Oxocarbenium Ions

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Stereoselective Synthesis of Tertiary Ethers through Geometric Control of Highly Substituted Oxocarbenium Ions**

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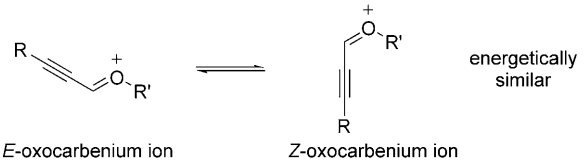
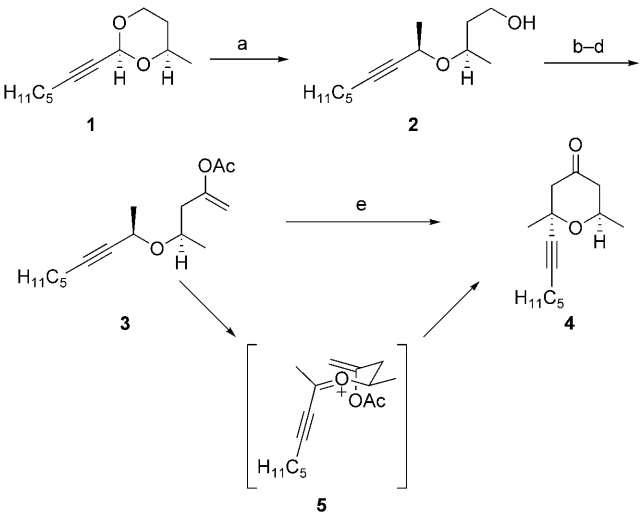
Oxocarbenium ions are intermediates in a number of synthetic processes including Prins cyclizations,[1] acid-mediated additions to acetals,[2] allyl group transfers,[3] and additions of carbonyls to electrophiles.[4] Stereocontrol in these transformations can be quite high as a result of the strong preference, calculated at approximately 2 kcal mol^{-1},[5] for monosubstituted oxocarbenium ions to exist in *E* configurations. However, reports of geometric control for 1,1-disubstituted oxocarbenium ions are rare[6] because the steric difference between the alkyl groups is generally smaller than the steric difference between an alkyl group and a hydrogen atom. General models that predict the geometry of disubstituted oxocarbenium ions would be valuable for designing syntheses of natural products or natural-product-like libraries[7] that contain tertiary ether groups. Recently, our research group reported[8] that intramolecular nucleophilic additions to alkynyl-substituted oxocarbenium ions proceed with minimal stereocontrol to provide *cis*- and *trans*-2,6-disubstituted tetrahydropyrans. This unusual lack of stereocontrol results from the approximate energetic equivalence of the *E* and *Z* oxocarbenium ions, which is a result of the small steric difference between an alkynyl group and a hydrogen atom (Scheme 1). Herein, we describe a rare application of



Scheme 1. Alkynyl-substituted oxocarbenium ions.

carbon–hydrogen bond functionalization for stereoselective syntheses of molecules that contain fully substituted carbon atoms. The approach is based on the development of a model that is able to predict the geometries of 1,1-disubstituted oxocarbenium ions involved in nucleophilic additions that form tertiary ethers with high stereocontrol. We also report a model that illustrates stereocontrol in intramolecular additions to monosubstituted oxocarbenium ions relative to a tertiary ether.

We postulated that 1,1-disubstituted oxocarbenium ions containing an alkyl group and an alkynyl group should exist in a conformation in which the two alkyl groups have a *trans* relationship in consideration of the minimal steric demands of alkynyl groups. We chose to employ a DDQ-mediated ether oxidation[9] protocol for carbocation formation to test this hypothesis because these conditions eliminate the potential for acid-induced solvolytic product decomposition[10] The synthesis of the ether linkage between the two branched carbon atoms in **2** (Scheme 2) was readily con-



Scheme 2. Stereocontrolled tertiary ether synthesis. Reagents and conditions: a) Me_3Al, toluene, 75%. b) Py·SO_3, Et_3N, DMSO, 92%. c) Bestmann–Ohira reagent,[13] K_2CO_3, MeOH. d) HOAc, [{(*p*-cymene)$RuCl_2$}$_2$], Fur_3P, Na_2CO_3, toluene,[14] 65%, two steps. e) DDQ, M.S. (4 Å), 2,6-Cl_2Py, 1,2-dichloroethane, 72%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethyl sulfoxide, Fur_3P = tri(2-furyl)phosphine, M.S. = molecular sieves, Py = pyridine.

