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Lewis Acid Promoted Carbon−Carbon Bond Cleavage of γ-Silyloxy-β-hydroxy-α-diazoesters

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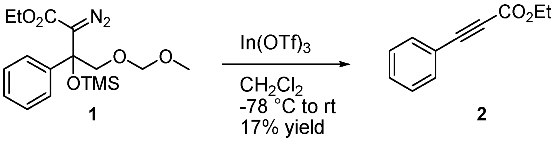
Chemical reactions that result in the fragmentation of carbon−carbon bonds are important transformations because they often unmask latent functional groups under chemoselective reaction conditions. Ring fragmentations are particularly useful because they result in two newly formed functional groups tethered at a predefined distance determined by the ring size. Fragmentations are not always obvious retrosynthetic disconnects, but they can efficiently provide functionalized synthetic intermediates.[1−3] Important examples of these transformations include the oxidative cleavage of 1,2-diols and the ozonolysis of olefins to provide tethered dicarbonyl compounds,[4−6] the Grob fragmentation to provide tethered alkenyl ketones,[2,7] and the Eschenmoser−Tanabe fragmentation to provide tethered alkynyl ketones.[8,9] A more efficient route to tethered alkynyl ketones was recently reported by Dudley and co-workers in which nucleophiles induce the fragmentation of vinylogous acyl triflates.[10]

Herein we report that γ-silyloxy-β-hydroxy-α-diazoesters (e.g., **4**, Scheme 2) undergo efficient rupture of the C_β−C_γ bond when treated with Lewis acids to provide an aldehyde and an ynoate product. When the C_β−C_γ bond is contained in a ring, tethered aldehyde ynoates are formed. Tethered aldehyde ynoates are versatile synthetic intermediates,[11] and this functional group combination is unique to this fragmentation.

We first observed this bond fragmentation during work with α-diazoester **1** (Scheme 1). The reaction of α-diazoester **1** with indium(III) triflate provided a complex mixture of products from which ethyl 3-phenylpropiolate (**2**) was isolated in 17% yield. The formation of propiolate **2** appeared to involve loss of the β-silyloxy group, loss of molecular nitrogen, and fragmentation of the C_β−C_γ bond.

Scheme 1. Initial Observation of C−C Bond Fragmentation



To explore the possibility of utilizing this unprecedented reactivity in a ring fragmentation reaction we prepared γ-silyloxy-β-hydroxy-α-diazoester **4** (Scheme 2).[12] Species of this type are easily prepared by the addition of ethyl lithiodiazoacetate to the corresponding ketone precursor.[13,14] We were pleased to find that treating diazoester **4** with freshly dried indium triflate resulted in observable gas evolution and provided ethyl 8-oxooct-2-ynoate (**5**) as the only observable product.

Scheme 2. Preparation and Ring Fragmentation of a γ-Silyloxy-β-hydroxy-α-diazoester

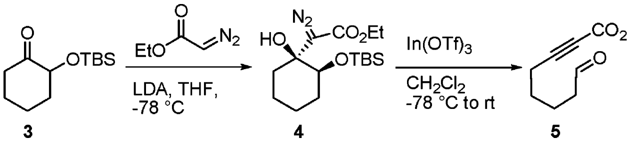
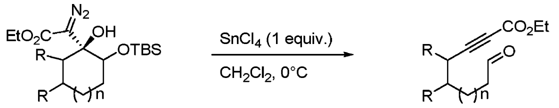
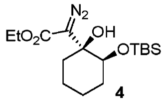
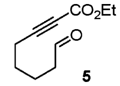
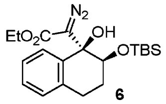
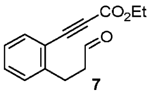
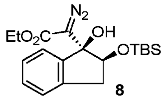
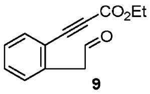
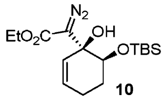
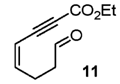
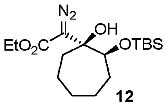
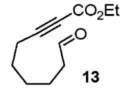
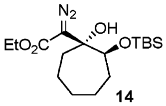
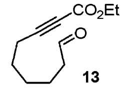
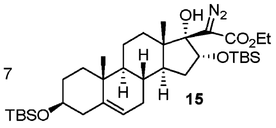
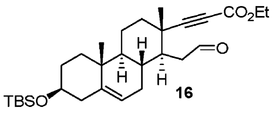
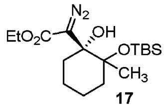
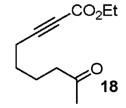


Table 1. Tin Tetrachloride Mediated Ring Fragmentation of γ-Silyloxy-β-hydroxy-α-diazoesters



