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Preparation of enol ester epoxides and their ring-opening to α-silyloxyaldehydes

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ABSTRACT

The Z-selective ruthenium-catalyzed addition of aromatic carboxylic acids to alkynes was followed by dioxirane epoxidation to furnish enol ester epoxides with cis configuration. Upon treatment of enol ester epoxides with *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine, synthetically useful α-silyloxyaldehydes were obtained. This novel transformation was facilitated by microwave irradiation.

The preparation of α-hydroxyaldehyde derivatives is a common prerequisite to many asymmetric syntheses of 1,2-difunctional compounds.[1] Nucleophilic additions and olefination reactions involving the aldehyde function of such compounds afford 1,2-diols and allylic alcohols, respectively (Fig. 1a).

α-Silyloxyaldehydes are widely applied in synthesis,[2] yet the commonly employed methods for preparation of enantiopure α-silyloxyaldehydes (e.g., multistep differential protection and oxidation of 1,2-diols, or diazotization and partial reduction of α-amino acid derivatives) are often quite unwieldy due to the need for functional group differentiations and protecting group interchanges. For example, a six-step sequence from malic acid was used to access aldehyde **1**[2a] and an 11-step sequence was used to prepare 2-silyloxynonanal **2**[2b] (Fig. 1b). Thus, access to α-silyloxyaldehydes can be more cumbersome when the precursors are beyond the scope of naturally abundant α-amino acids or α-hydroxyacids.

Although kinetic resolution[3] and organocatalytic α-oxidation of aldehydes[4] have offered great advances in accessibility of terminal 1,2-difunctional compounds, subsequent functional group manipulation steps are still required in order to reach the α-silyloxy- or α-hydroxyaldehydes. Convenience and efficiency of the access to α-hydroxy carbonyl compounds warrant further improvement, and therefore new approaches to these deceptively simple building blocks continue to emerge.[5]

In the course of our prior work involving radical addition chemistry of α-silyloxyaldehyde hydrazones,[6] we had occasion to consider alternatives to the aforementioned routes, and hypothesized that oxidative transformations of enol derivatives might offer some potential for improvements in versatility and efficiency. Although α-hydroxyketones may be synthesized by dihydroxylation of enol ethers[7] or oxidation of enolates,[8] the similar methodology for aldehydes results in formation of water-soluble hydrates or 'polar unidentified materials.' [9] Unprotected α-hydroxyaldehydes also exhibit oligomerization and tautomerization to hydroxyketones.[10] An oxidative conversion of terminal enol derivatives into α-silyloxyaldehydes, circumventing the difficulties in handling unprotected α-hydroxyaldehydes, would be an attractive complement to existing preparative methods. Here we describe the development of a new route to α-silyloxyaldehydes based on this hypothesis.

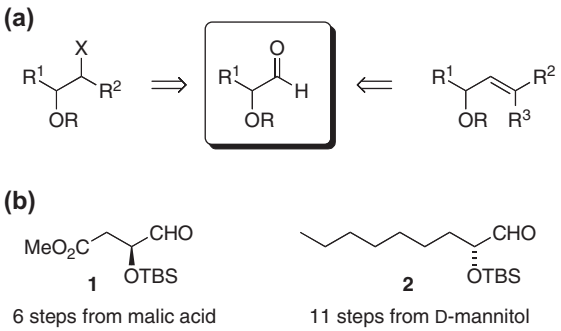

Figure 1. (a) Representative synthetic applications of α-hydroxyaldehyde derivatives. (b) Examples of α-silyloxyaldehyde preparations.