structed by applying Yamamoto's Me_3Al-mediated acetal opening protocol[11] to alkynyl acetal **1**. Functional group manipulations provided the cyclization substrate **3**, which was exposed to DDQ at room temperature and provided tetrahydropyran **4** as a single stereoisomer in 72% yield. This stereochemical outcome is consistent with our hypothesis that the reaction proceeds through the oxocarbenium ion **5**. Although tertiary and spirocyclic ethers have been prepared through intramolecular Prins-type additions to disubstituted

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oxocarbenium ions,[12] stereoselectivity has not been addressed aside from reactions that proceed through a specific isatin-derived ion.[6d–f]

This result led us to devise more generalized models of oxocarbenium ion geometry to guide substrate design for the stereocontrolled formation of cyclic tertiary ethers. One approach was based on expanding the model for the geometric control over 1,1-disubstituted oxocarbenium ions, and the other was based on control over the trajectory of nucleophilic approach by preexisting tertiary stereocenters (Figure 1). The generalized model for 1,1-disubstituted oxocarbenium ion geometric control (model **A**) places the smaller group (R_S) in a *cis* relationship with the opposite alkyl group and the larger group (R_L) in a *trans* relationship. Model **B** illustrates the manner by which preexisting tertiary stereocenters can influence the sense of nucleophilic addition into oxocarbenium ions. Thus R_S occupies an eclipsed orientation with the hydrogen atom of a monoalkyl oxocarbenium ion. These models are similar to the reactive conformation for the well-studied Corey–Bakshi–Shibata (CBS) ketone reduction (model **C**),[15] and successful structural classes for CBS reactions were used to guide substrate design in this study.

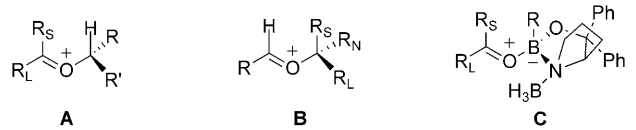
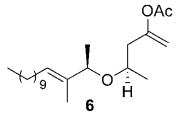
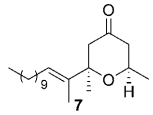
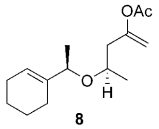
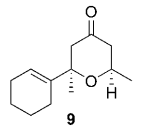
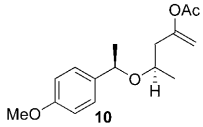
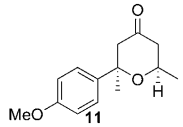
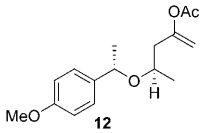
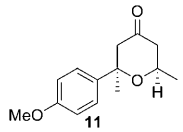
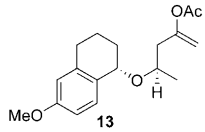
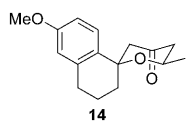
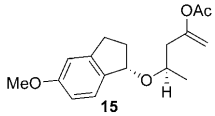
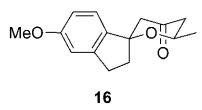
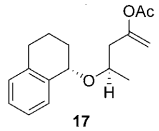
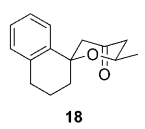
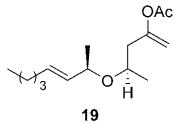
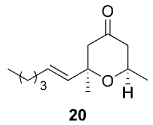
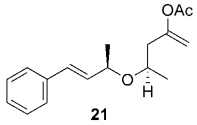
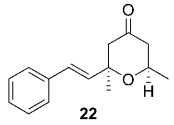


Figure 1. Models for geometrical control in highly substituted oxocarbenium ions. The large, small, and nucleophilic groups on the tertiary ether are labeled as R_L, R_S, and R_N, respectively.

Alkynes serve as the R_S substituent when compared to alkyl groups in model **A**, but alkenes and arenes could serve as the R_L group. Thus, secondary allylic and benzylic ethers should yield products that place the unsaturated groups in equatorial orientations. These substrates reacted with moderate stereocontrol in dichloroethane (not shown), but changing the reaction solvent to nitromethane led to a substantial improvement in selectivity. We postulate that the more polar solvent stabilizes the intermediate oxocarbenium ion, thus slowing the cyclization and lowering the barrier of oxocarbenium-ion rotation,[16] and thereby allowing the ions to equilibrate to their more stable isomers prior to ring closure.

