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Published on Web 04/20/2006

Tandem Nucleophilic Addition/Fragmentation Reactions and Synthetic Versatility of Vinylogous Acyl Triflates

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Abstract: A thorough analysis of the chemistry of vinylogous acyl triflates provides insight into important chemical processes and opens new directions in synthetic technology. Tandem nucleophilic addition/C−C bond cleaving fragmentation reactions of cyclic vinylogous acyl triflates **1** yield a variety of acyclic acetylenic compounds. Full details are disclosed herein. A wide array of nucleophiles, such as organolithium and Grignard reagents, lithium enolates and their analogues, hydride reagents, and lithium amides, are applied. The respective reactions produce ketones **2**, 1,3-diketones and their analogues **3**, alcohols **4**, and amides **5**. The present reactions are proposed to proceed through a 1,2-addition of the nucleophile to the carbonyl group of starting triflates **1** to form tetrahedral alkoxide intermediates **C**, followed by Grob-type fragmentation, which effects C−C bond cleavage to yield acyclic acetylenic compounds **2**−**5** and **7**. The potent nucleofugacity of the triflate moiety is channeled through the σ-bond framework of **1**, providing direct access to the fragmentation pathway without denying other typical reactions of cyclic vinylogous esters. The synthetic versatility of vinylogous acyl triflates, including functionalization reactions of the cyclic enone core (**1** → **6** or **8**), is also illustrated.

Introduction

Carbon−carbon bond formation is a major focus of research in organic synthesis. Tools for making such bonds are indispensable for the construction of complex molecules, and intense efforts are continuously directed toward developing novel and selective bond forming reactions. In contrast, C−C bond cleavage reactions receive less attention. Nonetheless, such bond cleavage reactions often emerge as ideal methods for the construction of new materials and complex molecules. The reverse processes of several C−C bond forming transformations, such as aldol,[1] Diels−Alder,[2] and Michael reactions,[3] have found utility in C−C bond cleavage. The Cope rearrangement[4] and oxidative cleavage of olefins[5] and diols[6] are also representative examples. Recent advances in transition metal chemistry have provided a variety of C−C bond cleaving methods, although substrates are often restricted either to highly strained molecules such as cyclopropanes and cyclobutanes or to properly designed molecules possessing a coordinating group around the reaction site.[7,8] Ring opening metathesis is another poignant example of C−C bond cleavage in synthetic chemistry.[9] Judicious use of such bond cleavage reactions can reveal frameworks that are otherwise difficult to prepare.[10]

Nearly 40 years have passed since Eschenmoser[11] and Tanabe[12] independently reported the ring opening reaction of epoxy-hydrazones to yield tethered alkynyl ketones (eq 1). The key step in the Eschenmoser−Tanabe process (**A** → **P**) is classified as a fragmentation, according to the criteria outlined by Grob.[13,14] Epoxy-hydrazones **S** are generally prepared by the condensation of tosylhydrazide with an appropriate cyclic enone

(1) (a) Mukaiyama, T. *Org. Synth.* **1982**, *28*, 203. (b) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133−238.
(2) (a) Rickborn, B. *Org. Synth.* **1998**, *52*, 1. (b) Sweger, R. W.; Czarnik, A. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 551−592.
(3) (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. Synth.* **1959**, *10*, 179. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 1−67.
(4) (a) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 785−826. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247.
(5) Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 541−591.
(6) Shing, T. K. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 703−717.
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(8) For reviews, see: (a) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610 and references therein. (b) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 97−129. (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (d) Tsuji, J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley: New York, 2002; Vol. 2, pp 2643−2653.
(9) (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (c) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565.
(10) Recent examples: (a) Salamone, S. G.; Dudley, G. B. *Org. Lett.* **2005**, *7*, 4443. (b) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334.
(11) (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.
(12) (a) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943. (b) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739.
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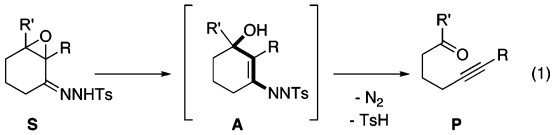
(14) For other reviews on the Grob-type fragmentations, see: (a) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 1041−1070. (b) Hesse, M. In *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991; pp 163−198.

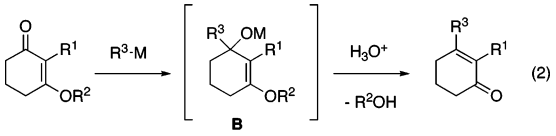
10.1021/ja0608085 CCC: $33.50

oxide in protic media (often methanol or acetic acid). The multistep sequence from cyclic enone to acyclic acetylenic ketone has received considerable attention through the years, both as a synthetic strategy[15] and as a pedagogical tool.[16]

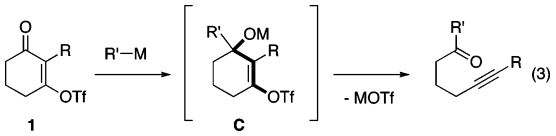
The Eschenmoser–Tanabe Fragmentation



Enone Formation from Vinylogous Acid Esters



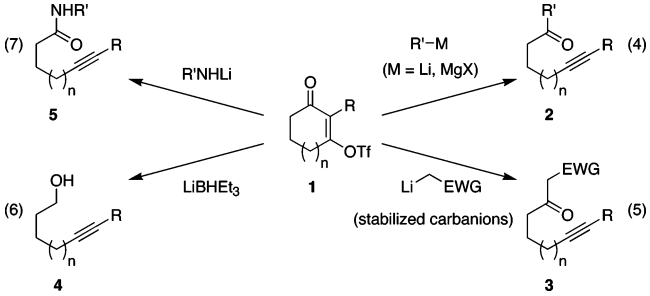
Tandem Addition/Fragmentation of Vinylogous Acyl Triflates



Equation 2 illustrates a common method for the synthesis of cyclic enones.[17] The presumed reaction intermediates, **A** and **B**, are strikingly similar, yet they generally decompose by distinct, unrelated mechanisms. Inducing species similar to **B** to fragment under mild conditions in an aprotic solvent would have important synthetic and mechanistic implications. We sought to achieve a crossover in reaction pathways via intermediate **C**, starting from cyclic vinylogous acyl triflates **1** (eq 3).

