Graphical abstract and ABSTRACT:

The relative reactivity of enol ether and allylsilane trapping groups toward a ketene dithioacetal derived radical cation has been examined with the use competition and cyclic voltammetry studies. The competition studies pit the olefinic trapping groups against an alcohol trapping group under conditions of both kinetic and thermodynamic control. With the enol ether trapping group, the chemoselectivity of the competition study favored C-C bond formation under all conditions. With the allylsilane trapping group, the chemoselectivity of the competition study favored C-O bond formation under all conditions. Cyclic voltammetry data was used to show that allylsilane trapping of the radical cation is much slower than enol ether trapping of the radical cation. However, the inefficiency of the allylsilane trapping reaction could not be attributed solely to a slow cyclization. Rather, it appears that a slow second oxidation step plays a role in determining the yield of the reaction.

KEYWORDS:

Radical Cations; Oxidative Cyclizations; Electrochemistry

Competition Studies and the Relative Reactivity of Enol Ether and Allylsilane Coupling Partners Toward Ketene Dithioacetal Derived Radical Cations

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Intramolecular anodic olefin coupling reactions are very useful for the construction of new C-C, C-O, and C-N bonds and the generation of a variety of ring skeletons.^{1,2} The first step in the reaction removes an electron from a molecule that contains an electron-rich double bond.³ This oxidation generates a radical cation intermediate and triggers a cyclization that adds a nucleophile to the double bond in a manner that is chemoselectively opposite to the cyclization that would typically result from an electrophilic initiation of the ring formation (Scheme 1).^{4,5} Through the years, a

Scheme 1. An electrochemical umpolung

large number of empirical observations have been made about the oxidative cyclizations leading to the general mechanistic model shown in Figure 1.⁶ In this model, the initial radical cation

Figure 1. Working mechanistic model

derived from the oxidation reaction undergoes a rapid, potentially reversible cyclization to form a cyclic radical cation. The cyclized radical cation is then converted to product through a series of steps that includes the loss of a second electron, solvent trapping and the loss of two protons. The timing of these final steps is not known.

While aware of the potential complexity of this mechanistic model, many of the empirical observations about the cyclizations could be explained nicely by consideration of the initial cyclization step (k_1). For example, Scheme 2 illustrates a pair of cyclization reactions that both originate from the oxidation of a ketene dithioacetal.⁷ Of the two reactions, the cyclization that took advantage of the enol ether terminating group (**1**) proceeded much better than the reaction that utilized the allylsilane terminating group (**2**). The reaction with the enol ether group could be altered so that the cyclization formed a quaternary carbon and a six-membered ring at the same time. The reaction with the allylsilane could not tolerate any change, even the simple addition of a methyl group to the allylsilane. These observations were consistent with earlier conclusions that enol ether trapping groups was more reactive toward enol ether derived radical cation intermediates than were allylsilane groups.⁸

Scheme 2. Enol ether vs. allylsilane trapping

The idea that the allylsilane group trapped the radical cation more slowly than did the enol ether group led to its use in efforts to identify radical cation intermediates that were more reactive toward carbon-carbon bond formation.⁹ Since an enol ether trapping group trapped all of the radical cations well and the allylsilane did not, new radical cations were tested for their ability to overcome the “barrier” associated with the allylsilane. Interestingly, the study concluded that all of the radical cation intermediates examined underwent relatively slow reactions with the allylsilane trapping group. What controlled the yield of cyclized product from the reactions was the relative stability of the initial radical cation intermediate toward the oxygen trapping, elimination, and polymerization reactions that lead to unproductive pathways. The conclusion was that if a radical cation had a long enough life-time, then “even the allylsilane could trap it.”

However, while the use of k_1 in this manner provides a consistent way to justify the yield of a radical cation cyclization, is the mechanistic picture it suggests correct? Recently, we have encountered

several anodic cyclization reactions that are reversible. The yield of these reactions depends on the rate of the second step (k_2).¹⁰ So does the chemistry shown in Scheme 2 really tell us anything about the relative rates of the radical cation trapping reaction (k_1), or is the cyclization reaction with the allylsilane also fast but reversible with a slow second oxidation step? If this is the case, then how would such a finding alter our conclusions about the relative reactivity of various radical cation intermediates, conclusions that were based upon the idea that the allylsilane cyclization was slow? We report here a mechanistic study that supports the initial conclusion that the difference observed between enol ether and allylsilane trapping of a ketene dithioacetal derived radical cation is indeed based upon the rate of the initial cyclization.

