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γ-Oxygenation of α,β-Unsaturated Esters by Vinylogous *O*-Nitroso Mukaiyama Aldol Reaction

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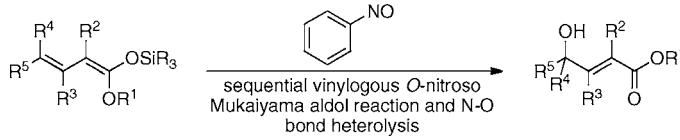
ABSTRACT



A practical procedure has been developed for γ-oxygenation of α,β-unsaturated esters by a vinylogous *O*-nitroso Mukaiyama aldol reaction followed by a one-pot N−O bond heterolysis of the in situ generated γ-aminoxy-α,β-unsaturated esters.

α-Oxygenation of carbonyl compounds is an important method for C−O bond formation. A number of reactions have been developed for this purpose. Most of them rely on oxidation of enolate or enol ether intermediates.[1] A recent variant based on nitroso aldol reactions to give α-aminoxy carbonyl compounds has also been developed.[2] In principle, a vinylogous extension of the α-oxygenation reactions to γ-enolizable α,β-unsaturated carbonyl compounds may be used to prepare γ-hydroxy-α,β-unsaturated carbonyl compounds,[3] structural motifs that are common to natural products. Indeed, oxidation of dienol ethers has been reported for vinylogous oxygenation of α,β-unsaturated carbonyl compounds in isolated cases.[4] However, as frequently encountered in vinylogous extensions of carbonyl group transformations, such oxidation reactions are sometimes complicated by unpredictable regioselectivities, and both α- and γ-oxygenation products may be generated. Thus, we were intrigued by the possibility of applying the vinylogous Mukaiyama aldol reaction with nitrosobenzene for γ-aminoxylation of α,β-unsaturated carbonyl compounds. Additionally, we expected that the N−O bond of the *in situ* generated γ-aminoxy moiety would be heterolytically cleaved by excess nitrosobenzene and lead to a one-pot procedure to γ-hydroxy-α,β-unsaturated carbonyl compounds.[5]

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(2) For reviews of *O*-nitroso aldol reactions, see: (a) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595–607. (b) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514–3525. (c) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292–4300. (d) Plietker, B. *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459. (e) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995–2997. For some references, see: (f) Momiyama, N.; Yamamoto, H. *Org. Lett.* **2002**, *4*, 3579–3582. (g) Momiyama, N.; Yamamoto, H. *Angew. Chem. Int., Ed.* **2002**, *41*, 2986–2988. (h) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039; correction *J. Am. Chem. Soc.* **2004**, *126*, 6498. (i) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247–4250. (j) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. (k) Bøgevig, A.; Sundøn, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112. (l) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115. (m) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5374–5378. (n) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080–1081. (o) Lu, M.; Zhu, D.; Lu, Y.; Zhen, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562–4563. (p) Yanagisawa, A.; Takeshita, S.; Izumi, Y.; Yoshida, K. *J. Am. Chem. Soc.* **2010**, *132*, 5328–5329.

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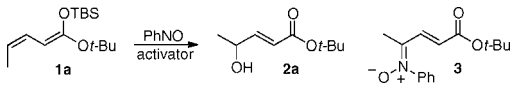
We put our hypothesis to test using the *tert*-butyldimethysilyl ketene acetal (**1a**) of (*E*)-*tert*-butyl pent-3-enoate as a model substrate for reaction with nitrosobenzene under acidic conditions.[6b] Our initial experiments with HOAc, TsOH, or TfOH as the activator in methylene chloride were not successful, and most of the starting materials appeared to be hydrolyzed under the reaction conditions (Table 1, entries 1−3). No desired product was isolated either when TMSOTf was used (entry 4). Thus we were excited by the finding that γ-hydroxy-α,β-unsaturated ester **2a** was indeed formed when the reaction was carried out in methylene chloride with HF-Py as the activator (entry 5). No α-oxygenation product could be detected. Using 1,2-dichloroethane or toluene as the solvent led to inferior results (entries 6 and 7). Other fluoride sources (entries 8 and 9) were also tested but proved to be ineffective for the reaction. Unexpectedly, an (*E*,*E*)-γ-nitrone **3** was formed as the only identifiable product when the reaction was carried out in methanol with acetic acid as the additive (entry 10).[7]

