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Oxidation of α-Alkoxy Allenes into α′-Alkoxy Enones

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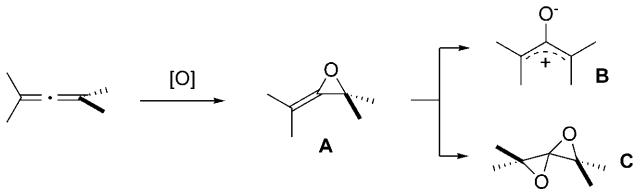
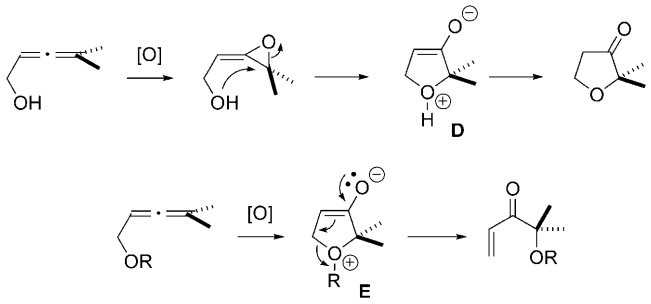
Oxygenation of allenes leads to the formation of reactive allene oxides (Scheme 1, **A**). This oxygenation reaction was first reported in 1934,[1] and has since then elicited considerable attention,[2] mostly because the high reactivity of allene oxides allows the selective insertion of oxygen atoms into carbon backbones, an endeavor that is undergoing a renaissance in recent years.[3] Nature has devised enzymes to harness the synthetic potential of allene oxides.[4] Depending on the conditions, they can open to oxyallyl cations (**B**)[5] or be oxidized again into spirodiepoxides (**C**).[6] Both routes have been used to access cyclic oxygenated compounds.[7]



Scheme 1. Oxygenation of allenes.

As part of our research program devoted to the design of new reactions involving allenes,[8] we decided to re-investigate the oxacyclization of allenols to oxa-cyclopentanones. The reaction presumably occurs via zwitterionic enolate **D** (Scheme 2), which gives the oxacycles after prototropy. We reasoned that a suitably modified enolate (as in **E**) might undergo a retro-Michael reaction to deliver α′-alkoxy ketones.[9] Such a pathway has been suggested only once,[10] but has never been thoroughly investigated. Herein, we report efficient conditions for the oxidative migration and evaluate its scope and limitations.



Scheme 2. Access to α′-alkoxy ketones.

We selected peracids and dimethyldioxirane (DMDO) as representative oxidizing systems employed for allene oxygenation.[7,11] Peracids generate nucleophilic carboxylic acids upon reduction, whereas DMDO does not, and we anticipated this might modulate the reactivity. Also, we expected that added steric hindrance at C1 could be a way to orient the reaction toward migration, because of the steric strain generated in the ring.

DMDO oxidation of dimethyl-substituted α-hydroxy allene **1a**, which has two isopropyl substituents at C1 led to dihydrofuran-3(2*H*)-one **3a** (Table 1, entry 1, conditions A), that is it did not lead to the migration. On the other hand, substrate **1b**—exhibiting a less sterically demanding cyclopentyl ring at C1—led exclusively to 4-hydroxydihydrofuran-3(2*H*)-one **4b** (Table 1, entry 2) as a result of double epoxidation of the starting allene (see Scheme 1). We imagined that formation of a diepoxide might be limited by switching to the less reactive *m*-chloroperbenzoic acid (*m*CPBA, con-

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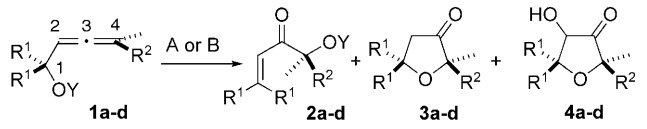
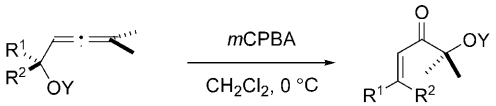
Table 1. Initial screening of substrates and reaction conditions.



