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Preparation of Tethered Aldehyde Ynoates and Ynones by Ring Fragmentation of Cyclic γ-Oxy-β-hydroxy-α-diazo Carbonyls

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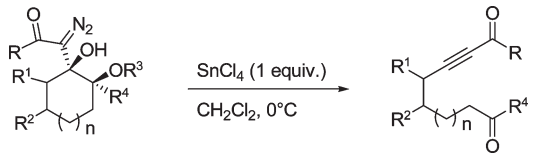

Cyclic γ-oxy-β-hydroxy-α-diazo carbonyls undergo Lewis acid induced ring fragmentation to provide either ynoates or ynones tethered to an aldehyde, ketone, or ester. The fragmentation precursors are convenient to prepare by adding lithiated α-diazo carbonyls to α-oxy ketones. The fragmentation appears general and provides a variety of functional group-rich products in good to excellent yield.

Introduction

Reactions that result in the cleavage of a carbon−carbon bond hold a special position in organic synthesis because they can unmask latent functional groups under chemoselective reaction conditions and they can provide functionalized synthetic intermediates that are otherwise difficult to prepare.[1−3] From a strategic standpoint, cleaving a ring system can be particularly useful in synthesis because (1) the resulting product will contain two newly formed functional groups that can be used in subsequent manipulations, (2) the new functional groups are tethered at a predefined distance determined by the ring size, (3) the fragmentation can provide a big structural change in the molecule that is not possible to achieve by other means, and (4) cyclic systems that contain stereocenters can fragment to linear compounds that contain the stereocenters. Unfortunately, only a limited number of synthetically useful ring cleaving reactions are known. For example, the ozonolysis of cyclic olefins and the oxidative cleavage of cyclic 1,2-diols are methods often used to prepare tethered dicarbonyl compounds.[4,5]

Reactions in which a molecule is broken into three fragments, a nucleofuge, an unsaturated fragment, and an electrofuge (Scheme 1, eq 1), were defined by Grob as fragmentations.[6−8] These transformations, now termed Grob fragmentations, occur when an electron-rich atom and a leaving group are separated by two intervening carbon atoms. In this process, two bonds are broken, and if one of the cleaved bonds is contained within a ring, then the ring is fragmented. For example, Wharton and Hiegel[9] reported that 1,10-decalinediol monotosylate **1** (Scheme 1, eq 2) smoothly fragments to ketone **2** upon treatment with base.

Few ring fragmentations result in the formation of alkynes.[2] The most notable example is the Eschenmoser−Tanabe fragmentation[10−13] in which the tosylhydrazone of an α,β-epoxy ketone fragments to provide an alkyne-tethered ketone or aldehyde. For example, α,β-epoxy cyclohexenone **3** (Scheme 1, eq 3) fragmented to tethered alkynyl ketone **4** upon treatment with tosylhydrazine.[14] More recently, Dudley and co-workers[15−18] reported an alternative route to tethered alkynyl ketones based on a nucleophile-induced

(1) Hendrickson, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 6748.
(2) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.
(3) Corey, E. J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 189.
(4) Shing, T. K. M. In *Comprehensive Organic Synthesis* Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 703.
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(6) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594.
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(8) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.
(9) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254.
(10) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708.
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(12) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943.
(13) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739.
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(16) Jones, D. M.; Kamijo, S.; Dudley, G. B. *Synlett* **2006**, 936.
(17) Kamijo, S.; Dudley, G. B. *Tetrahedron Lett.* **2006**, *47*, 5629.
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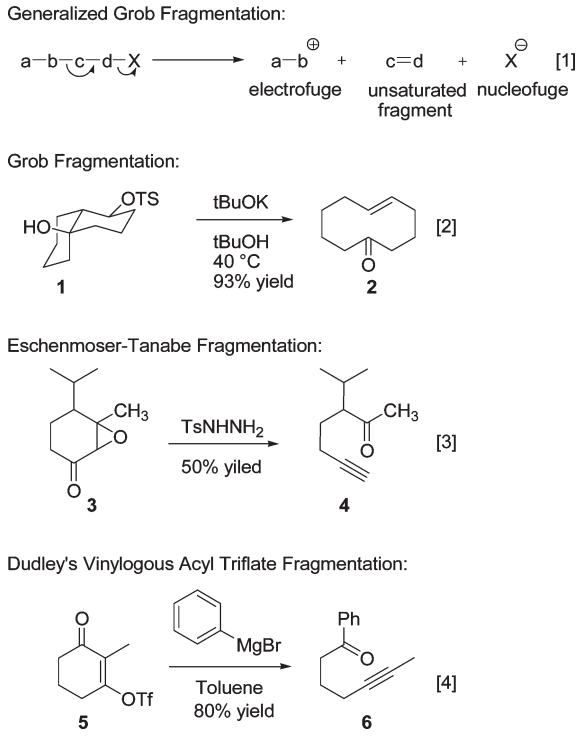
SCHEME 1. Examples of Synthetically Useful Fragmentation Reactions



fragmentation of vinylogous acyl triflates (e.g., Scheme 1, eq 4).