Table 1. Conditions for the γ-Oxygenation Reaction

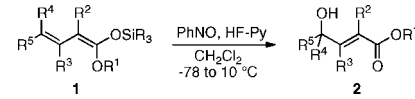


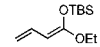
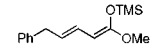
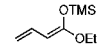
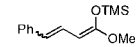
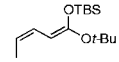
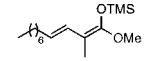
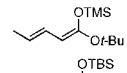
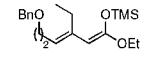
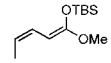
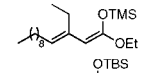
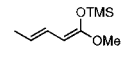
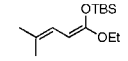
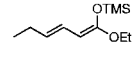
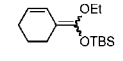
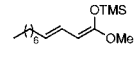
entry[a]	activator	solvent	**2a** (%)
1	HOAc	CH_2Cl_2	nd
2	TsOH	CH_2Cl_2	nd
3	TfOH	CH_2Cl_2	nd
4	TMSOTf	CH_2Cl_2	nd
5	HF-Py	CH_2Cl_2	67
6[b]	HF-Py	$(CH_2Cl)_2$	32
7	HF-Py	toluene	9
8	KF + HOAc	CH_2Cl_2	<5
9	TBAT[c] + HOAc	CH_2Cl_2	<5
10[d]	HOAc	MeOH	4 (64[e])

[a] Unless specified, these reactions were carried out with 2.4 equiv of nitrosobenzene and 2.4 equiv of the activator in the specified solvent at −78 °C for 5 h, warmed to 10 °C over 2 h. [b] The reaction was carried out at −30 °C, warmed to 10 °C. [c] TBAT = tetrabutylammonium difluorotriphenylsilicate. [d] The reaction was carried out with 2.4 equiv of nitrosobenzene and 2.4 equiv of acetic acid at −78 °C, warmed to rt over 2 h. [e] The yield of **3**.

We applied the oxidation reaction condition to a panel of silyl ketene acetals prepared from representative α,β-unsaturated esters (Table 2).[6] These reactions consisted of addition of the silyl ketene acetals to a dichloromethane solution of 2.4 equiv of nitrosobenzene and 2.4 equiv of HF-Py at −78 °C, followed by warming up to 10 °C over 2 h. Consistent with those observed for vinylogous Mukaiyama aldol reactions, (*E*)- double bonds were exclusively formed in all of the acyclic γ-hydroxy-α,β-unsaturated ester products. γ-Selective oxidation was generally observed for acyclic silyl ketene acetals except for entry 10 where a mixture (~1:4) of the α- and γ-oxidation products was generated. The electronic effects of the phenyl group might be responsible for the impaired regioselectivity. The oxygenation reactions appear to be most efficient with the silyl ketene acetals of γ-monosubstituted α,β-unsaturated esters and not affected much by the identities of the silyl and alkoxy groups or the double bond geometry of the silyl ketene acetals (entries 3, 5, and 6; however, we were unable to explain why the yield of entry 4 is comparatively low). Since vinylogous Mukaiyama aldol reactions typically occur through open transition states with the sp^2 carbon at the γ-position directly involved,[3] it is at first surprising that substitutions at the α- and β- positions (entries 11−13) affect reaction efficiencies more than those at the γ- position (entry 14). We surmise that the reduced reaction efficiencies of the α- and β-substituted silyl ketene acetals may be caused more by their reduced stability under the reaction conditions than by their differential reactivities in the vinylogous *O*-nitroso Mukaiyama aldol reactions. A cyclic silyl ketene acetal (entry 15) of methyl cyclohexene-1-carboxylate was also

Table 2. Substrate Scope of the γ-Oxygenation Reaction[a]



entry	substrate	**2** (%)	entry	substrate	**2** (%)
1		**2b**, 62	9		**2f**, 68
2[b]		**2b**, 39	10[c]		**2g**, 70
3		**2a**, 67	11		**2h**, 43
4[b]		**2a**, 43	12		**2i**, 34
5		**2c**, 70	13		**2j**, 20
6		**2c**, 77	14		**2k**, 44
7[b]		**2d**, 44	15[d]		**2l**, 72
8		**2e**, 74			

[a] All reactions were carried out with 2.4 equiv of nitrosobenzene and 2.4 equiv of HF-Py in CH_2Cl_2 at −78 °C. While the time needed for completion of the reactions varies, all the reactions were carried out for 48 h before warming up to 10 °C over 2 h. [b] The yields may have been negatively affected by the relatively low boiling point of the products and/or the low stability of the starting materials. [c] A mixture of α- and γ-oxidation products (α:γ = 1:4). [d] A mixture of α- and γ-oxidation products (α:γ = 1.9:1).

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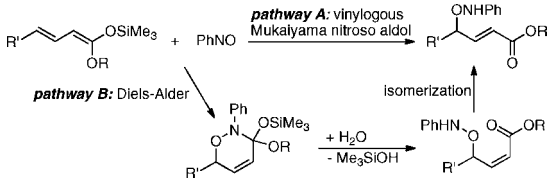
(7) The (*E*)-configuration of nitrone **3** was assigned on the basis of the characteristic ^{1}H NMR chemical shift of the α-methyl group (δ_H 2.42 ppm in $CDCl_3$). See: Bartoli, G.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1990**, *55*, 4456–4459.

oxidized by nitrosobenzene under the reaction condition. However, a mixture (1.9:1) of α- and γ-oxygenation products was obtained.