Initial success stemmed from the use of aryllithium and aryl Grignard reagents as nucleophilic triggers (eq 4, Scheme 1).[18] Optimization of the reaction conditions with regard to other nucleophilic agents enabled us to extend the scope to include alkyl-, alkynyl-, and vinyl-metal species, producing acetylenes tethered to alkyl ketones, conjugated alkynyl ketones, and α,β-unsaturated enones, respectively. Lithium enolates and their analogues were also applicable in the tandem addition/fragmentation reaction to form alkynes **3** bearing a 1,3-diketone-type moiety (eq 5).[19] Treatment of triflates **1** with excess amounts of $LiBHEt_3$ (Super-Hydride) promoted the reductive ring opening reaction to afford alcohols **4** (eq 6). When triflates **1** were subjected to nitrogen nucleophiles, a similar reaction took place to furnish corresponding amides **5** (eq 7). Herein, we report full details of our ongoing studies, which include a series of tandem nucleophilic addition/C−C bond cleaving fragmentation reactions (Scheme 1), as well as the utility of vinylogous acyl triflates **1** from a general synthetic perspective. Representative synthetic transformations are demonstrated (vide infra).

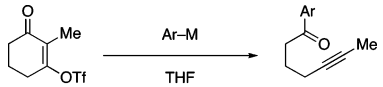
Scheme 1. Tandem Nucleophilic Addition/C−C Bond Cleaving Fragmentation Reactions of Vinylogous Acyl Triflates **1**



Results and Discussion

Synthesis of Aryl Ketones Using Aryl Grignard and Aryllithium Nucleophiles.[18] Table 1 summarizes the results of reactions between vinylogous acyl triflate **1a** (derived from 2-methyl-1,3-cyclohexanedione: R = Me, n = 1 in eq 4) and a variety of aryl Grignard and aryllithium reagents. When **1a** (1.1 equiv) was treated with phenylmagnesium bromide (Ph-MgBr, 1.0 equiv) in THF at 0 °C for 10 min and then at room temperature for 30 min, 1-phenyl-5-heptynone (**2a**) was obtained in 80% yield (entry 1, average of two runs).[20] Alternative

Table 1. Reaction of Triflate **1a** with Various Aryl Grignard and Aryllithium Reagents[a]



entry	Ar-M	conditions	2	yield, %[b]
1	Ph-MgBr	0 °C to rt	**2a**	80[c]
2	(*p*-MeO)C_6H_4-MgBr	0 °C to rt	**2b**	86
3	(*m*-MeO)C_6H_4-MgBr	0 °C to rt	**2c**	57
4	(*o*-MeO)C_6H_4-MgBr	0 °C to rt	**2d**	34
5	(*p*-Cl)C_6H_4-MgBr	0 to 60 °C	**2e**	61
6	(2-thienyl)-MgBr	0 to 60 °C	**2f**	63
7	Ph-Li	−78 °C to rt	**2a**	93[c]
8	(*m*-MeO)C_6H_4-Li	−78 °C to rt	**2c**	78
9	(*o*-MeO)C_6H_4-Li	−78 °C to rt	**2d**	57

[a] Typical reaction procedure: a mixture of triflate **1a** (0.55 mmol), Ar-M (0.50 mmol), and THF (2 mL) was stirred at the temperatures shown in Table 1 (reactions complete within 80 min). [b] Isolated yield. [c] Average of two runs.

6a

nucleofuges such as mesylate[21] and bromide[22] instead of triflate did not give the desired product (**2a**). THF was the solvent of choice for this initial study; reactions conducted under the same conditions in DMPU gave **2a** in ca. 50% yield and in toluene produced only a trace amount of **2a** with the formation of 2-methyl-3-phenyl-2-cyclohexenone (**6a**) in 66% yield. The reaction of **1a** with *para*-, *meta*-, and *ortho*-anisylmagnesium bromides afforded **2b**−**d**, respectively, in yields that increased

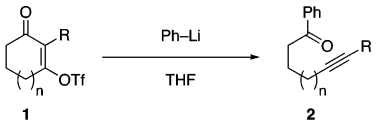
(15) For selected applications of the Eschenmoser−Tanabe fragmentation in total synthesis, see: (a) Murakami, Y.; Shindo, M.; Shishido, K. *Synlett* **2005**, 664. (b) Fehr, C.; Galindo, J.; Etter, O. *Eur. J. Org. Chem.* **2004**, 1953. (c) Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400. (d) Kocienski, P. J.; Ostrow, R. W. *J. Org. Chem.* **1976**, *41*, 398.
(16) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; Wiley: New York, 2001; p 1347.
(17) (a) Woods, G. F.; Tucker, I. W. *J. Am. Chem. Soc.* **1948**, *70*, 2174. (b) Zimmerman, H. E.; Nesterov, E. E. *J. Am. Chem. Soc.* **2003**, *125*, 5422.
(18) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028.
(19) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175.
(20) Related fragmentations have been reported, see: (a) Coke, J. L.; Williams, H. J.; Natarajan, S. *J. Org. Chem.* **1977**, *42*, 2380. (b) Shimizu, M.; Ando, R.; Kuwajima, I. *J. Org. Chem.* **1981**, *46*, 5246. (c) Shimizu, M.; Ando, R.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 1230.
(21) Lee, S.; Fuchs, P. L. *Tetrahedron Lett.* **1991**, *32*, 2861.
(22) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825.

with decreasing steric bulk (entries 2−4). The *para*-chlorophenyl adduct seemed to fragment slightly slower than the corresponding *para*-methoxy adduct; therefore, the reaction mixture was warmed to 60 °C to obtain the best yield of the product (**2e**, entry 5; 61% yield). It thus appears that the electron donating methoxy group on the aromatic ring promotes C−C bond cleaving fragmentation more smoothly, possibly due to favorable conjugation with the developing carbonyl group. The reaction with 2-thienylmagnesium bromide furnished the expected heteroaromatic product **2f** as well (entry 6; 63% yield).

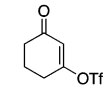
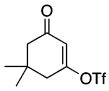
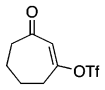
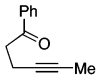
We further examined the addition/C−C bond cleaving fragmentation reaction employing aryllithium nucleophiles. The more ionic lithium alkoxide intermediates (cf. **C**, M = Li vs MgX, eq 3) seemed to fragment more readily to furnish the corresponding aryl ketones. In the case of phenyllithium (PhLi), appreciable C−C bond cleavage occurred at 0 °C, with the resulting ketone then being susceptible to overaddition. Initial cooling of the reaction mixture to −78 °C suppressed undesired reaction pathways, particularly the formation of the tertiary alcohol impurity, and provided aryl ketone **2a** in high yield (entry 7; 93% yield, average of two runs). The *meta*- and *ortho*-anisyllithiums afforded corresponding products **2b** and **2c** in 78 and 57% yields, respectively (entries 8 and 9)—distinct improvements over the corresponding Grignard reagents (cf. entries 3 and 4).