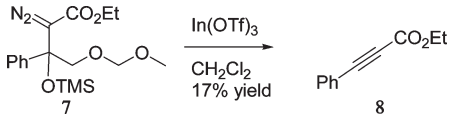
We recently reported our discovery that cyclic γ-silyloxy-β-hydroxy-α-diazo ethyl esters fragment when treated with Lewis acid to provide tethered aldehyde ethyl ynoate products in high yield.[19,20] The success of this fragmentation reaction, the small number of synthetically useful fragmentation reactions available, and our need for convenient access to tethered carbonyl alkynes for other ongoing studies in our laboratories[21,22] encouraged us to explore this reactivity profile further and we present our results here.

Results and Discussion

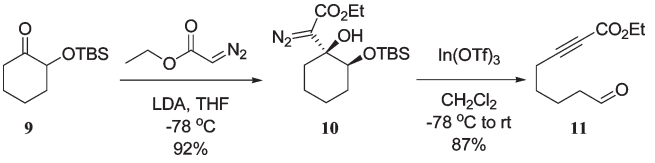
The first indication that β-hydroxy-α-diazo carbonyls with an additional oxygen substituent at the γ-position might be competent substrates in a fragmentation reaction occurred while working with α-diazo ester **7** (Scheme 2). Treating diazo **7** with indium(III) triflate provided a complex mixture of products from which ethyl 3-phenylpropiolate (**8**) was isolated in 17% yield. The formation of propiolate **8** appeared to involve loss of the β-silyloxy group, loss of molecular nitrogen, and fragmentation of the $C_\beta-C_\gamma$ bond.

With the above result in hand, we hypothesized that γ-oxy-β-hydroxy-α-diazo esters in which the $C_\beta-C_\gamma$ bond was contained within a ring would undergo efficient Lewis acid mediated ring fragmentation to provide tethered aldehyde ynoates. In order to promote the fragmentation step it

SCHEME 2. Initial Observation of Fragmentation



SCHEME 3. Application to the Fragmentation of a Ring



seemed logical to make the γ-oxygen more electron rich, and to test our hypothesis we prepared α-diazo ester **10** (Scheme 3) as a model system. Although α-diazo ester **10** may at first glance appear fairly complex, it is in fact trivial to prepare by simply adding LDA to a premixed solution of α-silyloxy ketone **9** and commercially available ethyl diazoacetate.[23−26]

Consistent with our hypothesis, treating diazo **10** with indium triflate resulted in vigorous gas evolution and provided tethered aldehyde ynoate **11** in 87% yield. In subsequent studies we observed that freshly dried indium triflate and freshly distilled tin tetrachloride most efficiently promoted the fragmentation; $BF_3\cdot OEt_2$, $MgBr_2\cdot OEt_2$, scandium triflate, titanium tetrachloride, and anhydrous HCl provided more complex product mixtures, and dibutyl tin dichloride, lithium perchlorate, and titanium isopropoxide failed to react. Due to the limited solubility of indium triflate in CH_2Cl_2, tin tetrachloride was chosen as the Lewis acid of choice and reproducibly provided the fragmentation product in 94% yield. Reducing the quantity of tin tetrachloride to 10 mol % promoted the fragmentation reaction, but unfortunately reduced the product yield to 85%. Changing the solvent from CH_2Cl_2 to toluene had little effect on the reaction, whereas DMF inhibited the reaction completely. It is interesting to note that when the Lewis acid was added to the diazo compound below −20 °C the solution immediately lost its characteristic yellow diazo color, but gas did not evolve until the temperature was increased to −20 °C. Good results were consistently obtained when the reaction was maintained at 0 °C.