Representative examples of these cyclization reactions are shown in Table 1. In each of these examples the alkenyl or aryl group is the R_L group. Allylic ethers **6** and **8** reacted quite efficiently and provided tetrahydropyrans **7** and **9** with excellent stereocontrol (Table 1, entries 1 and 2). Aryl analogues were effective substrates, with diastereomeric ethers **10** and **12** yielding **11** as a single stereoisomer (Table 1, entries 3 and 4). The formation of the same isomer starting from diasteromeric reagents provides support for a planar oxocarbenium ion intermediate. Spirocyclic ethers, which are subunits in many natural products,[17] are also accessible through this protocol as shown in entries 5, 6, and 7 of Table 1. These reactions were quite fast and extremely stereoselective. Entries 8 and 9 of Table 1 show the effect of using *trans*-1,2-disubstituted alkene substrates. Allylic ether **19** reacted with excellent efficiency, though the diastereocontrol was modest (3:1). This outcome is consistent with the lower steric demand of a disubstituted alkene relative to a trisubstituted alkene. The diastereomeric products were separable, however, and the major product could be isolated

Table 1: Synthesis of tertiary ethers from oxidation of allylic and benzylic ethers.[a]

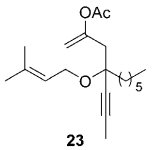
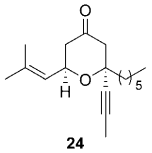
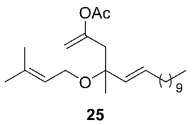
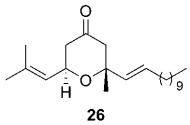
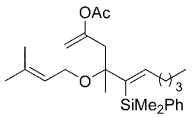
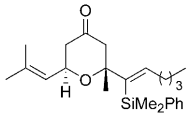
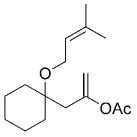
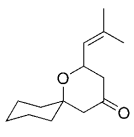
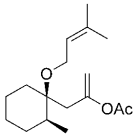
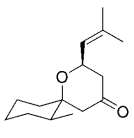
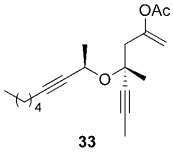
Entry	Substrate[b]	Product	*t* [h]	d.r.[c]	Yield [%][d]
1	 **6**	 **7**	12	26:1	84
2	 **8**	 **9**	2.5	100:0	86
3	 **10**	 **11**	2	100:0	78
4	 **12**	 **11**	2	100:0	74
5	 **13**	 **14**	0.67	100:0	82
6	 **15**	 **16**	0.5	100:0	84
7	 **17**	 **18**	7	100:0	67
8	 **19**	 **20**	5.5	3:1	85[e]
9[f]	 **21**	 **22**	4	10:1	82

[a] Typical procedure: a 0.1 M solution of the substrate and 2,6-dichloropyridine in $MeNO_2$ was treated with DDQ and stirred at 0°C or at RT for the indicated time period. See the Supporting Information for details on specific reactions. [b] See the Supporting Information for details on substrate synthesis. [c] d.r. = diastereomer ratio normalized to 100. [d] Yields refer to isolated, purified material unless otherwise noted. [e] Yield corresponding to the mixture of stereoisomers.[f] Reaction was conducted at −60°C in $EtNO_2$.

as a pure compound in good yield. Cinnamyl ethers are significantly more reactive than allylic ethers, and allowed the reaction of **21** to be conducted at −60 °C in nitroethane to provide **22** in 82 % yield as a 10:1 mixture of diastereomers within 4 hours.

Our success in this phase of the project led us to explore applications of model **B**, in which tertiary ethers serve to direct the generation of new stereocenters. Prenyl ethers were used in this study because of their exceptional efficiency in these reactions. The results of these cyclization reactions are shown in Table 2. Propargylic ether **23** smoothly reacted to form **24** as a single stereoisomer (Table 2, entry 1). The stereochemical outcome of this reaction is consistent with the alkynyl group serving as the R_S substituent. In contrast to model **A**, alkenyl groups act as the R_S substituent in this model, as shown in the cyclizations of **25** and **27** to form tetrahydropyrans **26** and **28**, respectively (Table 2, entries 2 and 3). The potential for alkyl groups to occupy the R_S site was demonstrated through the cyclization of **29** to form spirocycle **30** (Table 2, entry 4). While diastereocontrol was not an issue for this reaction, the transformation was important for expanding the scope of the process to include saturated tertiary ether substrates. Diastereocontrol was demonstrated in the cyclization of **31** to **32** (Table 2, entry 5), in which the unbranched group was the R_S substituent and the branched group was the R_L substituent. These spirocyclization reactions were quite rapid, and allowed the transformations to be conducted at −30 °C to maximize stereocontrol. Unfortunately, attempts to prepare tetrahydropyrans with two quaternary stereocenters failed, as demonstrated by the DDQ oxidation of **33** (Table 2, entry 6). No reaction was observed at room temperature and nonspecific decomposition of the starting material was observed at elevated temperatures. Presumably the steric interactions in this system are simply too significant to overcome through ether oxidation.