Entry	Substrate	R^1	R^2	Y	Conditions[a]	Yield [%] (**2**/**3**/**4**)[b]
1	**1a**	*i*Pr	Me	H	A	67 (0:1:0)
2	**1b**	$(CH_2)_2$	Me	H	A	74 (0:0:1)
3	**1b**	$(CH_2)_2$	Me	H	B[c]	93 (1:5.6:5)[d]
4	**1c**	Ph	Et	H	A	50 (2.6:1:0)[d]
5	**1c**	Ph	Et	H	B	74 (2:1:0)[d]
6	**1c**	Ph	Et	H	B[e]	83 (2.5:1:0)[d]
7	**1c**	Ph	Et	H	B[f]	81 (2.1:1:0)[d]
8	**1d**	Ph	Me	Me	A	55 (1:0:0)
9	**1d**	Ph	Me	Me	B	91 (1:0:0)

[a] Conditions A: DMDO, acetone, −30 °C, 20 min; Conditions B: *m*CPBA (1.1 equiv), CH_2Cl_2, 0 °C, 5 h. [b] Isolated yield. [c] Using 1.5 equiv of *m*CPBA. [d] Separated. [e] 10 % aq $NaHCO_3$ added. [f] TsOH (1 equiv) added.

Table 2. Oxidation of tertiary α-alkoxy allenes with a quaternary center at C1.



Entry	Allene	R^1	R^2	Y	Yield [%] (*E*/*Z*)
1	**1e**	Ph	Ph	Bn	93
2	**1f**	Ph	Ph	allyl	78
3	**1g**	Ph	Ph	propargyl	68
4	**1h**	Ph	Ph	$CH_2CH(OCH_2)_2$	86
5	**1i**	Ph	Ph	$SiMe_3$	94
6	**1j**	Ph	Ph	$Si(iPr)_3$	0
7	**1k**	Me	Me	Bn	87
8	**1l**	$(CH_2)_2$	$(CH_2)_2$	Bn	95
9	**1m**	Me	Ph	Bn	85 (5.7:1)
10	**1n**	Me	*i*Pr	Bn	89 (1:0)
11	**1o**	(*E*)-styryl	Ph	Bn	76 (1:0)

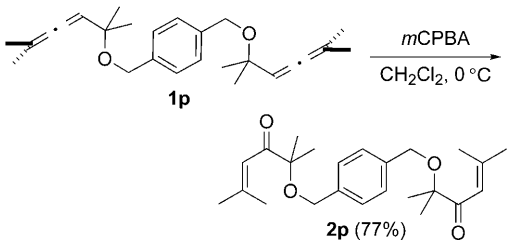
ditions B). Besides, the preparation and manipulation of DMDO are both hazardous. Nonetheless, *m*CPBA led to a roughly equimolar mixture of oxacycles **3b** and **4b**. Yet, we were pleased to observe the desired enone **2b** as a minor product of the reaction (Table 1, entry 3).

We have shown in a previous report that aromatic groups at C1 provide an entry to new reactivities.[12] In the present case, introduction of a *gem*-diphenyl group blocked the bis-oxidation (Table 1, entries 4 and 5). Also, enone **2c** was now the major product, but it was still accompanied by a large amount of cyclic ketone **3c**. The use of additives such as sodium hydrogen carbonate (Table 1, entry 6) or *p*-toluene sulfonic acid (TsOH, Table 1, entry 7) did not markedly change the ratios. Overall, these combined results suggest that the formation of spirodiepoxides is delayed by steric factors at C1, but it appears that the prototropy leading to products **3** is too fast to be avoided even in sterically demanding cases.

We therefore decided to protect the alcohol functionality. Gratifyingly, enone **2d** was then isolated as the only product under both experimental conditions, albeit the yield was better when *m*CPBA was used (Table 1, entries 8 and 9). A typical reaction is thus carried out with the allene in the presence of *m*CPBA (1.1 equiv) in dichloromethane at 0 °C. The conditions B were chosen to illustrate the scope and limitations of the methodology (Table 2). Both alkyl and silyl ethers underwent efficient migration to C4. However, the sterically demanding triisopropylsilyloxy group prevented any reaction occurring (Table 2, entry 6). In addition, various combinations of alkyl and aryl groups at C1 could be used (only achiral or racemic allenes were used). This shows that i) the prototropy is the major obstacle to the migration in α-alkoxy allenes, and ii) that the other factor steering the reactivity away from oxacyclization is the steric hindrance at C1.

Interestingly, the migration is stereoconvergent and generally selective. Except in one case (Table 2, entry 9), the *E* isomer was the only product (Table 2, entries 10 and 11).[13] Notably, when several oxidizable groups were present on the molecules, oxidation occurred exclusively at the allene framework, and not on the allyl, styryl, or propargyl moieties. Lastly, the facile transformation of substrates containing protecting groups, such as benzyl (Bn, Table 2, entries 1, 7–11), and, above all, trimethylsilyl (Table 2, entry 5), provided an access to synthetically useful α′-hydroxy enones.