In considering a possible mechanism for this fragmentation we noted Wenkert and McPherson's[27] report that β-hydroxy-α-diazo esters derived from aldehydes (e.g., **12**, Scheme 4, eq 1) reacted with Lewis acids to provide ynoates. To account for this reactivity they proposed that the Lewis acid promotes elimination of the β-hydroxy substituent to provide a vinyl diazonium intermediate (**14**), which in turn eliminates molecular nitrogen to provide the ynoate product. Subsequent studies by Padwa and co-workers have shown that β-hydroxy-α-diazo esters derived from ketones (e.g., **16**,

(19) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766.
(20) Draghici, C. Discovery of a novel ring fragmentation reaction; Efficient preparation of tethered aldehyde ynoates and N-containing heterocycles; Radical addition approach to asymmetric amine synthesis. Ph.D., University of Vermont, Burlington, VT, February **2009**.
(21) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, *11*, 2189.
(22) Draghici, C.; Huang, Q.; Brewer, M. *J. Org. Chem.* **2009**, *74*, 8410.
(23) Schöllkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 301.
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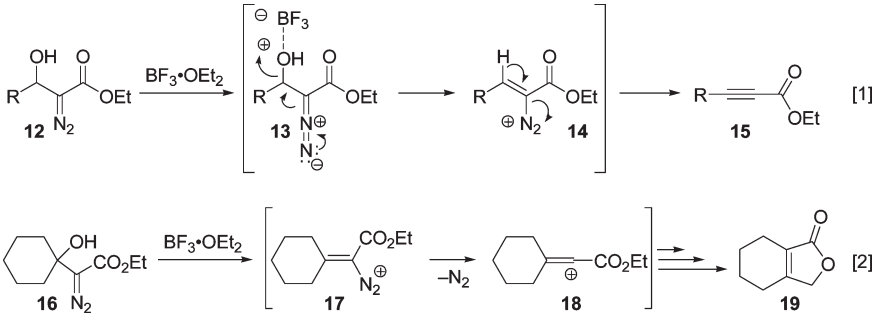
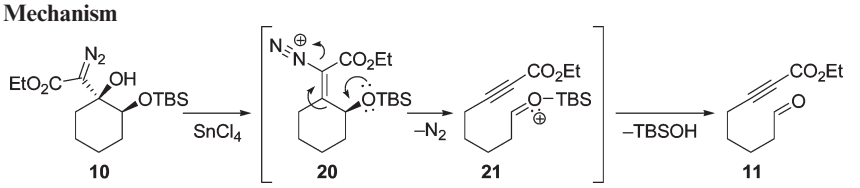
(25) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(26) Doyle, M. P.; Mckervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; Chapter 10.
(27) Wenkert, E.; McPherson, C. A. *Synth. Commun.* **1972**, *2*, 331.

SCHEME 4. Known Reactivity of β-Hydroxy-α-diazo Compounds



SCHEME 5. Proposed Mechanism



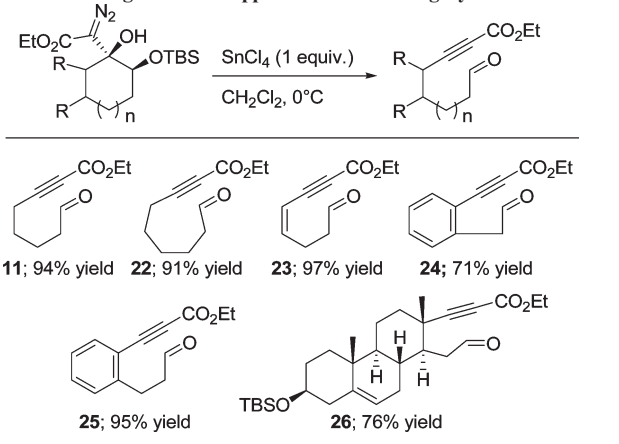
Scheme 4, eq 2) also react with Lewis acids to provide vinyl diazonium intermediates that in turn lose molecular nitrogen to provide the corresponding vinyl cations (e.g., **18**) which react further.[28]

With the above data in mind, we propose that the ring fragmentation we observed occurs as shown in Scheme 5. Similar to the above cases, Lewis acid induced elimination of the β-hydroxy group from diazo **10** would provide vinyl diazonium intermediate **20**. However, unlike the previous examples, intermediate **20** would be able to undergo a Grob-type fragmentation in which electron donation from the γ-oxygen and loss of molecular nitrogen would provide the alkyne product. Subsequent loss of the *tert*-butyldimethylsilyl group would provide tethered aldehyde ynoate **11**.