We next probed the scope of triflates **1** for this addition/fragmentation reaction using PhLi as the nucleophile (Table 2).

Table 2. Reaction of Various Triflates **1** with PhLi[a]



1 **2**

entry	1	2	yield, %[b]
1	 **1b**	 **2g**	65
2	 **1c**	 **2h**	96
3	 **1d**	 **2i**	79
4	 **1e**	 **2j**	61

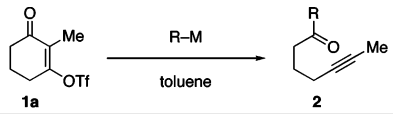
[a] Triflate **1** (0.55 mmol), PhLi (0.50 mmol), and THF (2 mL), −78 to 60 °C within 80 min. [b] Isolated yield.

6b

Mild heating proved to be optimal in the case of triflate **1b** (derived from 1,3-cyclohexanedione), which gave rise to ketone **2g** (entry 1; 65% yield). When this reaction was quenched at room temperature, a large amount of 3-phenyl-2-cyclohexenone **6b** (50% yield) was obtained along with the desired product **2g** (26% yield). Triflate **1c**, which bears a geminal dimethyl group, afforded **2h** in excellent yield. Seven- and five-membered cyclic triflates **1d** and **1e** also furnished expected products **2i** and **2j** in 79 and 61% yields, respectively (entries 3 and 4). Compound **2j**, also known as capillon, is a natural product isolated from the Japanese shrub *Artemisia capillaries*.[23]

Synthesis of Alkyl Ketones Using Alkyllithium and Alkyl Grignard Nucleophiles. Although various arene nucleophiles were applicable in the addition/fragmentation reaction described in the previous section, analogous reactions using *n*-butyllithium (*n*-BuLi) did not proceed with acceptable efficiency. After some examination, we concluded that the *n*-BuLi addition to **1a** is sensitive to reagent quality and choice of solvent.[24] Using a fresh supply of *n*-BuLi, alkyl ketone **2k** (R = Me, R′ = Bu, *n* = 1 in eq 4) was obtained in 63% yield in THF under the same reaction conditions applied in entry 7 of Table 1. Alternatively, the inclusion of TMEDA[25] in the reaction mixture seemed to make the reaction more tolerant of minor impurities in the *n*-BuLi reagent, but the optimal yield of **2k** remained almost the same (65% yield). After further tuning of the reaction conditions, toluene emerged as the best solvent, providing improvements in the yield, reproducibility, and efficiency of the reaction. This finding was key to extending the scope of effective nucleophiles to include the range of alkyllithium and alkyl Grignard reagents illustrated in Table 3. Our recent synthesis of (*Z*)-6-heneicosen-11-one, a sex attractant of the Douglas fir tussock moth, features this tandem addition/C−C bond cleaving fragmentation reaction conducted in toluene.[26]

Table 3. Reaction of Triflate **1a** with Various Alkyllithium and Alkyl Grignard Reagents[a]



1a **2**

entry	R–M	2	yield, %[b]
1	*n*-BuLi	**2k**	76
2	*i*-PrLi	**2l**	26
3	*t*-BuLi	**2m**	20[c]
4	MeLi	**2n**	63[d]
5	Me_3SiCH_2Li	**2n**	74[e]
6		**2o**	61
7		**2p**	74
8	*n*-BuMgCl	**2k**	63[c]
9	$PhCH_2MgCl$	**2q**	73[c]

[a] Typical reaction procedure: triflate **1a** (0.55 mmol), R-M (0.50 mmol), and toluene (2 mL), −78 °C to room temperature within 50 min. [b] Isolated yield. [c] The reaction mixture was warmed to 60 °C for 30 min after the typical reaction procedure. [d] **2n** was obtained in 65% yield in THF. [e] Cleavage of the Me_3Si group occurred during purification on silica gel, and **2n** was obtained as the final product.

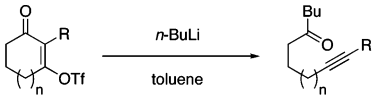
The treatment of triflate **1a** (1.1 equiv) with *n*-BuLi (1.0 equiv) in toluene at −78 °C for 10 min, at 0 °C for 10 min, and then at room temperature for 30 min gave the corresponding alkyl ketone, 9-undecyn-5-one (**2k**), in 76% yield (entry 1).

(23) Harada, R. *Nippon Kagaku Kaishi* **1956**, *77*, 990, ibid, *Chem. Abstr.* **1957**, *51*, 18489. (b) Harada, R. *Nippon Kagaku Kaishi* **1956**, *77*, 1036, ibid, *Chem. Abstr.* **1959**, *53*, 21773.
(24) Impurities in aged stock solutions of *n*-BuLi, such as LiOH and *n*-BuOLi, may cause decomposition of **1a** or may alter the aggregation properties of the nucleophile. TMEDA seemed to abrogate this effect.
(25) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.
(26) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936.

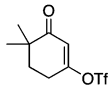
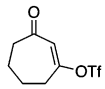
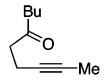
Yields suffered when we screened aggressively reactive and hindered alkyllithium reagents such as *i*-PrLi and *t*-BuLi (entries 2 and 3). Conversely, nucleophilic reagents derived from relatively stabilized carbanions were more effective. For example, the addition of MeLi and (trimethylsilyl)methyllithium[27,28] afforded the same product (**2n**), with the latter reaction providing a higher yield (entries 4 and 5). Interestingly, the reaction of **1a** with MeLi took place even in THF, and almost the same yield of **2n** was observed (65% yield).[18] The pyridine-[29] and dithiane-containing[30] organolithium reagents gave the alkyl ketones **2o** and **2p**, respectively, in good yields (entries 6 and 7). The reaction employing alkyl Grignard reagents, such as *n*-BuMgCl and $PhCH_2MgCl$, proceeded smoothly in toluene to furnish the corresponding products **2k** and **2q**, although mild heating was essential to complete the fragmentation (entries 8 and 9).

