favor of other methods for preparing alkynyl ketones. Generally in this process, epoxy–hydrazones (**1**) are prepared from cyclic enone oxides in protic media (acetic acid or methanol); they then decompose (**1** → **2**) with loss of nitrogen and a sulfinic acid. Scheme 2 illustrates a common method for preparing cyclic enones (**4**): nucleophilic addition to **3**, followed by acidic hydrolysis.[6]

The presumed intermediates in Schemes 1 and 2 (**A** and **B**) are strikingly similar, yet they generally decompose by distinct, unrelated mechanisms. Inducing **B** to fragment under mild conditions in an aprotic solvent would have important synthetic and mechanistic implications. We achieved this crossover in reaction pathways (**B** → **2**) using vinylogous acid triflates, and this Communication describes our preliminary investigations.

Table 1 summarizes our screening of reaction protocols, using phenylmagnesium bromide (PhMgBr) as the carbanion source. Entries 1–3 reveal a clear advantage for the ethereal solvent (THF) over DMPU or toluene for production of **8a**. Alternative nucleofuges (entries 4[7] and 5[8]) did not fragment under our solution-phase conditions.[9,10] Varying the reaction concentration did not have a discernible effect.

Entries 1 and 2 illustrate that choice of solvent enables one to choose between the two reaction pathways (**3** → **2** or **4**). This provides an additional level of diversity with respect to the synthesis of small molecule libraries.[11] No attempt was made to optimize the yield of **7** (entry 2).

We then explored the reaction of enol triflate **5a** with a variety of Grignard reagents (Table 2, entries 1–6). We prepared **5a** by a modified procedure[12] that provides efficient and inexpensive access to a range of stable triflates in good yields.

As mentioned above, PhMgBr provided the corresponding alkynyl ketone **8a** in 80% yield (entry 1, average of two runs). The reaction with *para*-anisylmagnesium bromide afforded **8b** smoothly in 86% yield (entry 2). In contrast, the *para*-chlorophenyl adduct (entry 5) fragmented more slowly; mild heating provided the best yield of **8e**. It thus appears that electron-donating groups accelerate C–C bond cleavage, perhaps due to favorable conjuga-

Scheme 1. Fragmentation of Epoxy–Hydrazones
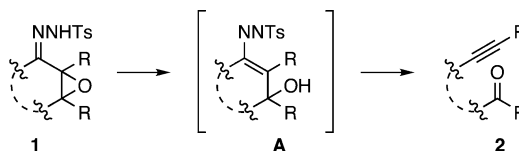
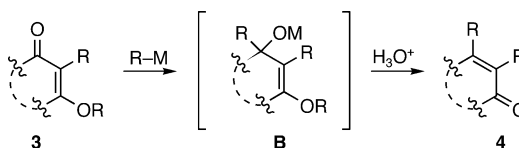**Scheme 2.** Preparation of Enones from Vinylogous Esters

**Table 1.** Initial Screening of Addition/Fragmentation Conditions[a]

entry	X	solvent	observed products
1	OTf (**5a**)	THF	**8a** (78–83% isolated)
2	OTf (**5a**)	toluene	**7**[b] (66% isolated), **8a** (trace)
3	OTf (**5a**)	DMPU	**8a** (ca. 50%[c])
4	OMs (**5b**)	THF	**6**
5	Br (**5c**)	THF	**6**

[a] See Supporting Information for details. [b] **6** presumably hydrolyzes to **7** when X = OTf. [c] Estimated by ^{1}H NMR spectroscopy.

tion with the developing carbonyl.[13] The heteroaromatic nucleophile in entry 6 yielded the expected product (**8f**, 63%) without any difficulty.

We also examined the C–C bond cleavage reaction employing organolithium nucleophiles (entries 7–10). The more ionic lithium alkoxide fragments more readily. In the case of phenyllithium (PhLi), appreciable bond cleavage occurred at 0 °C, with the resulting ketone then being susceptible to over-addition. Initial cooling to −78 °C suppressed formation of a tertiary alcohol impurity and provided alkynyl ketone **8a** in 93% yield (average of two runs). The *meta*- and *ortho*-anisyl reagents afforded the corresponding products (**8c** and **8d**) in 78 and 57% yields, respectively (entries 8 and 9). This is an improvement over Grignard-derived yields (entries 3 and 4). Methyllithium is also applicable as a nucleophilic reagent in this transformation, yielding alkynyl ketone **8g**[14] (65%, entry 10).