To test the generality of this diazo-based fragmentation reaction, we prepared a variety of substrates such that the ring that fragments differs (Table 1). Overall, this transformation appears to be fairly general, and changing the initial ring size from 6 to 7 members had no effect on product yield (94% vs 91%), whereas 5-membered rings fragmented in slightly lower yield (71% and 76%). Aryl rings and olefins were well tolerated in this transformation, and when these groups were adjacent to the β-carbon, conjugated ynoate products were formed in high yield. As a more structurally complex example, a steroid derivative productively fragmented to give ynoate **26** in 76% yield. This latter substrate shows the stability of both distal olefins and silyl ethers to the reaction, and highlights the important point that tethered aldehyde ynoates bearing chiral centers along the tether can be formed using this methodology.

In most of the above examples, addition of the ethyl lithiodiazoacetate to the ketone occurred preferentially from the face opposite the α-silyloxy group to give the *cis*-diol isomer as the major product. In fact, α-silyloxy cyclohexanone reacted to give the *cis*-diol product almost exclusively (30:1 *cis* to *trans* ratio). However, addition of the diazo fragment to the more structurally complex steroid derivative provided isolable quantities of the *trans*-diol product. We were interested to observe that subjecting the *trans*-diol diastereomer to the fragmentation conditions provided dramatically lower yield of the ynoate product than the corresponding *cis*-diol diastereomer; whereas the *cis*-diol diastereomer fragmented to give the desired product in 76% yield, the *trans*-diol diastereomer (Figure 1) afforded the ynoate in only 5% yield. We hypothesize that the difference in reactivity between these diastereomers is the consequence of suboptimal stereoelectronics in the *trans*-diol diastereomer which inhibit the first step of the fragmentation pathway,

TABLE 1. Fragmentation Applied to Various Ring Systems



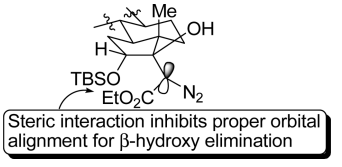
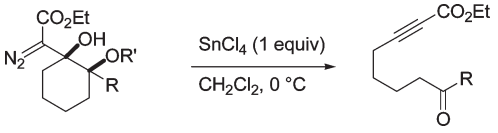
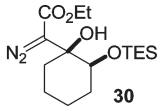
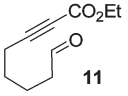
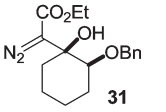
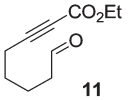
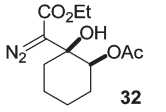
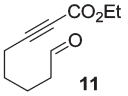
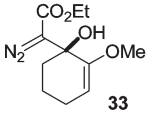
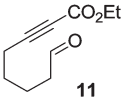
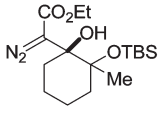
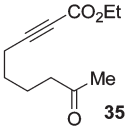
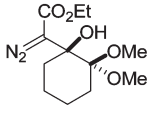
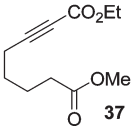


FIGURE 1. Proposed steric inhibition of fragmentation.

(28) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, *118*, 1.

TABLE 2. Fragmentation of Substrates with Modified γ-Oxy Substituents

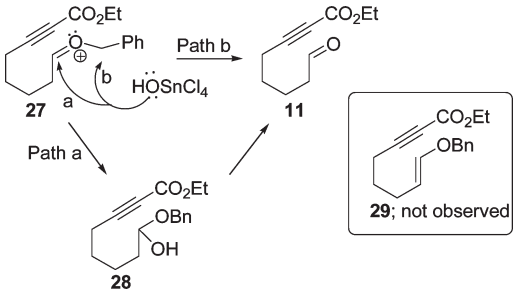


Entry	α-Diazoketone	Product	Yield %
1	 **30**	 **11**	95
2	 **31**	 **11**	90
3	 **32**	 **11**	----
4	 **33**	 **11**	----
5	 **34**	 **35**	27
6	 **36**	 **37**	45

the elimination of the β-hydroxyl. That is, steric interactions between the γ-silyloxy group and the diazo ester in the *trans*-diol diastereomer likely prevent the diazo ester from adopting the conformation required for productive orbital overlap leading to elimination of the β-hydroxyl (Figure 1).

To further probe the scope of this fragmentation, and to explore the ability of this fragmentation reaction to provide ynoates tethered to functional groups other than aldehydes, we prepared several fragmentation precursors in which the γ-oxy group was modified to something other than a *tert*-butyldimethylsilyl ether. As shown in Table 2, changing the γ-oxy substituent to a triethylsilyl ether had no effect on the fragmentation and the expected aldehyde ynoate **11** was isolated in 95% yield. Benzyl ether derivative **31** (entry 2) was also a competent fragmentation substrate and we were interested to observe that once again aldehyde ynoate **11** was the isolated product (90% yield). In this case, the fragmentation likely proceeds by a mechanism similar to that shown in Scheme 5 above to provide oxonium

SCHEME 6. Possible Mechanisms for Loss of Benzyl



intermediate **27** (Scheme 6). Loss of the benzyl group could then occur either by way of hemiacetal **28** (path a), or more directly by nucleophilic attack at the benzylic carbon (path b). Enol ether **29**, a potential alternative product, was not observed.