We then carried out the present tandem addition/fragmentation reaction using a variety of vinylogous acyl triflates **1** and *n*-BuLi (Table 4). 1,3-Cyclohexanedione-derived triflate **1b** afforded **2r**

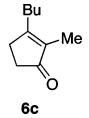
Table 4. Reaction of Various Triflates **1** with *n*-BuLi[a]



1 **2**

entry	1	2	yield, %[b]
1	 **1b**		**2r**	63
2	 **1f**		**2s**	52
3	 **1d**		**2t**	39
4	 **1e**		**2u**	14[c]

[a] Triflate **1a** (0.55 mmol), *n*-BuLi (0.50 mmol), and toluene (2 mL), −78 °C to room temperature within 50 min. [b] Isolated yield. [c] The reaction mixture was warmed to 60 °C for 30 min after the typical reaction procedure, and **6c** was obtained in 33% yield.

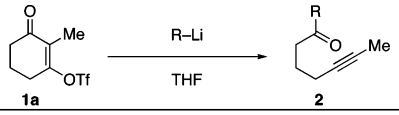


6c

in 63% yield (entry 1). Triflate **1f**, bearing a geminal dimethyl substituent adjacent to the carbonyl group, gave **2s** in moderate yield (entry 2). Seven-membered triflate **1d** furnished **2t** in allowable yield (entry 3). On the other hand, five-membered triflate **1e**, derived from 2-methyl-1,3-cyclopentanedione, gave alkyl ketone **2u** in only 14% yield along with the formation of cyclopentenone derivative **6c** in 33% yield (entry 4).

Synthesis of α,β-Unsaturated Ketones Using Alkynyl and Vinyllithium Nucleophiles. The next series of experiments was designed to verify that alkynyl- and vinyllithium reagents are suitable for the synthesis of α,β-unsaturated ketones (Table 5). The reaction between triflate **1a** and alkynyllithiums generated from phenylacetylene and (trimethylsilyl)acetylene gave the corresponding alkynyl ketones **2v** and **2w** in moderate yields (entries 1 and 2). Treatment of **1a** with the vinyllithium species derived from dihydropyran[31] afforded the expected conjugated enone **2x** in 64% yield (entry 3). These results indicate that not only aryl- and alkyllithium reagents but also alkynyl- and vinyllithium species are applicable in this process.

Table 5. Reaction of Triflate **1a** with Alkynyl and Vinyllithium Reagents[a]



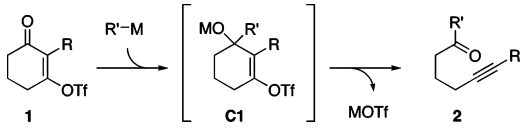
1a **2**

entry	R–Li	2	yield, %[b]
1	Ph–C≡C–Li[c]	**2v**	56
2	Me_3Si–C≡C–Li[c]	**2w**	48
3		**2x**	64

[a] Triflate **1a** (0.55 mmol), R-Li (0.50 mmol), and THF (2 mL), −78 °C to room temperature within 50 min. [b] Isolated yield. [c] Terminal acetylene (0.60 mmol) was treated with *n*-BuLi (0.50 mmol) in THF at −78 °C for 30 min to generate the alkynyllithium species. [d] 3,4-Dihydro-2*H*-pyran (0.60 mmol) was treated with *t*-BuLi (0.50 mmol) in THF at −78 °C for 10 min and then at room temperature for 20 min to generate the vinyllithium species.

The mechanistic pathway for the present tandem nucleophilic addition/C−C bond cleaving fragmentation reactions of vinylogous acyl triflates **1** using various carbanionic metal reagents is proposed as depicted in Scheme 2. Initially, alkoxide intermediate **C1** is formed by 1,2-addition of the carbanion species. Subsequent collapse of the tetrahedral intermediate **C1** via C−C bond cleavage (Grob-type fragmentation)[13,14] would produce ketones **2**. The formation of cyclic enone side products **6a**−**c** in some cases would strongly suggest the intervention of intermediate **C1** in the reaction process. We assume a similar fragmentation pathway as proposed for the Eschenmoser−Tanabe sequence,[11,12] except that it operates under distinctly different (and in many cases more efficient) conditions.

Scheme 2. Proposed Mechanistic Pathway for the Tandem Carbanion Addition/C−C Bond Cleaving Fragmentation of Vinylogous Acyl Triflates **1**



1 **C1** **2**

Synthesis of Tertiary Alcohols via Double Addition of Alkyllithium Nucleophiles. Encouraged by the success of the ketone synthesis via the reaction between cyclic vinylogous acyl triflates **1** and various organolithium reagents, we investigated the formation of acyclic alkynols **7** using excess amounts of

(27) Reactions of (trimethylsilyl)methyllithium with enol ethers of 1,3-cyclohexanedione derivatives have been reported, see: (a) Horiguchi, Y.; Kataoka, Y.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3327. (b) Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. (c) Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917.

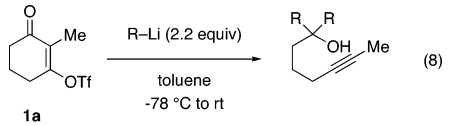
(28) Cleavage of the Me_3Si group occurred during purification.

(29) (a) Beumel, O. F., Jr.; Smith, W. N.; Rybalka, B. *Synthesis* **1974**, 43. (b) Roussel, R.; Guerrero, M. O. D.; Galin, J. C. *Macromolecules* **1986**, *19*, 291.

(30) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988.

(31) Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317.

organolithium reagents (eq 8). When triflate **1a** was subjected to 2.2 equiv of MeLi in toluene (−78 °C to room temperature within 50 min), the double addition of MeLi took place as expected to afford alkynol **7a** in 55% yield. In the case of *n*-BuLi, the corresponding alkynol **7b** was obtained in 77% yield. In addition to providing alkynols **7** in one step, these results indicate that lithium alkoxide intermediate **C1** (with its pendant vinyl triflate) is compatible with excess amounts of alkyllithium reagents.



(8)

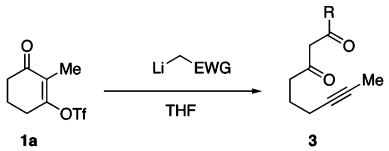
Synthesis of 1,3-Diketones Using Lithium Enolate Nucleophiles.[19] Whereas alkyllithium and Grignard reagents typically add in a 1,2-fashion to unsaturated ketones, enolates and other stabilized carbanions are more likely to react in a 1,4-manner (Michael reaction pathway). Nonetheless, the cross-coupling reaction of **1** with lithium enolates and their analogues proceeded to give 1,3-diketone-type compounds tethered to alkynes **3** (eq 5, Scheme 1). This reaction may be viewed as a direct mechanistic analogue of the Claisen condensation,[32] using a vinylogous carboxylic acid ester as a starting material.