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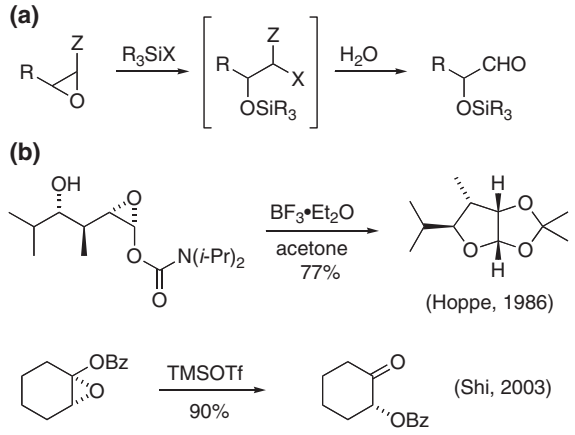
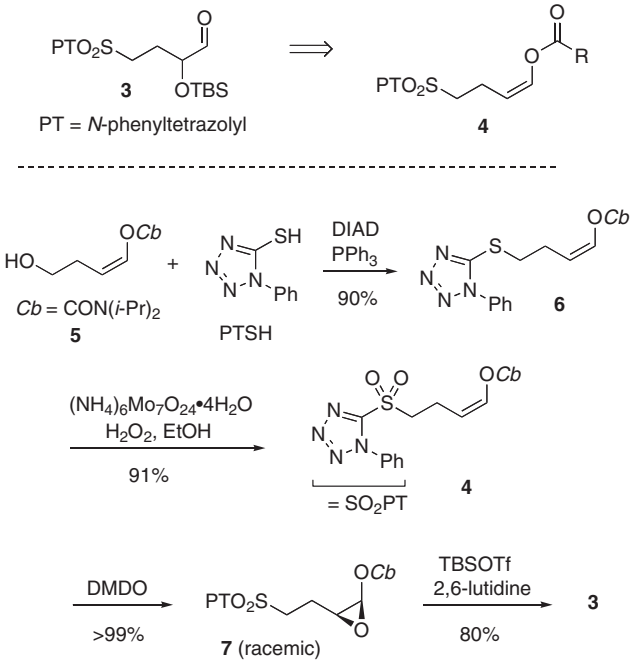


Figure 2. (a) Hypothesis for epoxide ring-opening route to α-silyloxyaldehydes (*Z* = carboxylate or other leaving group, *X* = OTf, Cl, etc.). (b) Relevant precedents involving ring-opening of enol ester epoxides.



Scheme 1. Proof of principle experiments for enol ester epoxide ring-opening to α-silyloxyaldehydes.

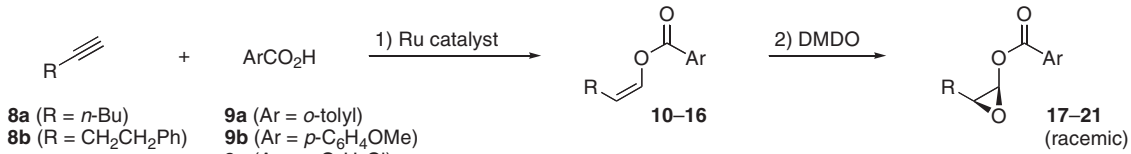
The novel reaction design in the proposed sequence is a silyl cation-induced ring opening of an epoxide derived from an enol derivative such as an enol ether or enol ester (Fig. 2a). In the presence of a silyl cation source, for example, a silyl triflate, the epoxide would be expected to be activated toward ring opening. We reasoned that, if the carboxylate group of an enol ester could serve dual roles as both a cation-stabilizing and leaving group, then the ring opening to an oxocarbenium ion could be followed by a simple hydrolysis to afford the desired α-silyloxyaldehyde. Precedent for such a reaction was sparse. Two examples are found in the work of Hoppe and Shi, each of whom described an isolated example (Fig. 2b).

The γ-sulfonyl α-silyloxyaldehyde **3** (Scheme 1) was needed in the pursuit of another synthetic objective, and presented an opportunity to test the feasibility of the above approach for preparing **3** from enol ester **4**. The *Z*-enol ester moiety was generated using the Hoppe allyl carbamate method,[11] homologating an allylic anion with formaldehyde to furnish the (*Z*)-enecarbamate **5** in 74% yield. Mitsunobu reaction with *N*-phenyltetrazolylthiol followed by oxidation of sulfide **6** provided the corresponding sulfone **4**. In the feasibility test, the enol ester was epoxidized with dimethyldioxirane (DMDO, generated in situ from oxone and acetone) to furnish chromatographically stable epoxide **7** in quantitative isolated yield. Upon treatment of **7** with TBSOTf and 2,6-lutidine at room temperature, aldehyde **3** was obtained in 80% yield, showing that the ring-opening pathway was indeed feasible.

With preparation of **3** establishing the proof of principle for the silyl cation-induced epoxide opening, we sought to link this key reaction to a convenient preparation of the requisite enol ester epoxides. Here, practical developments by Goossen in regio- and stereoselective Ru-catalyzed addition to alkynes[12] drew our attention; the ready availability of alkynes, either commercially or from a variety of precursors, is an important consideration for the scope of future applications.