Entry	Substrate	Product	Yield (%)
1	 **4**	 **5**	94
2	 **6**	 **7**	95
3	 **8**	 **9**	71
4	 **10**	 **11**	97
5	 **12**	 **13**	91
6	 **14**	 **13**	76
7	 **15**	 **16**	76
8	 **17**	 **18**	27

Preliminary optimization of the reaction conditions indicate that freshly dried indium triflate and freshly distilled tin tetrachloride provide the best results. Older batches of tin tetrachloride provided more complex product mixtures as did $BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$, scandium triflate, titanium tetrachloride, and anhydrous HCl. Dibutyl tin dichloride failed to promote the reaction. Due to the

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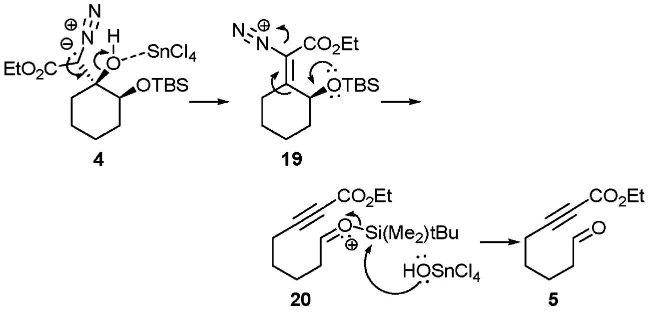
Scheme 3. Proposed Mechanism



limited solubility of indium triflate in CH_2Cl_2, tin tetrachloride was chosen as the Lewis acid of choice for further studies. Reducing the quantity of tin tetrachloride to 10 mol % promoted the fragmentation reaction, but product yield was reduced. Changing the solvent from CH_2Cl_2 to toluene had little effect on the reaction, whereas DMF inhibited the reaction completely.

To test the generality of this ring fragmentation we prepared several additional γ-silyloxy-β-hydroxy-α-diazoesters (Table 1); this reaction appears to be quite general. Tin mediated fragmentation of cyclohexanone derivative **4** provided ethyl 8-oxooct-2-ynoate (**5**) in 94% yield while 1-tetralone derivative **6** and 1-indanone derivative **8** provided the corresponding homologous aryl-substituted ynoates **7** and **9** in 95% and 71% yield, respectively.[15] The more highly conjugated (*Z*)-ethyl 8-oxooct-4-en-2-ynoate (**11**) was formed in 97% yield from cyclohexenone derivative **10**.[16] The easily separable diastereomeric cycloheptanone derivatives **12** and **14** were formed in a 1 to 2.8 ratio, and these fragmented to ethyl 9-oxonon-2-ynoate (**13**) in 91% and 76% yield, respectively. Dehydroisoandrosterone derivative **15** fragmented to provide the desired ynoate aldehyde **16** in 76% yield.[17] This example is notable because the steroid-derived product would not be straightforward to prepare by other means. Finally, the 2-methyl-2-silyloxycyclohexanone derivative **17** fragmented to the tethered ketone ynoate **18** in only 27% yield.[18]

Our current mechanistic hypothesis for this transformation is based on Padwa et al.'s[19] report that β-hydroxy-α-diazoesters react with $BF_3{\cdot}OEt_2$ to provide vinyl diazonium species, and ultimately vinyl cations, via elimination of the β-hydroxyl group. We hypothesize that γ-silyloxy-β-hydroxy-α-diazoesters react similarly with tin tetrachloride to provide vinyl diazonium **19** (Scheme 3) in which the $C_\beta-C_\gamma$ bond and the C−N bond are coplanar. As molecular nitrogen leaves, lone pair donation from the γ-oxygen atom would result in $C_\beta-C_\gamma$ bond fragmentation to provide ynoate **20**. Subsequent loss of the *tert*-butyldimethylsilyl group would provide tethered aldehyde ynoate **5**.

The Lewis acid promoted fragmentation of γ-silyloxy-β-hydroxy-α-diazoesters provides a simple and efficient way to prepare tethered aldehyde ynoates with varying tether length. Further studies on the scope and mechanism of this fragmentation and synthetic applications of the tethered aldehyde ynoate products are underway.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material if available free of charge via the Internet at http://pubs.acs.org.

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(15) Compounds **6** and **8** were obtained as 10:1 mixtures of diastereomers.
(16) Hydrogenation of compounds **10** and **4** over Pd/C provides identical saturated products and confirms the *cis*-diol stereochemistry of **10**.
(17) The relative stereochemistry of **15** was established through 2D NMR analysis.
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