γ-Acetoxy derivative **32** and enol ether **33** were not competent fragmentation substrates, and upon treatment with $SnCl_4$, both returned complex product mixtures. These results are consistent with the mechanism discussed above as the fragmentation of these substrates would result in high-energy acyloxycarbenium ion[29] or ketenium ion[30] intermediates respectively. Substrate **34** (entry 5), in which the γ-oxy functionality was derived from a tertiary alcohol, successfully fragmented to provide keto ynoate **35**, albeit in a more modest 27% yield. In this case, the low yield may again be due to steric interactions between the substituents at the γ-quaternary center and the diazo ester impeding the diazo ester from adopting the conformation required for elimination of the β-hydroxyl. Finally, we were pleased to observe that dimethyl acetal derivative **36** (entry 6) successfully fragmented to provide tethered diester **37** in 45% yield. These later two results were obtained using the standard reaction conditions and it is possible that product yield may improve with optimized reaction conditions or by using an alternative Lewis acid.

Having successfully modified both the ring that fragments, and the γ-oxy group, we sought to further explore the scope of this fragmentation reaction by varying the diazo portion of the fragmentation precursor. To this end, we are pleased to report that γ-silyloxy-β-hydroxy-α-diazoketones (e.g., **38**, Table 3) are also viable fragmentation precursors that provide tethered aldehyde ynone products (e.g., **39**) in good overall yield. Ynones are versatile synthetic intermediates that undergo a variety of reactions including 1,4-additions,[31] 1,2-additions,[32] isomerization to dienes,[33] [4 + 2] cycloadditions,[34] and α-additions.[32]

Each of the γ-silyloxy-β-hydroxy-α-diazoketone fragmentation precursors shown in Tables 3−5 were conveniently prepared by the aldol-type condensation of the corresponding lithiated diazo ketone with 2-*tert*-butyldimethylsilyloxy cyclohexanone (**9**).[24,26] The versatility of this method lies in the fact that a wide variety of α-diazo ketones can be conveniently prepared by treating carboxylic acid chlorides

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(30) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.
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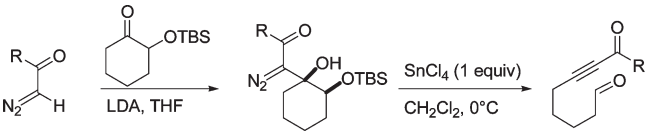
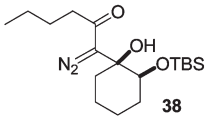
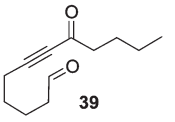
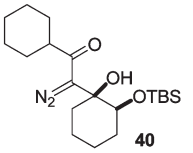
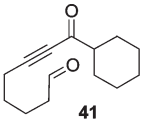
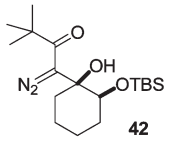
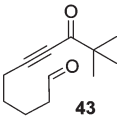
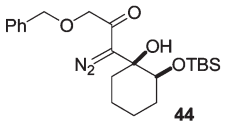
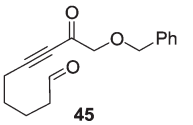
(32) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417.
(33) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.
(34) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378.

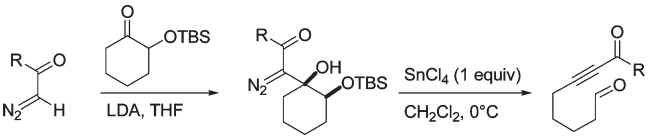
TABLE 3. Fragmentations Yielding Tethered Aldehyde Alkyl Ynones

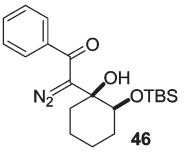
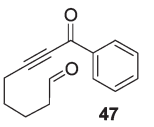
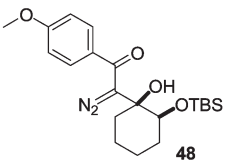
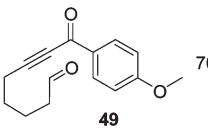
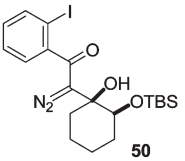
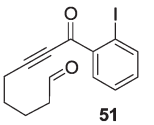
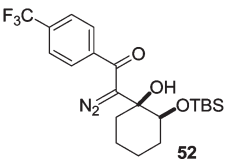
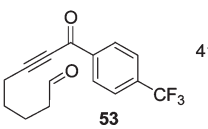