Using Goossen's procedure, anti-Markovnikov addition of several substituted benzoic acids to 1-hexyne (**8a**, Table 1) or 4-phenyl-1-butyne (**8b**) occurred with 1 mol % loading of a Ru catalyst generated from commercial $[Ru(p\text{-cymene})Cl_2]_2$ and tri(*o*-chlorophenyl)phosphine in the presence of DMAP. The resulting enol esters were subjected to epoxidation with DMDO generated in situ under aqueous conditions, affording high yields of chromatographically stable epoxides **17**–**21**. The compatibility of these enol ester epoxides with the aqueous dioxirane conditions is notable, and suggests the potential for future application of catalytic asymmetric Shi epoxidation or related methodology.[13] The dimethylami-

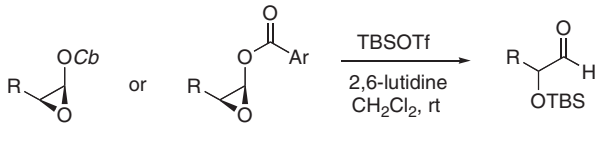
Table 1
Preparation of enol ester epoxides[a]



Entry	R^1	Ar	Yield, enol ester	Yield, epoxide
1	*n*-Bu	*o*-Tolyl	93%, **10**	95%, **17**
2	*n*-Bu	*p*-Anisyl	80%, **11**	90%, **18**
3	*n*-Bu	$p\text{-}C_6H_4Cl$	55%, **12**	74%, **19**
4	*n*-Bu	$p\text{-}C_6H_4NMe_2$	72%, **13**	—[b]
5	CH_2CH_2Ph	*o*-Tolyl	44%, **14**	86%, **20**
6	CH_2CH_2Ph	*p*-Anisyl	80%, **15**	91%, **21**
7	CH_2CH_2Ph	$p\text{-}C_6H_4NMe_2$	75%, **16**	—[b]

[a] Conditions: (1) $((p\text{-cymene})RuCl_2)_2$, $(p\text{-}ClC_6H_4)_3P$, DMAP, 60 °C; (2) oxone, acetone, $NaHCO_3$, H_2O. For details, see endnotes.[15]
[b] A mixture of epoxides was obtained.

Table 2
Ring opening of enol ester poxides



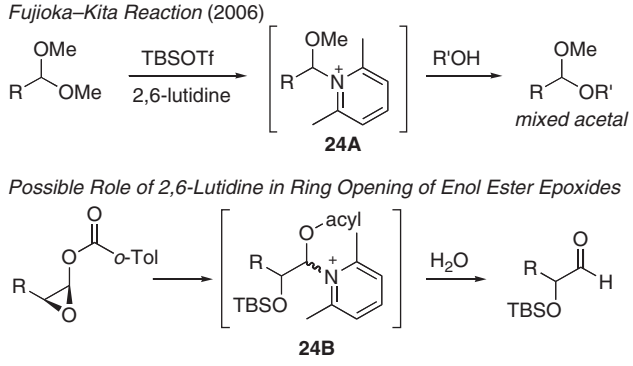
7 (racemic) **17–21** (racemic) **3, 22, 23**

Entry	Method	Epoxide	R	Yield, aldehyde
1	A	**7**	$CH_2CH_2SO_2PT$	80%, **3**
2	B	**17**	*n*-Bu	97%, **22**
3	B	**18**	*n*-Bu	97%, **22**
4	B	**19**	*n*-Bu	79%, **22**
5	A	**20**	CH_2CH_2Ph	86%, **23**
6	B	**20**	CH_2CH_2Ph	86%, **23**

nobenzoic acid-derived enol esters **13** and **16** gave mixtures of epoxides under these conditions.

Next, silyl cation-induced ring opening was examined by exposing enol ester epoxides **17–20** to TBSOTf and 2,6-lutidine in CH_2Cl_2. Initially, the reactions were attempted at room temperature (Table 2, entries 1 and 5). Though successful in some instances, this procedure proved capricious, sometimes requiring additional aliquots of reagents to provide variable chemical yields over reaction times of 1–2 days or more. To minimize the exposure of the product to the reaction conditions, and thereby alleviate the potential for product loss through decomposition pathways, microwave irradiation was applied. This shortened the required reaction time to just 30 min. A comparison of substituents on the benzoate component (entries 2–4) showed that the reaction was compatible with either electron-donating or electron-withdrawing groups, albeit with diminished yield in the latter case (entry 4). Comparison of microwave vs non-microwave conditions for a selected example **20** (entries 5 and 6) shows that the microwave may not be essential for good yields in all cases, but it is recommended for greater reliability.