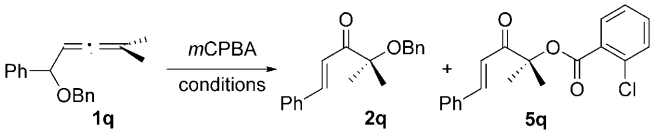
Smooth double migration was achieved from oxidation of the bis-allene **1p** (Scheme 3). Using 2 equiv of *m*CPBA, the reaction proceeded within 2 h at 0 °C to deliver diketone **2p** in 77 % yield. No traces of over oxidation product could be detected.



Scheme 3. Oxidation of a bis-allene derivative.

More in-depth analysis also showed that the substitution pattern at C1 plays an important role. Diphenyl-substituted α-alkoxy allene **1e** led exclusively to enone **2e** in 93 % yield (Table 2, entry 1). When one phenyl ring was removed, as in **1q**, ketoester **5q** was formed as a byproduct (Table 3). This byproduct is the result of intermolecular attack of *m*-chlorobenzoic acid onto the intermediate allene oxide. Decreasing the temperature to −78 °C (Table 3, entries 2 and 3), slightly modified the ratio in favor of the enone. The ratio remained unchanged even when commercial *m*CPBA was purified to remove traces of the acid (Table 3, entry 4). We could suppress the byproduct by carrying out the reaction under biphasic conditions (CH_2Cl_2/water) in the presence of sodium

Table 3. Case of a tertiary center at C1.

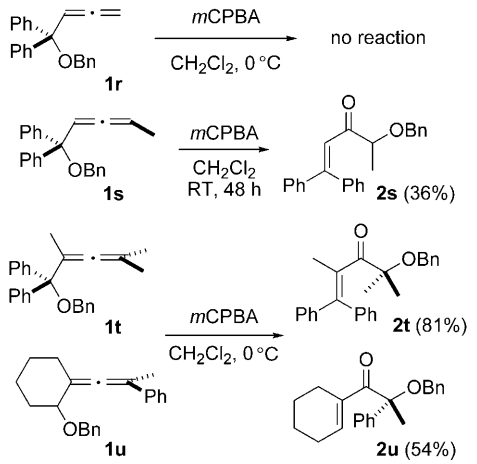


Entry	Conditions	Yield [%] (**2q**/**5q**)[a]
1	CH_2Cl_2, 0 °C, 2 h	55 (3:1)
2	CH_2Cl_2, −10 °C, 2 h	62 (4:1)
3	CH_2Cl_2, −78 °C to RT, 5 h	58 (4:1)
4	Purified *m*CPBA, CH_2Cl_2, −10 °C, 2 h	45 (4:1)
5	CH_2Cl_2/H_2O (biphasic), $NaHCO_3$, RT, 2 h	53 (1:0)
6	Xylenes/H_2O (biphasic), $NaHCO_3$, RT, 2 h	77 (1:0)

[a] Isolated, not separated.

hydrogen carbonate, which ushered the carboxylate out of the organic phase (Table 3, entry 5). Using xylenes as the organic phase resulted in a significant improvement of the yield (77%, Table 3, entry 6), which considerably broadened the scope of the migration.

The influence of the allene substitution was investigated next (Scheme 4). Monosubstituted allene derivative **1r** was not nucleophilic enough to react with *m*CPBA (1.1 equiv) in

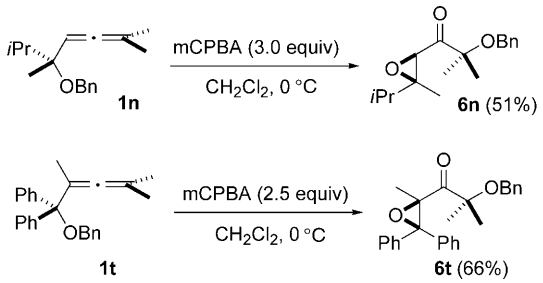


Scheme 4. Influence of the allene substitution pattern. Compound **1u** was used as a single diastereomer.

our hands. Introduction of one substituent delivered enone **2s** after prolonged reaction time, and it was obtained in moderate yield. On the other hand, the fully substituted allene **1t** gave 81% of **2t**. Allene **1u** was obtained as a single diastereomer, the relative configuration of which was not determined. Indeed, the oxidative migration is a stereoconvergent process. Reaction of **1u** yielded 54% of **2u**.

Epoxy ketones could be prepared in one step using an excess of *m*CPBA (Scheme 5).[14] Both tertiary and quaternary allene systems **1n** and **1t** underwent the oxidative migration/oxidation cascade as planned.