Table 2: Tertiary ether substrates in stereoselective cyclization reactions.[a]

Entry	Substrate[b]	Product	*t* [h]	d.r.[c]	Yield [%][d]
1	 **23**	 **24**	2.5	100:0	79
2	 **25**	 **26**	2	15.7:1	95
3	 **27**	 **28**	0.5	100:0	76
4	 **29**	 **30**	0.3	–	88
5[e]	 **31**	 **32**	5	100:0	81
6[f]	 **33**	–	–	–	–

[a] Typical procedure: a solution of the substrate and 2,6-dichloropyridine in 1,2-dichloroethane was treated with DDQ and stirred for the indicated time period. [b] See the Supporting Information for details on substrate synthesis. [c] d.r. = diastereomer ratio normalized to 100. [d] Yields refer to isolated, purified material. [e] Reaction was conducted at −30 °C. [f] no reaction occurred.

A postulate for the steric differences of alkenes in models **A** and **B** is shown in Figure 2. The conjugation between the alkene and the oxocarbenium ion in model **A** forces the substituent on the alkene to project across the ether linkage in the disfavored configuration. The alkenyl groups in model **B** can orient their sterically undemanding flat faces toward the substituents across the ether linkage to minimize steric interactions. An electrostatic attraction between the π electrons and the electron deficient formyl hydrogen atom[18] could further stabilize this conformation. From a synthesis perspective the fact that alkenyl groups serve as the smaller substituent in this model illustrates that stereochemically complementary unsaturated products can be prepared by judicious substrate design.

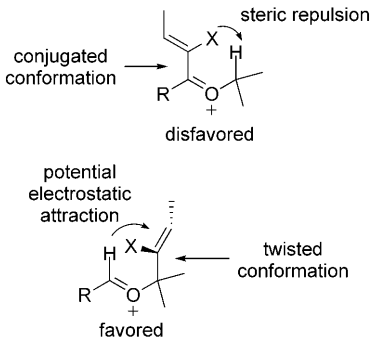
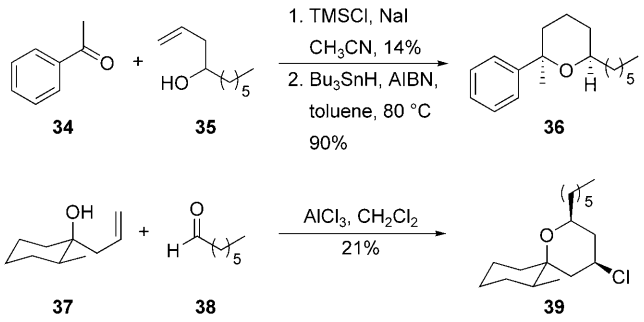


Figure 2. Steric interactions for alkenes in models **A** and **B**.

The applicability of models **A** and **B** to related reactions is shown in Scheme 3. The condensation of acetophenone (**34**) with homoallylic alcohol **35** in the presence of TMSCl and NaI[12c] provided, after radical-mediated removal of iodide, tetrahydropyran **36** as a single isomer. Aldehyde **38** condensed with tertiary alcohol **37** and $AlCl_3$[19] and yielded chlorotetrahydropyran **39**, also as a single stereoisomer. The yields of these reactions were rather low because of the competitive ionization and of the oxonia-Cope-type reactions,[20] but the procedures were not optimized because our



Scheme 3. Applications to acid-mediated Prins reactions. AIBN = azobisisobutyronitrile, TMS = trimethylsilyl.

main interest was focused on determining the stereochemical outcomes of these transformations.

In conclusion, we have shown that two models can be applied to design stereocontrolled reactions that yield tetrahydropyrans with tertiary ethers. In one model the geometry of unsaturated 1,1-disubstituted oxocarbenium ions can be predicted based on the steric differences between the two substituents. The other model uses preexisting quaternary centers to control the geometry of oxocarbenium ions. While oxidative carbocation formation was employed to initiate the majority of the reactions in this study, these models are applicable to oxocarbenium ions derived from other processes and are consistent with the results of previously reported reactions that proceed through highly substituted ions.[3a,b,6] The generality of the models described here will serve as a guide for future efforts in the synthesis of molecules that contain fully substituted stereocenters.

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Keywords: carbocations · C–H activation · conformational analysis · oxidation · stereoselectivity

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