The importance of 2,6-lutidine in the success of the reaction is worth further note. Fujioka and Kita's interesting disclosure of a novel pathway for non-aqueous cleavage of acetals[14] may be of relevance: Upon treatment with TESOTf and lutidine or collidine, aldehyde acetals are selectively cleaved to moderately stable pyridinium salts **24A** (Scheme 2) which are aldehyde adducts of the N,O-acetal type. In the silyl cation-induced ring opening of enol ether epoxides, a similar role may be speculated for the 2,6-lutidine, which could trap an oxocarbenium ion generated upon ring opening to form intermediate **24B** and avoid destructive side reactions.



Scheme 2. Mechanistic considerations in enol ester epoxide ring-opening.

In summary, a novel silyl cation-induced ring opening of enol ester epoxides has been discovered. This reaction may be linked with anti-Markovnikov Ru-catalyzed addition to alkynes to open a new and efficient access to synthetically valuable α-silyloxyaldehydes from readily available alkynes. Further expansion of scope is underway.

Acknowledgments

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14. Representative experimental procedures: (a) *Enol ester preparation*. The catalyst was prepared from $((p\text{-cymene})RuCl_2)_2$ (8.5 mg, 0.013 mmol), tri(*p*-chlorophenyl)phosphine (14.4 mg, 0.04 mmol) and DMAP (6.4 mg, 0.053 mmol) in toluene (4 mL) by heating the mixture to 60 °C for 45 min. A solution of anisic acid (200 mg, 1.31 mmol) and 4-phenyl-1-butyne (0.24 mL, 1.71 mmol) in toluene (10 mL) was transferred by cannula into the catalyst mixture. The reaction was heated at 60 °C for 24–48 h and then allowed to reach room temperature, then filtered through a silica gel plug. Concentration and radial chromatography (petroleum ether/EtOAc) afforded the *Z*-enol ester **15** (298 mg, 80.4% yield). IR (film) 2934, 2840, 1726, 1606, 1511 1496, 1454, 1317, 1166 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 9.0 Hz, 2H), 7.31–7.16 (m, 6H), 6.94 (d, J = 9.0 Hz, 2H), 4.86 (dd, J = 12.3, 1.5 Hz, 1H), 3.88 (s, 3H), 2.86 (dd, J = 8.4, 7.2 Hz, 2H), 2.68–2.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.72, 163.87, 141.08, 132.24, 128.57, 126.25, 122.21, 113.90, 102.18, 55.68, 35.46, 33.17; HRMS (ES) Calcd. for $C_{18}H_{18}O_3$ ($[M]^+$): 282.1256, Found: 282.1248. (b) *Epoxidation of enol esters*. To a solution of *Z*-enol ester **11** (125 mg, 0.534 mmol) in acetone (2 mL) were added water (4 mL), acetone (4 mL), and sodium bicarbonate (2.7 g, 60 equiv) at −10 °C (ice–salt mixture). Oxone (3.3 g, 10 equiv) was added to the reaction in portions. After 24 h, the reaction mixture was diluted with water and extracted with EtOAc (60 mL). Concentration and radial chromatography (petroleum ether/EtOAc) afforded the desired epoxide **18** (120 mg, 90.3%). IR (film) 2958, 2932, 1727, 1606, 1512, 1462, 1257, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 5.77 (d, J = 2.7 Hz, 1H), 3.87 (s, 3H), 3.08 (ddd, J = 6.3, 6.3, 2.7 Hz, 1H), 1.87–1.69 (m, 2H), 1.63–1.36 (m, 4H), 0.96–0.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.06, 164.18, 132.15, 121.63, 114.04, 76.57, 57.01, 55.69, 28.40, 26.94, 22.67, 14.17; HRMS (ES) Calcd. for $C_{14}H_{18}O_4$ ($[M]^+$): 250.1205, Found: 250.1206. (c) *Epoxide ring-opening*. To a solution of epoxide

18 (27.3 mg, 0.109 mmol) in CH_2Cl_2 (3 mL) in a microwave reactor tube were added 2,6-lutidine (0.025 mL, 0.22 mmol) and *tert*-butyldimethylsilyloxy triflate (0.028 mL, 0.119 mmol) under argon atmosphere. The tube was sealed and subjected to microwave irradiation (100 W, 50 °C, 60 psi) for 30 min. The reaction mixture was quenched with aqueous saturated ammonium chloride solution and extracted with CH_2Cl_2 (15 mL). Concentration and radial chromatography (petroleum ether/EtOAc) afforded α-silyloxyaldehyde **22** (24.4 mg, 97% yield), a known compound: Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 3047–3050.

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