Having established a reasonable range of nucleophilic partners, we next examined the scope of cyclic enol triflates. Mild heating proved optimal in the case of the unsubstituted enol triflate (**9**; n = 1; R^2, R^3 = H), affording the corresponding alkynyl ketone (**10a**)[15] in 65% yield. When the reaction was quenched at room temperature, a large amount of 3-phenyl-2-cyclohexenone[6] (analo-

Table 2. Scope with Respect to Nucleophiles[a]
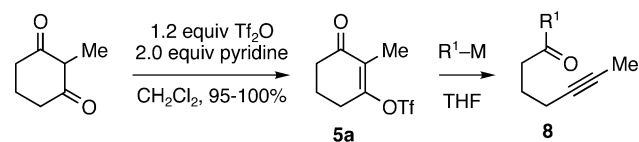
entry	R[1]−M	conditions	8	yield (%)[b]
1	Ph−MgBr	0 °C to rt	8a	80[c]
2	p-MeO−C₆H₄−MgBr	0 °C to rt	8b	86
3	m-MeO−C₆H₄−MgBr	0 °C to rt	8c	57
4	o-MeO−C₆H₄−MgBr	0 °C to rt	8d	34
5	p-Cl−C₆H₄−MgBr	0−60 °C	8e	61
6	2-thienyl−MgBr	0−60 °C	8f	63
7	Ph−Li	−78 °C to rt	8a	93[c]
8	m-MeO−C₆H₄−Li	−78 °C to rt	8c	78
9	o-MeO−C₆H₄−Li	−78 °C to rt	8d	57
10	Me−Li	−78 °C to rt	8g	65

[a] Typical procedure: enol triflate **5a** (0.55 mmol) in 2 mL of cold THF was treated with R[1]−M (0.50 mmol). All reactions were complete within 90 min. See Supporting Information for details. [b] Isolated yield. [c] Average of two runs.

Table 3. Scope with Respect to Cycloalkenones[a]
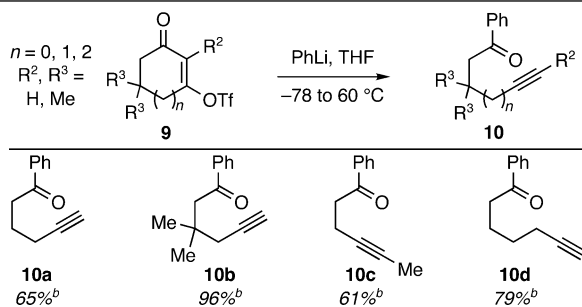
[a] Enol triflates **9** (0.55 mmol) in 2 mL of cold THF were treated with PhLi (0.50 mmol). All reactions were complete within 90 min. See Supporting Information for details. [b] Isolated yield.

Scheme 3. Mechanistic Hypothesis
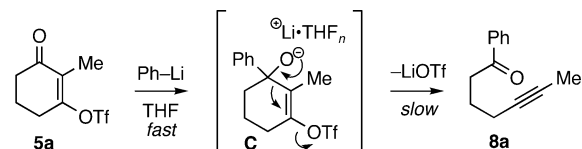
gous to **7**) was obtained. The six-membered enol triflate bearing a geminal dimethyl group afforded **10b**[16] in excellent yield, indicating that there is no significant "reverse Thorpe−Ingold effect" in the fragmentation. Five- and seven-membered enol triflates also afforded the desired products (**10c** and **10d**) in 61 and 79% yields, respectively. Capillon (**10c**) is a natural product isolated from the Japanese shrub, *Artemisia capillaris*.[17]

Our working mechanistic hypothesis (Scheme 3) includes several guiding assumptions: (1) decomposition of intermediate **C** is the rate-limiting step; (2) lithium triflate is released as dissociated ions that subsequently combine;[18] (3) increasing the ionic character of **C** promotes fragmentation; and (4) the stability of the product ketone and of the dissociated ion pair are reflected in the transition state.[13,19] Note that epoxy−hydrazones (**1**) fragment to afford regioisomers of the alkynyl ketones described herein. Experiments aimed at elucidating further mechanistic details are planned.

In conclusion, we report a facile C−C bond cleavage reaction induced by the nucleophilic addition of Grignard or lithium reagents to vinylogous carboxylic acid triflates. Tethered keto−alkynes can thus be obtained efficiently by a unified and operationally simple approach. The present reaction proceeds under mild conditions, and the enol triflate substrates are easily prepared in one step from the corresponding diketones. Further studies on the scope and synthetic applications will be reported in due course.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H NMR spectra for compounds **8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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