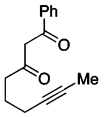
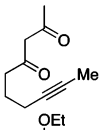
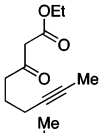
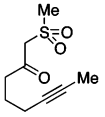
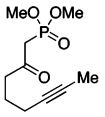
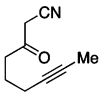
Table 6 summarizes the results of reaction between vinylogous acyl triflate **1a** (derived from 2-methyl-1,3-cyclohexanedione) and a variety of lithium enolates and their analogues. When **1a** (1.0 equiv) was treated with the lithium enolate of acetophenone (2.2 equiv) in THF between −78 and 60 °C within 80 min, the corresponding alkynyl-1,3-diketone **3a**[33] was obtained in 85% yield (entry 1). The mild heating (to 60 °C) was necessary for best results. Reaction stoichiometry had a significant effect on the yield of **3a**. The reaction of triflate **1a** with a slight excess amount of the lithium enolate (1.2 equiv) gave **3a** in 56% yield along with recovered **1a**. This stoichiometric requirement suggests that the relatively acidic dicarbonyl product (**3**) consumes 1 equiv of base as it forms, which is consistent with the traditional Claisen condensation. Among the various solvents tested, the present Claisen-type addition/fragmentation reaction proceeded most efficiently in THF. Inclusion of DMPU as a cosolvent was detrimental to the yield of **3a**, and the overall transformation was slower in toluene. The lithium enolate derived from acetone reacted with **1a** to give diketone **3b** in moderate yield (entry 2). The ethyl acetate enolate produced ketoester **3c** in 88% yield (entry 3). Lithiated dimethyl sulfone reacted with **1a** to furnish *β*-ketosulfone **3d** in moderate yield along with a small amount of the diyne **3d′** (entry 4). Similar reactions using dimethyl methylphosphonate and acetonitrile provided the corresponding products **3e** and **3f** in low yields (entries 5 and 6, unoptimized).

We then explored the Claisen-type addition/fragmentation reaction using various triflates **1** and the lithium enolate of acetophenone (Table 7). Triflate **1b** afforded the corresponding diketone **3g** in excellent yield (entry 1). The six-membered triflates **1f**, **1c**, and **1g** bearing a geminal dimethyl group were next examined. The reaction of **1f**, which bears a sterically congested quaternary center *alpha* to the carbonyl group, resulted in decomposition; no desired product **3h** was detectable (entry 2). On the other hand, the triflates such as **1c** and **1g**, in which the carbonyl groups are progressively less hindered, furnished the corresponding products **3i** and **3j** in 45 and 79% yields, respectively (entries 3 and 4). Accordingly, the reaction appears to be sensitive to steric influences around the initial 1,2-addition.[34] The seven-membered cyclic triflate **1d** gave the desired product **3k** in high yield (entry 5).

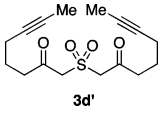
A plausible mechanistic pathway for the Claisen-type addition/C−C bond cleaving fragmentation reaction of vinylogous

Table 6. Reaction of Triflate **1a** with Lithium Enolates and Their Analogues[a]



entry	prenucleophile	product	3	yield, %[b]
1			**3a**	85
2			**3b**	42
3			**3c**	88
4[c]			**3d**	53[d]
5			**3e**	21
6	MeCN		**3f**	22

[a] Typical reaction procedure: triflate **1a** (0.50 mmol), lithium enolate (1.1 mmol; generated by the treatment of 1.2 equiv of prenucleophile with 1.1 mmol of LiHMDS), and THF (2 mL), −78 to 60 °C within 80 min. [b] Isolated yield. [c] *n*-BuLi was used instead of LiHMDS. [d] Diyne **3d′** was obtained in 8.4% yield.

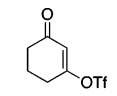
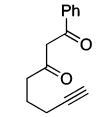
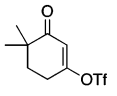
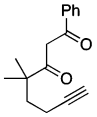
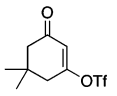
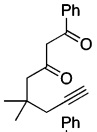
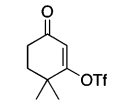
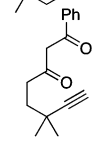
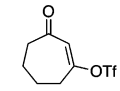
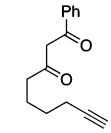


(32) For reviews on the Claisen condensation, see: (a) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 795−863. (b) Hauser, C. R.; Hudson, D. E. *Org. React.* **1942**, *1*, 266. (c) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59. For a review on the Dieckman condensation, see: (d) Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1.

(33) 1,3-Diketones **3a**, **3b**, **3g**, and **3i**−**k** exist predominantly in the enol form in $CDCl_3$. See Supporting Information for details.

(34) The reactions of enolates derived from more hindered esters such as ethyl valerate and ethyl isobutyrate with triflate **1a** did not proceed well. In the former case, we could detect the corresponding product in the crude mixture by mass spectrometry (ESI, $C_{14}H_{22}0_3Na$; $M^+ = 261.1$); however, the yield was quite low, and we could not isolate the desired product in acceptable purity. In the latter case, the reaction resulted in the decomposition of triflate **1a**, and a significant amount of ethyl isobutyrate was recovered.

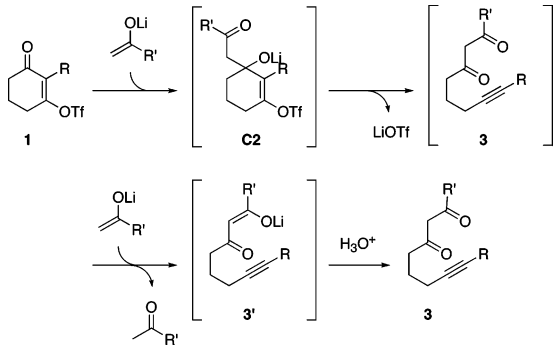
Table 7. Reaction of Various Triflates **1** with Lithium Enolate of Acetophenone[a]

entry	triflate	1	product	3	yield, %[b]
1		**1b**		**3g**	95
2		**1f**		**3h**	–
3		**1c**		**3i**	45
4		**1g**		**3j**	79
5		**1d**		**3k**	90

[a] Triflate **1** (0.50 mmol), lithium enolate of acetophenone (1.1 mmol), and THF (2 mL), −78 to 60 °C within 80 min. [b] Isolated yield.