In conclusion, we have developed an original and rapid access to α′-alkoxy enone derivatives by selective oxidation of α-alkoxy allenes. This reaction proceeds smoothly and



Scheme 5. Double oxidation leading to α′-alkoxy oxiranyl ketones.

tolerates various substitution patterns. Further work will focus on β-alkoxy allenes and higher homologues, amino allenes, as well as the asymmetric version of the migration.

Experimental Section

Oxidative rearrangements of the allenyl ethers (Table 2): The allenic ether was dissolved in CH_2Cl_2 (0.1 M) and *m*CPBA (77 wt%) was added in one portion at RT. The resulting mixture was stirred at RT until disappearance of the starting material (TLC monitoring, usually within 2 h). The mixture was then added to a 10% aq solution of Na_2CO_3. The aqueous phase was extracted twice with CH_2Cl_2 (15 mL each time). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The desired ketones were purified by flash chromatography over silica gel. See the Supporting Information for the product descriptions.

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Keywords: allenes · epoxidation · ketones · oxidation · rearrangement

[1] J. Boeseken, *Rec. Trav. Chim. Pays-Bas* **1934**, *54*, 657.
[2] A. Horvath, J. E. Bäckvall in *Modern Allene Chemistry, Vol. 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, p. 973.
[3] a) K. Chen, P. S. Baran, *Nature* **2009**, *459*, 824; b) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783.
[4] a) E. J. Corey, M. d'Alarcao, S. P. T. Matsuda, P. J. Lansbury, Jr., *J. Am. Chem. Soc.* **1987**, *109*, 289; b) A. N. Grechkin, M. Hamberg, *FEBS Lett.* **2000**, *466*, 63.
[5] Oxyallyl cations undergo facile closure to cyclopropanones, see: T. S. Sorensen, F. Sun, *Can. J. Chem.* **1997**, *75*, 1030.
[6] a) T. H. Chan, M. P. Li, W. Mychajlowski, D. N. Harpp, *Tetrahedron Lett.* **1974**, *15*, 3511; b) A. W. Fort, *J. Am. Chem. Soc.* **1962**, *84*, 4979; c) T. H. Chan, B. S. Ong, W. Mychajlowskij, *Tetrahedron Lett.* **1976**, *17*, 3253; d) M. Shipman, H. Thorpe, I. R. Clemens, *Tetrahedron Lett.* **1997**, *38*, 897; e) P. Ghosh, S. D. Lotesta, L. J. Williams, *J. Am. Chem. Soc.* **2007**, *129*, 2438; f) P. Ghosh, Y. Zhang, T. J. Emge, L. J. Williams, *Org. Lett.* **2009**, *11*, 4402; g) Y. Zhang, J. R. Cusick, P. Ghosh, N. Shangguan, S. Katukojvala, J. Inghrim, T. J. Emge, L. J.

Williams, *J. Org. Chem.* **2009**, *74*, 7707; P. Ghosh, J. R. Cusick, J. Inghrim, L. J. Williams, *Org. Lett.* **2009**, *11*, 4672.

[7] a) J. Grimaldi, M. Bertrand, *Tetrahedron Lett.* **1969**, *10*, 3269; b) J. Grimaldi, M. Bertrand, *Bull. Soc. Chim. Fr.* **1971**, *3*, 957; c) J. Grimaldi, M. Malacria, M. Bertrand, *Tetrahedron Lett.* **1974**, *15*, 275; d) J. Grimaldi, M. Malacria, M. Bertrand, *Bull. Soc. Chim. Fr.* **1975**, *7*, 1726; e) M. Malacria, M. L. Roumestant, *Tetrahedron* **1977**, *33*, 2813; f) A. Doutheau, J. Sartoretti, J. Gore, *Tetrahedron* **1983**, *39*, 3059; g) A. Doutheau, J. Gore, J. Diab, *Tetrahedron* **1985**, *41*, 329. For related work on allenyl ketones, see: h) J. K. Crandall, E. Rambo, *Tetrahedron Lett.* **1994**, *35*, 1489. On the other hand, allenes with alcohol, amine, phosphoric or carboxylic acid functionalities, have been oxidized into various types of heterocycles, see: i) M. Bertrand, J. P. Dulcère, G. Gil, P. Sylvestre-Panthet, *Tetrahedron Lett.* **1976**, *17*, 1507; j) M. Bertrand, J. P. Dulcère, G. Gil, J. Grimaldi, P. Sylvestre-Panthet, *Tetrahedron Lett.* **1976**, *17*, 3305; k) J. K. Crandall, D. J. Batal, *Tetrahedron Lett.* **1988**, *29*, 4791; l) R. S. Macomber, *J. Org. Chem.* **1978**, *43*, 1832; m) J. K. Crandall, E. Rambo, *Tetrahedron* **2002**, *58*, 7027. For a recent application in total synthesis, see n) J. A. Malona, K. Cariou, A. J. Frontier, *J. Am. Chem. Soc.* **2009**, *131*, 7560. For the oxidation of heteroallene derivatives, see o) H. Xiong, R. P. Hsung, C. R. Berry, C. Rameshkumar, *J. Am. Chem. Soc.* **2001**, *123*, 7174; p) J. Huang, R. P. Hsung, *J. Am. Chem. Soc.* **2005**, *127*, 50; q) C. Rameshkumar, H. Xiong, M. R. Tracey, C. R. Berry, L. J. Yao, R. P. Hsung, *J. Org. Chem.* **2002**, *67*, 1339. For a general review, see: r) W. Adam, C.-G. Zhao, K. Jakka, *Org. React.* **2007**, *69*, 1.