Entry	α-diazoketone	Yield (%)[a] Cis : Trans	Ynone	Yield (%)[b]
1	 **38**	66 (4:1)	 **39**	82
2	 **40**	85 (9:1)	 **41**	83
3	 **42**	50 (4:1)	 **43**	80
4	 **44**	46 (4:1)	 **45**	50[c]

[a]Combined yield of cis and trans diastereomers. [b]Yield of product from reaction of major diastereomer. [c]2 equiv of $SnCl_4$ was used.

TABLE 4. Fragmentations Yielding Tethered Aldehyde Aryl Ynones



Entry	α-diazoketone	Yield (%)[a] Cis : Trans	Ynone	Yield (%)[b]
1	 **46**	83 (9:1)	 **47**	60
2	 **48**	88 (1:0)	 **49**	70
3	 **50**	70 (2:1)	 **51**	69
4	 **52**	77 (7:1)	 **53**	41

[a]Combined yield of cis and trans diastereomers. [b]Yield of product from reaction of major diastereomer.

or anhydrides with diazomethane.[25,35,36] Interestingly, in these cases the diastereoselectivity of the aldol-type addition varied significantly, which may be a reflection of the known reversibility of the addition process.[24]

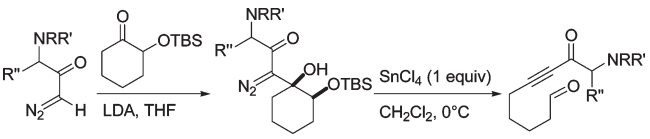
Treating alkyl diazoketones (Table 3) with 1 equiv of $SnCl_4$ at 0 °C provided the corresponding tethered aldehyde alkyl ynones in nearly pure form in the crude reaction mixtures. In contrast to the steroid case discussed above (Figure 1), here both diastereomers appear to fragment in comparable yields. This difference in reactivity is likely due to the increased conformational flexibility of the more structurally simple cyclohexane based ring systems, which would alleviate the steric hindrance described in the steroid case.[37] It is interesting to note that the steric bulk of the alkyl substituent played no role in the reaction outcome; diazoketones bearing *n*-butyl (**38**), cyclohexyl (**40**), and *tert*-butyl (**42**) substituents fragmented to the corresponding ynone products in 82%, 83% and 80% yield, respectively. Incorporating a benzyl ether into the diazo portion of the fragmentation precursor (**44**) provided the more functionalized ynone derivative **45** albeit in a more modest 50% isolated yield. A 2 equiv portion of $SnCl_4$ was necessary to facilitate this later transformation, perhaps because the oxygen-rich side chain can bind 1 equiv of the Lewis acid.

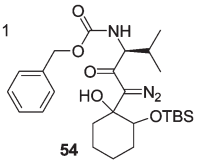
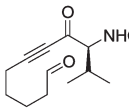
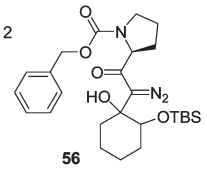
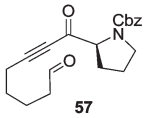
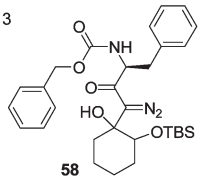
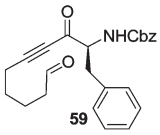
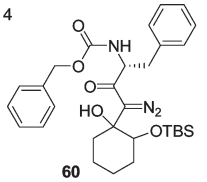
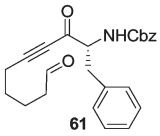
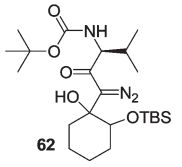
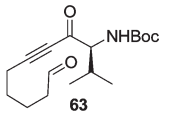
Aryl diazo ketones (Table 4) were also competent fragmentation substrates but provided slightly diminished isolated yields relative to the alkyl ketone substrates. The isolated yield of the product depended on the electronics of the system and the lower isolated yields may be due to the reactive nature of the aryl ynone products, which appear to decompose during purification by column chromatography. Electron-rich and neutral aryl species provided product in higher isolated yield (entries 1−3, 60−70%) than an aryl ring bearing an electron-withdrawing group (entry 4, 41%).