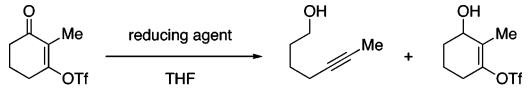
acyl triflates **1** is shown in Scheme 3.[35] 1,2-Addition of the lithium enolate to the carbonyl group of **1** generates tetrahedral aldolate intermediate **C2**. Steric congestion around the reacting site would retard this addition process, and the prolonged exposure of triflates **1** to the reaction conditions would lead to their decomposition. The Grob-type fragmentation[13,14] effects C−C bond cleavage along with extrusion of LiOTf to give 1,3-diketone products **3**. In the reaction mixture, however, a second equivalent of the enolate abstracts a proton from the newly formed active methylene moiety of **3** to furnish enolate intermediate **3′**, which yields **3** upon aqueous workup.

Scheme 3. Proposed Mechanistic Pathway for the Claisen-Type Tandem Addition/C−C Bond Cleaving Fragmentation of Vinylogous Acyl Triflates **1**



Synthesis of Alcohols Using Nucleophilic Hydride Reagents. Having realized successful addition/fragmentation of vinylogous acyl triflates using a range of stabilized and unstabilized carbon nucleophiles, we then turned our attention to non-carbon reagents, starting with hydrides. We anticipated that utilization of a reducing agent would bring about the formation of aldehydes. Unfortunately, intensive investigations using a combination of vinylogous acyl triflate **1a** and equimolar amounts of various hydride sources resulted in failure; in most of cases, a complex mixture of compounds was formed, which included a small amount of aldehydes as determined by ^{1}H NMR analysis of the crude mixtures. On the basis of these results, we treated triflate **1a** (R = Me, n = 1) with excess hydride reagent to obtain alcohol **4a** (eq 6, Scheme 1). The results of the effect of reducing agents are listed in Table 8. When **1a** (1.0 equiv) was treated with a very strong hydride donor, $LiBHEt_3$ (Super-Hydride, 2.2 equiv), in THF at −78 to 60 °C within 80 min, the expected alcohol, 5-pentyn-1-ol (**4a**), was obtained in 65% yield (entry 1). $LiBH(s\text{-}Bu)_3$ (L-Selectride) gave a moderate yield of **4a** (entry 2). Other hydride sources, such as $LiBH_4$, $NaBH_4$, and $LiAlH_4$, were far less effective for the formation of **4a**, yielding cyclohexenol **9a** as a major product (entries 3−5). Interestingly, $(i\text{-}Bu)_2AlH$ (DIBALH) produced **9a** solely in almost quantitative yield (entry 6).[36] Returning to $LiBHEt_3$ as the hydride source, we determined that mild heating was not necessary, and the optimal yield of **4a** was obtained when the reaction was quenched at room temperature (entry 7; 73% yield). Analogous reducing agents, such as $NaBHEt_3$ and $KBHEt_3$, also afforded **4a** in good yield as a single product (entries 8 and 9).

Table 8. Reactivity of Reducing Agent To Promote the Reductive Ring Opening Reaction of Triflate **1a**[a]



1a **4a** **9a**

		yield, %[b]	
entry	reducing agent	**4a**	**9a**
1	$LiBHEt_3$	65[c]	0
2	$LiBH(s\text{-}Bu)_3$	42	0
3	$LiBH_4$	9	62
4	$NaBH_4$	4	72
5	$LiAlH_4$	4	12
6	$(i\text{-}Bu)_2AlH$	0	99[c]
7[d]	$LiBHEt_3$	73	0
8[d]	$NaBHEt_3$	55	0
9[d]	$KBHEt_3$	67	0

[a] Typical reaction procedure: triflate **1a** (0.50 mmol), reducing agent (1.1 mmol), and THF (2 mL), −78 to 60 °C within 80 min. [b] Estimated yield based on ^{1}H NMR unless otherwise noted. [c] Isolated yield. [d] The reaction was quenched at room temperature.

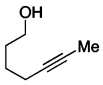
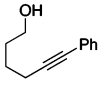
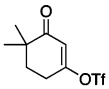
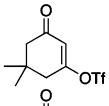
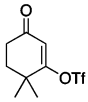
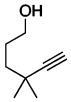
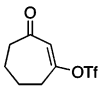
Table 9 reflects efforts to determine the scope and limitations of this reductive ring opening reaction of triflates **1**, using $LiBHEt_3$. Treatment of **1a** with $LiBHEt_3$ afforded **4a** in 73% yield as mentioned previously (entry 1). The phenyl substituted triflate **1h** furnished the corresponding alcohol **4b** in 62% yield (entry 2), but the reaction of the triflate **1b** (derived from 1,3-cyclohexanedione) did not afford alcohol **4c** (entry 3). Triflates **1f** and **1g**, bearing a geminal dimethyl substituent adjacent to either the carbonyl group or the enol triflate moiety, gave the corresponding products **4d** and **4f** in moderate yields, respec-

(35) A further mechanistic discussion can be found in our earlier paper; see ref 19.

(36) 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.

tively, although it was necessary to warm the reaction mixture to 60 °C after the typical procedure to facilitate the transformation (entries 4 and 6). In the case of **1c**, the desired product **4e** was formed in only modest yield (entry 5). The seven-membered cyclic triflate **1d** furnished **4g** in 63% yield (entry 7).

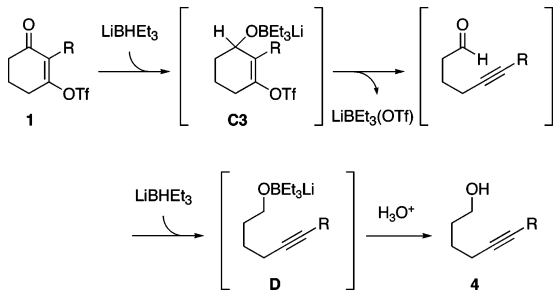
Table 9. Reductive Ring Opening Reaction of Triflate **1** Using $LiBHEt_3$[a]

entry	1		4	yield, %[b]
1		**1a**		**4a**	73
2		**1h**		**4b**	62
3[c]		**1b**		**4c**	–[d]
4[c]		**1f**		**4d**	56
5[c]		**1c**		**4e**	30
6[c]		**1g**		**4f**	50
7		**1d**		**4g**	63

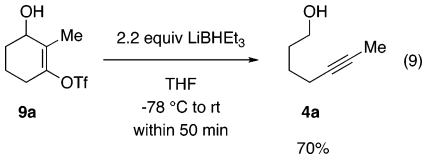
[a] Typical reaction procedure: triflate **1a** (0.50 mmol), $LiBHEt_3$ (1.1 mmol), and THF (2 mL), −78 °C to room temperature within 50 min. [b] Isolated yield. [c] The reaction mixture was heated to 60 °C for 30 min after the typical reaction procedure. [d] Complex mixture was formed under the typical reaction conditions, and decomposition occurred when the reaction was warmed to 60 °C.