[8] a) B. Delouvrié, L. Fensterbank, E. Lacôte, M. Malacria, *Tetrahedron Lett.* **1999**, *40*, 11395; b) E. Mainetti, L. Fensterbank, M. Malacria, *Synlett* **2002**, 0923; c) G. Lemière, V. Gandon, N. Agenet, J.-P. Goddard, A. de Kozak, C. Aubert, L. Fensterbank, M. Malacria, *Angew. Chem.* **2006**, *118*, 7758; *Angew. Chem. Int. Ed.* **2006**, *45*, 7596; d) O. Buisine, V. Gandon, C. Aubert, L. Fensterbank, M. Malacria, *Synlett* **2008**, 751; e) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993.

[9] α′-Alkoxy ketones are desirable synthetic intermediates, and several ways to prepare them have been described. For recent synthetic applications of α′-hydroxy enones, see, for example, [3+2] cycloadditions: a) C. Palomo, M. Oiarbide, E. Arceo, J. M. García, R. López, A. González, A. Linden, *Angew. Chem.* **2005**, *117*, 6343; *Angew. Chem. Int. Ed.* **2005**, *44*, 6187; for [4+2] cycloadditions, see: b) C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003**, *125*, 13942; for Michael additions, see: c) C. Palomo, R. Pazos, M. Oiarbide, J. M. García, *Adv. Synth. Catal.* **2006**, *348*, 1161; d) S. Lee, C. J. Lim, S. Kim, R. Subramaniam, J. Zimmerman, M. P. Sibi, *Org. Lett.* **2006**, *8*, 4311; Friedel–Crafts reaction: e) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154; for Pd-catalyzed oxidative cyclizations, see: f) M. Reiter, H. Turner, R. Mills-Webb, V. Gouverneur, *J. Org. Chem.* **2005**, *70*, 8478. For applications in total synthesis, see g) S. Sörgel, C. Azap, H.-U. Reißig, *Eur. J. Org. Chem.* **2006**, 4405. For the synthesis of α′-alkoxy ketones, see F. Pierre, D. Enders, *Tetrahedron Lett.* **1999**, *40*, 5301.

[10] M. Bertrand, J. P. Dulcère, G. Gil, *Tetrahedron Lett.* **1980**, *21*, 4271.

[11] Other potential oxidants are *t*BuOOH/$VOacac_2$, H_2O_2/PhCN, ozone, oxone, H_2O_2/PCWP, and $NaIO_4$/$RuCl_3$, see: a) J. K. Crandall, W. W. Conover, *J. Chem. Soc. Chem. Commun.* **1973**, 340; b) J. K. Crandall, D. J. Batal, *J. Org. Chem.* **1988**, *53*, 1338; c) S. Sakaguchi, S. Watase, Y. Katayama, Y. Sakata, Y. Nishiyama, Y. Ishii, *J. Org. Chem.* **1994**, *59*, 5681; d) M. Laux, N. Krause, *Synlett* **1997**, 765.

[12] P. Cordier, M. Malacria, E. Lacôte, V. Gandon, *Angew. Chem.* **2009**, *121*, 8913; *Angew. Chem. Int. Ed.* **2009**, *48*, 8757.

[13] This result is not consistent with a concerted migration as described in Scheme 2. It warrants further mechanistic determination. Nonetheless, we hypothesize that the opening of the allene oxide may require some activation (protonation or complexation of the oxygen atom), which would stabilize the enolate formed. The cation part of the zwitterion may thus have time to equilibrate to the most stable rotamer before collapsing to give the final product.

[14] α′-Alkoxy oxiranyl ketones are also valuable synthetic intermediates and key subunit of natural products, see, for example: L. F. Tietze, K. M. Gericke, I. Schuberth, *Eur. J. Org. Chem.* **2007**, 4563.

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