Of final note, several fragmentation precursors in which the α-diazo ketone was derived from N-Cbz protected α-amino acids (Table 5) were prepared. These more complex and heteroatom-rich substrates were formed as a mixture of two diastereomers, and these diastereomeric mixtures successfully fragmented to provide tethered α-amino-ynone aldehyde products in good yield (entries 1−4). α-Amino ynones have recently been shown to be precursors of pyrrolin-4-ones.[38] Exchanging the CBZ protecting group for Boc (entry 5) afforded the N-Boc-protected α-amino ynone **63** in a modest 36% yield. In this case, greater than normal gas evolution was observed during the

(35) Ye, T.; McKervey, M. A. *Tetrahedron* **1992**, *48*, 8007.
(36) Scott, L. T.; Minton, M. A. *J. Org. Chem.* **1977**, *42*, 3757.
(37) The results shown in Tables 3 and 4 are for the fragmentation of the isolated major diastereomer. In several cases, the minor diastereomer was also subjected to fragmentation and provided comparable yields of product. The results shown in Table 5 are for mixtures of diastereomers.
(38) Gouault, N.; Le Roch, M.; Cornée, C.; David, M. l.; Uriac, P. *J. Org. Chem.* **2009**, *74*, 5614.

TABLE 5. Fragmentations Yielding Tethered α-Amino Ynone Aldehydes



Entry	α-diazoketone	Yield (%)[a] (Diastereomer ratio)	Product	Yield (%)[b]	$[\alpha]_D^{20}$
1	 **54**	80 (5:4)	 **55**	69	+21.9
2	 **56**	70 (1:1)	 **57**	62	-46.9
3	 **58**	76 (3:2)	 **59**	74	+17.6
4	 **60**	74 (3:2)	 **61**	74	-15.8
5	 **62**	69 (3:2)	 **63**	36	+35.7

[a]Combined yield of diastereomers. [b]Yield of product from reaction of diastereomer mixture.

fragmentation, and it is likely that the low product yield is due to the instability of the Boc group under the Lewis-acidic reaction conditions.

In conclusion, the fragmentation of γ-oxy-β-hydroxy-α-diazo carbonyls appears to be quite general and provides either ynoates or ynones tethered to an aldehyde, ketone, or ester in good to excellent yield. The ring that fragments, the γ-oxy group, and the diazo portion of the fragmentation precursor can each be modified, thus providing access to a wide variety of functional group rich products. The efficiency of the fragmentation is notable; proton NMR of the crude reaction mixtures are very clean and show few if any side products.[39]

(39) In some cases the aldehyde product was susceptible to oxidation and during purification, or upon standing, would convert to the corresponding tethered ynone carboxylic acid.

Experimental Section

2-(2-(*tert*-Butyldimethylsilyloxy)-1-hydroxycyclohexyl)-1-cyclohexyl-2-diazoethanone (40): A solution of lithium diisopropylamide [prepared by the addition of *n*-butyllithium in hexanes (2.32 mL, 3.29 mmol) to a solution of diisopropylamine (0.52 mL, 3.73 mmol) in THF (10 mL) at −78 °C] was added via cannula over a period of 30 min to a stirred −78 °C solution of 2-(*tert*-butyldimethylsilyloxy)cyclohexanone (**9**) (0.50 g, 2.19 mmol) and 1-cyclohexyl-2-diazoethanone (0.54 g, 3.5 mmol) in THF (10 mL). The mixture was maintained at −78 °C until complete conversion was achieved as monitored by TLC (ca. 1 h). Saturated aqueous NH_4Cl solution (40 mL) was added to the cold reaction mixture, and upon reaching room temperature the mixture was diluted further with saturated aqueous NH_4Cl. The aqueous layer was extracted with two 40 mL portions of EtOAc, and the combined organic layers were washed with brine (40 mL), dried over anhydrous $CaCl_2$, and concentrated under reduced pressure to provide the product as a separable mixture of diastereomers in a 9:1 ratio. The residue was subjected to flash silica gel chromatography (5:1 hexane/Et_2O) to afford the major diastereomer of γ-silyloxy-β-hydroxy-α-diazoketone **40** (0.65 g, 78% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (dd, J = 10.6, 5.7 Hz, 1H), 3.23 (d, J = 2.1 Hz, 1H), 2.47 (tt, J = 11.5, 3.3 Hz, 1H), 2.10 (tq, J = 13.6, 2.2 Hz, 1H), 1.81 − 1.18 (m, 17H), 0.9 (s, 9H), 0.04 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 73.8, 72.1, 71.6, 47.2, 33.5, 31.5, 29.7, 28.4, 26.0, 25.7, 23.7, 21.0, 18.0, −4.0, −4.7; MS (ESI) calcd for $[C_{20}H_{36}N_2O_3SiNa]^+$ 403.2393, found 403.2379.