Since radical cation intermediates can be very reactive and have extremely short lifetimes, it can be difficult to make direct measurements of their reaction rates. For this reason, we have been using competition studies to provide insight into the relative rates of different radical cation reaction pathways.¹¹ For example, the competition study illustrated in Scheme 3 was used to investigate the relative reactivity of sulfonamide anions and alcohols with electron-rich olefins under oxidative conditions.^{6f}

Scheme 3. An early competition study

From this study, we learned that the trapping of an olefinic radical cation was faster than the cyclization between the sulfonamide group and the olefin but reversible. In fact, cyclization with the alcohol led to kinetic products while cyclization with the sulfonamide group led to thermodynamic products. The kinetic products were generated at low temperature and high oxidation rates (acceleration of k_2 in Figure 1). Thermodynamic products were generated at high temperature and lower oxidation rates.

The ability to run the alcohol trapping reaction under conditions that are already known to give either kinetic or thermodynamic product makes it an ideal baseline cyclization for studying other reactive coupling partners. A second coupling partner for the reaction that traps the radical cation intermediate instead of the alcohol at low temperature and high current must react with the olefinic radical cation faster than the alcohol because it is known that the alcohol cyclization is not reversible under those conditions. If the alcohol does trap first, then repeating the reaction at higher temperature and low current will allow the alcohol cyclization reverse, a situation that allow one to probe the effectiveness of the second coupling partner when it is given more time.

With this in mind, two new competition experiments were designed; one with an enol ether to compete with the alcohol nucleophile (**5**) and the second with an allylsilane (**6**, Schemes 4 and 5).¹²

Enol ether substrate **5** was studied first (Scheme 4). The oxidation was first carried out at low

Scheme 4. Enol ether vs. alcohol trapping

Entry	Temp (°C)	Current (mA)	Yield (7)	Yield (8)
1	0	60	61%	12%
2	45	6	90%	--

temperature and a high rate of current at a reticulated vitreous carbon (RVC) anode in order to insure the formation of a kinetic product if the alcohol trapped the radical cation. Under these conditions, the only products observed were derived from trapping of the radical cation by the enol ether group. Product **8** is derived from hydrolysis of the methoxy dithio ortho ester product **7**, a side reaction that occurred more readily with higher current. Clearly, enol ether trapping of the radical cation gives rise to the kinetic product from the reaction.

When the reaction was repeated using conditions that have generated thermodynamic product in past cyclizations (higher temperature and low current), the reaction again afforded only product derived from trapping of the radical cation by the enol ether. It is not known whether the formation of **7** using these reaction conditions is the result of carbon-carbon bond formation being thermodynamically favorable or if the formation of the carbon-carbon bond is not reversible.

In contrast to cyclizations originating from substrate **5**, the anodic oxidation of **6** under both sets of conditions led only to initial trapping of the radical cation by the alcohol group (Scheme 5). Once again, cleavage of the dithio ortho ester product occurred more readily at high current.¹³ In both cases, the allylsilane group remained untouched in the product.

Scheme 5. Allylsilane vs. alcohol trapping

Entry	Temp (°C)	Current (mA)	Yield (9)	Yield (10)
1	0	60	68%	9%
2	45	6	72%	--

The complete absence of the carbon-carbon formation from the oxidation of **6** was not due to an insurmountable barrier to the cyclization with the allylsilane. When the alcohol in **6** was protected as a TBDMS ether and the substrate oxidized (Scheme 6) with a current of 6 mA, product **12** was obtained

Scheme 6. The “parent” allylsilane trapping reaction

in an 8% yield along with 17% of the recovered starting material. When kinetic conditions were used for the oxidation (60 mA of current), the yield of product **12** was raised to 31% along with 19% of the recovered starting material. The lower yield and poor mass balance for the reaction was consistent with previous reactions that examined the trapping of a non-polar radical cation with an allylsilane.⁹ Yet while the reaction led to a poor yield of product and a low mass balance, product **12** was obtained and could be easily isolated. Hence, the observation that no C-C bond formation arose from the oxidation of **6** was a direct result of the alcohol being present. The allylsilane was indeed less reactive toward the

ketene dithioacetal radical cation than either the enol ether moiety, the alcohol, or for that matter the sulfonamide group used in earlier studies (Scheme 3).