The proposed mechanistic pathway for the reductive ring opening reaction of vinylogous acyl triflates **1** parallels that proposed in Scheme 2 for carbanionic nucleophiles, except for the role of excess hydride (Scheme 4). Initially, alkoxyboronate intermediate **C3** presumably forms by 1,2-reduction of **1** with $LiBHEt_3$, and subsequent C−C bond cleaving fragmentation (Grob-type fragmentation)[13,14] would produce intermediate aldehydes. The remaining $LiBHEt_3$ reacts with these aldehydes to give intermediate **D**, and aqueous workup furnishes alcohols **4** as a final product. We assume that our inability to isolate the intermediate aldehydes in good yield results from their inherent instability to the reaction conditions as compared to the corresponding acetylenic ketones.

Scheme 4. Proposed Mechanistic Pathway for the Reductive Ring Opening Reaction of Vinylogous Acyl Triflates **1**

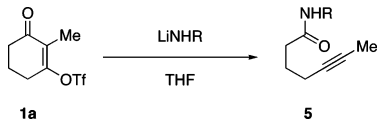


We then conducted the reaction between cyclohexenol **9a** and excess amounts of $LiBHEt_3$ to confirm the possible intervention of alkoxybononate **C3** during the transformation to afford alcohol **4a**. Indeed, the expected alcohol was obtained in 70% yield (eq 9), which corresponds to the result obtained in entry 1 of Table 9.



Synthesis of Amides Using Lithium Amide Nucleophiles. Along with the development of tandem addition/C−C bond cleaving fragmentation reactions employing a range of organometallic and hydride nucleophiles, we became interested in the potential application of heteroatom nucleophiles, which would afford products at the carboxylic acid oxidation level. After screening several possible classes of reagents, the amidative ring opening reaction of vinylogous acyl triflates **1** emerged as the most promising choice (eq 7, Scheme 1). Reaction of triflate **1a** (1.0 equiv; R = Me, n = 1) with the lithium amide generated from $PrNH_2$ (2.4 equiv) and *n*-BuLi (2.2 equiv) in THF gave the desired ring opened product, *N*-propyl-5-heptynamide (**5a**), in 91% yield (entry 1). The same reaction in toluene was less efficient (73% yield). Conducting the reaction in THF using 1.2 equiv of $PrNH_2$ and 1.1 equiv of *n*-BuLi resulted in a small but distinct decrease in the yield of **5a** (80 vs 91% with excess lithium amide). We then surveyed the amidative ring opening reaction of triflate **1a** with a variety of lithium amides (Table 10). Typical alkylamines, such as $PrNH_2$ and *i*-$PrNH_2$, afforded the corresponding products **5a** and **5b**, respectively, in high yields (entries 1 and 2), whereas the bulkier *t*-$BuNH_2$ gave **5c** in moderate yield (entry 3).

Table 10. Amidative Ring Opening Reaction of Triflate **1a** Using Various Lithium Amides[a]



entry	RNH_2	5	yield, %[b]
1	$PrNH_2$	**5a**	91
2	*i*-$PrNH_2$	**5b**	87
3	*t*-$BuNH_2$	**5c**	49
4	$PhCH_2NH_2$	**5d**	91
5	$PhNH_2$	**5e**	79
6	(*p*-MeO)$C_6H_4NH_2$	**5f**	82
7	(*p*-CF_3)$C_6H_4NH_2$	**5g**	77
8	$LiNH_2$[c]	**5h**	–[d]

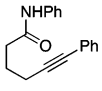
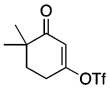
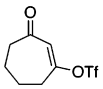
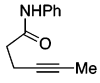
[a] Triflate **1a** (0.50 mmol), RNH_2 (1.2 mmol; pretreated with 1.1 mmol of *n*-BuLi), and THF (2 mL), −78 to 60 °C within 80 min. [b] Isolated yield. [c] $LiNH_2$ was purchased and used as received. [d] Significant recovery of **1a** was observed.

Benzylamine furnished **5d** in high yield (entry 4). Anilines produced the respective amide products **5e**−**g** in good yields (entries 5−7), irrespective of the electronic nature of substituents on the aromatic ring. No reaction was observed between triflate **1a** and lithium amide ($LiNH_2$) (entry 8). Thus far, only primary amines have functioned effectively in this tandem addition/fragmentation reaction, whereas secondary amines such as Pr_2-

NH, $(i\text{-Pr})_2$NH, and Ph_2NH resulted mainly in the decomposition of the starting triflate **1a**.

We next examined the amidative ring opening reaction utilizing a variety of triflates **1** and the lithium amide of $PhNH_2$ (Table 11). Phenyl-substituted triflate **1h** afforded the corresponding amide **5i** in high yield (entry 1). Triflate **1b** derived from 1,3-cyclohexanedione furnished **5j** in 58% yield (entry 2). The six-membered triflate **1f**, bearing a geminal dimethyl substituent adjacent to the carbonyl group, gave **5k** in very low yield (entry 2). This result again suggests that the transformation is sensitive to the steric demands of substrates. Seven-membered triflate **1d** produced the expected product **5l** in high yield (entry 4). Five-membered triflate **1e** afforded amide **5m** in only 20% yield (entry 5).

Table 11. Amidative Ring Opening Reaction of Various Triflates **1** Using PhNHLi[a]

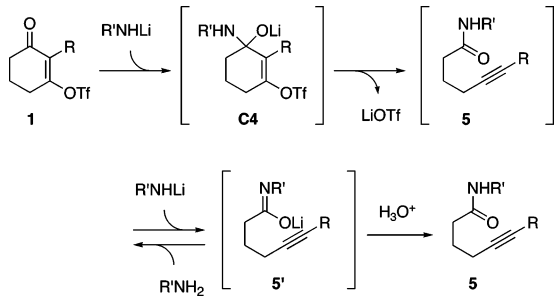
entry	1		5	yield, %[b]
1		**1h**		**5i**	84
2		**1b**		**5j**	59
3		**1f**		**5k**	< 7
4		**1d**		**5l**	88
5		**1e**		**5m**	20

[a] Triflate **1** (0.50 mmol), $PhNH_2$ (1.2 mmol; pretreated with 1.1 mmol of *n*-BuLi), and THF (2 mL), −78 to 60 °C within 80 min. [b] Isolated yield.