8-Cyclohexyl-8-oxooct-6-ynal (41). $SnCl_4$ (0.52 mmol, 0.52 mL of a 1 M solution in CH_2Cl_2) was added in a steady stream to a 0 °C solution of γ-silyloxy-β-hydroxy-α-diazoketone **40** (0.20 g, 0.52 mmol, 1 equiv) in anhydrous CH_2Cl_2 (8 mL) under a nitrogen atmosphere. The yellow solution turned colorless, and gas evolution was observed. After gas evolution ceased completely (ca. 10 to 30 min), saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel containing additional saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (20 mL). The organic layers were combined, washed with water (80 mL) and brine (80 mL), and dried over anhydrous $CaCl_2$. The solvents were removed in vacuo, and the residue was subjected to flash silica gel chromatography (4:1 hexane/ethyl acetate) to afford 8-cyclohexyl-8-oxooct-6-ynal (**41**, 0.095 g, 83% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 2.50 (t, J = 7.2, 2H), 2.41 (t, J = 7.2, 2H), 2.36 (tt, J = 10.6, 3.7 Hz, 1H), 1.96 (d, J = 10.4 Hz, 1H), 1.80- 1.74 (m, 3H), 1.65−1.61(m, 4H), 1.40 (qd, J = 11.7, 2.6 Hz, 2H), 1.45−1.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 191.5, 93.6, 80.5, 52.2, 43.2, 28.2, 27.1, 25.8, 25.3, 21.2, 18.8; IR (film): 2929, 2854, 2209, 1706, 1664, 1449 cm^{-1}; MS (ESI) calcd for $[C_{14}H_{20}O_2Na]^+$ 243.1361, found 243.1362.

(*S*)-Benzyl 3,10-Dioxo-1-phenyldec-4-yn-2-ylcarbamate (59). $SnCl_4$ (0.31 mmol, 0.31 mL of a 1 M solution in CH_2Cl_2) was added in a steady stream to a 0 °C solution of γ-silyloxy-β-hydroxy-α-diazoketone **58** (0.171 g, 0.31 mmol, 1 equiv) in anhydrous CH_2Cl_2 (3 mL) under a nitrogen atmosphere. The yellow solution turned colorless, and gas evolution was observed. After gas evolution ceased completely (ca. 10 to 30 min), water (10 mL) was added, and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel containing additional water (10 mL). The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (20 mL). The organic layers were combined, washed with water (80 mL) and brine (80 mL), and dried over anhydrous $CaCl_2$. The solvents were removed in vacuo, and the residue was subjected to flash chromatography on Davisil solid support (4:1 to 3:1 hexane/ethyl acetate) to afford (*S*)-benzyl

3,10-dioxo-1-phenyldec-4-yn-2-ylcarbamate (**59**, 0.090 g, 74% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.36−7.21 (m, 8H), 7.13 (d, J = 7.5 Hz, 2H), 5.30 (d, J = 7.8 Hz, 1H), 5.09 (s, 2H), 4.71 (dd, J = 13.5, 6.1 Hz, 1H), 3.25 (dd, J = 14.2, 5.7 Hz, 1H), 3.19 (dd, J = 14.1, 5.9 Hz, 1H), 2.47 (t, J = 7.1 Hz, 2H), 2.40 (t, J = 6.9 Hz, 2H), 1.76−1.70 (m, 2H), 1.63−1.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 185.5, 155.7, 136.4, 135.6, 129.6, 128.7, 128.6, 128.3, 128.2, 127.2, 98.1, 79.6, 67.1, 62.4, 43.2, 37.3, 27.1, 21.3, 19.1; IR (film) 3323.1, 2933.5, 2210.7, 1701.6, 1674.3; MS (ESI) calcd for $[C_{24}H_{25}O_4NNa]^+$ 414.1681, found 414.1687; $[\alpha]^{20}_D$ +17.6 (*c* 1.00, CH_2Cl_2).

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Supporting Information Available: General experimental methods, detailed experimental procedures, as well as characterization data and NMR spectra for compounds **11**, **30**, **31**, and **36**−**63**. This material is available free of charge via the Internet at http://pubs.acs.org.