While the allylsilane was less reactive toward the radical cation than the other groups, the data shown in Scheme 5 did leave open two possibilities for the origin of the lower reactivity (Scheme 7). In the first, allylsilane trapping of the radical cation would be so much slower than alcohol trapping

Scheme 7. The mechanistic possibilities

of the radical cation in substrate **6** that C-C bond formation did not even compete with the alcohol cyclization under thermodynamic conditions. In this case, the rate of carbon-carbon bond formation (k_1) would be slower than both the initial cyclization with the alcohol nucleophile (k_3) and conversion of the alcohol cyclization intermediate into the final product (k_4). In the second, the rate of C-C bond formation with the allylsilane would be faster than the rate of C-O bond formation, but that the reverse reaction (k_{-1}) would also be fast and the conversion of the cyclized intermediate into the final product (k_2) much slower than both k_3 and k_4 . Understanding which of the two possibilities is most likely is important if one wants to improve the yield of the reaction shown in Scheme 6. Was the problem with the reaction a slow cyclization and decomposition of the uncyclized radical cation or a problem with the reaction downstream of the cyclization. If the first scenario operates, then raising the yield of C-C bond formation would require an increase in the rate of the cyclization reaction relative to other competing processes. If the second scenario operates, then raising the yield of C-C bond formation would require increasing the rate of the second oxidation reaction (k_2). There would be no need to manipulate the rate of the initial cyclization.

Cyclic voltammetry data can be used to shed light on which of the two mechanistic possibilities gives rise to the poor reaction with the allylsilane trapping group. Because the observed oxidation potential of a substrate is the result of an equilibrium between the substrate and the radical cation intermediate formed from the transfer of an electron to the anode surface, the observed potential is sensitive to reactions that rapidly consume the radical cation.¹⁴ Hence, shifts in the observed oxidation

potential for a particular functional group can be used to determine the relative rates of various radical cation trapping reactions.^{9,15} For the current study, CV data for three substrates were examined (Table 1). In the first (**13**), the oxidation of the ketene dithioacetal was examined in the absence of an effective trapping group. This experiment provided a baseline potential of + 1.046 (vs. Ag/AgCl) for oxidation of

Table 1. CV data indicating the rate of initial cyclization

Substrate	R ₁	R ₂	E _{p/2} vs. Ag/AgCl
13	H	TBS	+ 1.05 V
14	OMe	TBS	+ 0.94 V
11	CH ₂ TMS	TBS	+ 1.02 V

Conditions: CV data was obtained in a 1:1 THF:MeOH solution with 0.1 M LiClO₄ electrolyte and a sweep rate of 200 mV/s (range 0-1500 mV).

the ketene dithioacetal. When an enol ether was added to the substrate in order to trap the radical cation, the potential measured for the ketene dithioacetal shifted by 110 mV indicating a fast cyclization that occurred at or near the electrodes surface. When an allylsilane was added to the substrate as a trapping-group, the potential of the ketene dithioacetal dropped by only 30 mV. The much smaller shift in potential for the allylsilane-based substrate indicated that allylsilane trapping of the ketene dithioacetal derived radical cation was significantly slower than enol ether trapping of the radical cation. Still, the presence of the allylsilane did shift the potential of the ketene dithioacetal, a result that is consistent with trapping of the radical cation intermediate still being fast and occurring at or near the surface of the anode. This observation suggests that the lack of reactivity associated with the allylsilane group may not be due to an overly slow cyclization, but rather a problem “downstream” of the initial cyclization. Typically, such observations are consistent with the second oxidation reaction needed for product formation not being fast enough to overcome either an unstable cyclic radical cation or a reversible cyclization and an unstable initial radical cation. The data illustrated in Scheme 6 does support the application of this general conclusion to the allylsilane trapping reaction. The higher yield of product and increase in mass balance associated with the use of higher current is consistent with an increase in the rate of the second oxidation step.^{2a,6f} With this in mind, efforts to further optimize the yield of the

allylsilane reaction will focus on increasing the rate of k_2 and formation of the desired product from the cyclic radical cation.