The γ-oxygenation reactions proceeded through initial formation of γ-aminoxy-α,β-unsaturated ester intermediates.[8] Nitrosobenzene is an excellent dienophile and readily undergoes hetero-Diels−Alder reactions with dienes.[9] Thus, in addition to the vinylogous nitroso Mukaiyama aldol reaction pathway (Scheme 1, pathway A), a mechanistic

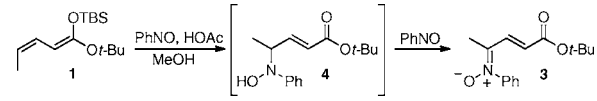
Scheme 1. Proposed Oxygenation Reaction Mechanisms



possibility that involves an initial hetero-Diels−Alder reaction of nitrosobenzene with the electron-rich silyl ketene acetals, followed by ring opening and isomerization of the thus formed (*Z*)-double bond, can also be envisioned for formation of the γ-aminoxy-α,β-unsaturated ester intermediates (Scheme 1, pathway B). However, our experimental results suggest that such a mechanistic pathway is unlikely since (*E*)-double bonds are formed exclusively in reactions of acyclic silyl ketene acetals. In addition, the diene moiety of the cyclic silyl ketene acetal of methyl 1-cyclohexene-1-carboxylate (Table 2, entry 15) is locked into a *s-trans* configuration that precludes the substrate from participating in a hetero-Diels−Alder reaction pathway.[10]

Formation of nitrone **3** presumably proceeded by initial formation of a γ-*N*-phenylhydroxyamino-α,β-unsaturated ester (**4**) by the vinylgous *N*-nitroso Mukaiyama aldol reaction (Scheme 2),[11] which was further oxidized by the

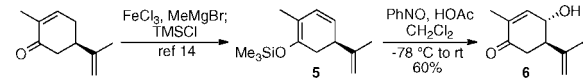
Scheme 2. Proposed Mechanism for Nitrone (**3**) Formation



excess nitrosobenzene to give nitrone **3**.[12] While such a dichotomy of nitrosobenzene reactivities (*O*- vs *N*-electrophilicities and reduction vs oxidation) has been known for some time,[13] it is interesting to observe that two sets of similar reaction conditions lead to very different reaction pathways.

Our preliminary studies to extend the scope of the reaction showed that silyl dienol ether **5**, readily prepared from (−)-carvone with the Kharasch reagent and trimethylsilyl chloride,[14] can be γ-oxygenated by the vinylogous *O*-nitroso Mukaiyama aldol reaction. Acetic acid proved to be a better promoter than HF-Py in this case and gave (+)-5α-hydroxycarvone (**6**) in 60% yield (Scheme 3). This com-

Scheme 3. γ-Oxygenation of (−)-Carvone



pound was previously synthesized in 9 steps from (−)-carvone and also isolated in small quantities from natural sources.[15,16]

In summary, a practical procedure for γ-oxygenation of α,β-unsaturated esters is described. To the best of our knowledge, this constitutes the first report of the vinylogous nitroso Mukaiyama aldol reaction. Studies to extend the scope and identify asymmetric versions of the vinylogous *O*-nitroso aldol reaction will be the focus of future research.

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

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(8) While the reactions were typically carried out in one pot, the γ-aminoxy-α,β-unsaturated ester intermediates could be isolated and characterized. See Supporting Information for full characterization of the γ-aminoxy-α,β-unsaturated ester intermediate (**7**) of Table 2, entry 14.

(9) For some reviews, see: (a) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031–2043. (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348. (c) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107–1117.

(10) One of the reviewers raised an interesting possibility that the reaction proceeds by an initial *N*-nitroso aldol reaction followed by a [2,3]-sigmatropic rearrangement of the resulting α-*N*-phenylhydroxyamino-β,γ-unsaturated ester to give the γ-aminoxy-α,β-unsaturated ester intermediate. While we cannot rule out this possibility, related studies of nitroso aldol reactions with aldehydes and ketones suggest that *O*- instead of *N*-nitroso aldol products are likely to be preferred under the current reaction conditions as a result of the difference in basicities of the oxygen and nitrogen atoms. See ref 2a and Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912–13913.

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(15) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Org. Chem.* **1985**, *50*, 3377–3380.

(16) (a) Canova, L. *An. Acad. Bras. Cienc.* **1972**, *44*, 273–277. (b) Ichimura, N.; Matsuura, Y.; Kato, Y. Abstracts of Papers, 25th Terupen, Seiyu oyobi Koryo ni kansuru Toronkai, Yamaguchi, Oct 1981, p 18.