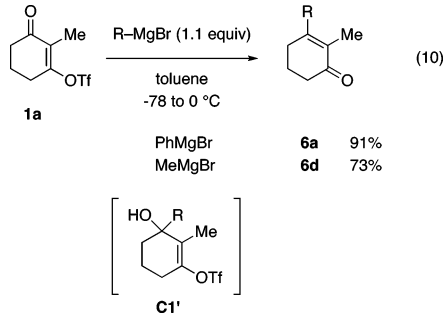
The mechanistic pathway for the present amidative ring opening reaction of vinylogous acyl triflates **1** with lithium amides can be proposed as shown in Scheme 5. The lithium amide adds to the carbonyl group of triflates **1** in a 1,2-fashion to form tetrahedral hemiaminal-type intermediate **C4**.[37] Steric congestion around the reacting site would retard this process, and the prolonged exposure of triflates **1** under the reaction conditions would lead to their decomposition. Similarly, amides that function better as basic reagents than as nucleophiles (i.e., LDA) may abstract the acidic α-proton of **1** rather than proceed along the desired addition/fragmentation pathway. Subsequent C−C bond cleavage of **C4** via the Grob-type fragmentation[13,14] furnishes amides **5**. In the reaction mixture, however, amide **5** may be subject to lithiation to afford **5′**, which explains the benefit of using excess amide reactants to obtain an optimal yield of **5** upon workup.

Synthetic Versatility of Vinylogous Acyl Triflates. Vinylogous acyl triflates embody multiple modes of potential reactivity, which allows one, in principle, to elaborate this single

Scheme 5. Proposed Mechanistic Pathway for the Amidative Ring Opening Reaction of Vinylogous Acyl Triflates **1**



starting material in diverse synthetic directions.[38,39] We therefore evaluated the synthetic utility and versatility of cyclic vinylogous acyl triflates **1** through selective functionalization of the enone core. One straightforward transformation that illustrated the versatility of **1a** was the synthesis of cyclohexenone derivatives **6** using Grignard reagents as depicted in eq 10.[17] 1,2-Addition of a nucleophilic Grignard reagent to the carbonyl group of triflate **1a** formed an intermediate tentatively assigned as alcohol **C1′** upon aqueous workup.[40] This material was subjected to chromatographic purification on silica gel to furnish cyclohexenones **6**. Treatment of **1a** with PhMgBr in toluene at −78 °C for 10 min and then at 0 °C for 10 min gave **6a** in 91% yield after chromatography. The reaction between **1a** and MeMgBr produced **6d** in good yield as well.



Alkylation of the enone core of vinylogous acyl triflate **1a** provides substituted triflates **8** (eq 11). This alkylation, in conjunction with addition and hydrolysis reactions analogous to those presented in eq 10, recalls the Stork−Danheiser alkylation strategy.[41] Deprotonation of **1a** was accomplished by LiHMDS in a mixture of THF and DMPU at −78 °C. Treatment of the derived lithium enolate with allyl iodide gave allylated triflate **8a** in 59% yield, whereas alkylation with ethyl iodoacetate afforded **8b** in 78% yield. The success of these reactions illustrates the durability of the triflate moiety in the face of transformations that are designed to impact other functionalities within the starting materials.

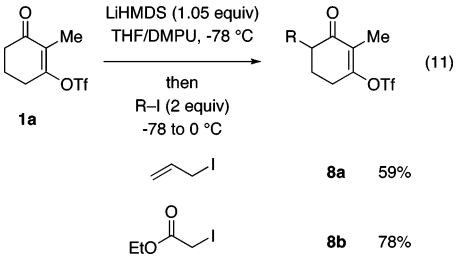
(37) Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113.

(38) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867.

(39) For reviews on combinatorial chemistry, see: (a) *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H.; Eds.; American Chemical Society: Washington, DC, 1997. (b) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small Molecular-Weight Compound Libraries*; Pergamon: Oxford, 1998. (c) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, J. F., Jr., Eds.; Wiley: New York, 1998.

(40) ^{1}H NMR data consistent with metastable intermediate **C1′** were routinely observed during spectroscopic analysis of the crude reaction mixtures.

(41) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.



(11)

Conclusion

We have developed facile C−C bond cleaving fragmentation reactions induced by the addition of nucleophiles to cyclic vinylogous acyl triflates **1** to produce acyclic acetylenic compounds. A variety of reactants such as organolithium and Grignard reagents, lithium enolates, $LiBHEt_3$, and lithium amides yield a wide array of ketones **2**, 1,3-diketones and their analogues **3**, alcohols **4**, and amides **5**, respectively, as final products. This tandem reaction was successfully extended to prepare acetylenes **7** tethered to tertiary alcohols by adjusting the stoichiometry of the organolithium reagents. Moreover, we demonstrated the synthetic versatility of vinylogous acyl triflates **1** by functionalizing their common cyclic enone core. Enolate alkylation of the vinylogous acyl triflate (**1** → **8**) and the addition/hydrolysis reactions (**1** → **6**) proceeded by analogy to reactions of other vinylogous esters popularized by the Stork−Danheiser alkylation strategy. The diverse range of product classes (**2**−**8**) available in one step from cyclic vinylogous acyl triflates creates opportunities for building compound libraries for high-throughput screening. In addition, all of the tandem reactions proceeded under mild conditions by simple and unified experimental operations, and the starting triflates **1** were easily prepared in one step from the corresponding cyclic diketones.

Acknowledgment. This research was supported by a grant from the James and Ester King Biomedical Research Program, the Florida Department of Health, the Donors of the American Chemical Society Petroleum Research Fund, an award from the Research Corporation, and by the FSU Department of Chemistry and Biochemistry. S.K. is a recipient of the Postdoctoral Fellowship for Research Abroad (2004) from the Japan Society for the Promotion of Science (JSPS). We are profoundly grateful to all of these agencies for their support. We thank Dr. Joseph Vaughn for assistance with the NMR facilities, Dr. Umesh Goli for providing the mass spectrometry data, and the Krafft Lab for access to their FT-IR instrument.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0608085