In conclusion, the competition studies shown in Scheme 4 and Scheme 5 when combined with the CV data presented in Table 2 indicate that earlier conclusions about the relative reactivity of enol ether and allylsilane groups toward ketene dithioacetal derived radical cations were correct. The enol ether is a better kinetic trapping group for the radical cation than is the allylsilane. Furthermore, we can now rank the order of reactivity for four different groups with respect to their ability to trap a ketene dithioacetal derived radical cation. Reactions between the radical cation and an enol ether coupling partner are faster than reactions between the radical cation and an alcohol group. Reactions involving the alcohol are faster than (but competitive with) reactions with a sulfonamide anion coupling partner. Reactions with an allylsilane coupling partner are the slowest of the group. Yet in spite of the slower rate of cyclization with the allylsilane, the cyclization is fast enough to cause shifts in the oxidation potential of the ketene dithioacetal substrate, and efforts to improve the cyclization will capitalize on this observation

The chemistry described shows how a combination of competition studies and cyclic voltammetry is enabling us to build a framework for understanding the success or failure of oxidative radical cation cyclizations. This framework is being extended to include other trapping groups and the use of alternative radical cation intermediates.

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Footnote:

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References:

- (1) For a review see Moeller, K. D. *Synlett*. **2009**, 8, 1208.
- (2) For recent examples see: (a) Smith, J. A.; Moeller, K. D. *Org. Lett.* **2013**, 15, 5818. (b) Redden, A.; Perkins, R. J.; Moeller, K. D. *Angew. Chem. Int. Ed.* **2013**, 52, 12865.
- (3) For recent reviews of electrochemical reactions see: (a) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, 35, 605. (b) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2009**, 108, 2265. (c) Frontana-Urbe, B. S.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. *Green Chem.* **2010**, 12, 2099.
- (4) For applications of radical cations in synthesis see: (a) Okada, T.; Akaba, R.; Chiba, K. *Org. Lett.* **2009**, 11, 1033. (b) Floreancig, P. E. *Synlett* **2007**, 2, 0191-0203. (c) Jung, H. H.; Seiders II, J. R.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2007**, 46, 8464. (d) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2008**, 47, 7317. (e) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem.*

- Int. Ed.* **2008**, *47*, 4184. (f) Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5894. (g) Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152. (h) Devery III, J. J.; Conrad, J. C.; MacMillan, D. W. C.; Flowers II, R. A. *Angew. Chem. Int. Ed. Eng.* **2010**, *49*, 6106 and references therein. (i) Beeson, T. D.; Mastracchio, A.; Hong, J. -B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (j) Jang, H. -Y.; Hong, J. -B.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (k) Baran, P. S.; Ambhaikar, N. B.; Guerrero, C. A.; Hafensteiner, B. D.; Lin, D. W.; Richter, J. M. *ARKIVOC* **2006**, 310. (l) Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667. (m) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572. (n) Okada, Y.; Nishimoto, A.; Akaba, R.; Chiba, K. *J. Org. Chem.* **2011**, *76*, 3470. (o) Nguyen, T. M.; Monohar, N.; Nicewicz, D. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 6198. (p) Nicewicz, D. A.; Nguyen T. M. *ACS Catalysis* **2014**, *4*, 355.
- (5) For radical cation initiated cyclizations derived from chemical and photoelectron-transfer based oxidations see: (a) Crich, D.; Ranganathan, K.; Neelamkavil, S.; Huang, X. *J. Am. Chem. Soc.* **2003**, *125*, 7942. (b) Crich, D.; Shirai, V.; Brebion, F.; Rumthao, S. *Tetrahedron* **2006**, *62*, 6501. (c) Crich, D.; Ranganathan, K. *J. Am. Chem. Soc.* **2005**, *127*, 9924. (d) Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* **2003**, *5*, 3767. (e) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640. (f) Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015. (g) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (h) Nguyen, T. M.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 10334.
- (6) (a) Hudson, C. M.; Moeller, K. D. *J. Am. Chem. Soc.* **1994**, *116*, 3347. (b) Frey, D. A.; Reddy, S. H. K.; Wu, N.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805. (c) Sun, Y.; Moeller, K. D. *Tetrahedron Lett.* **2002**, *43*, 7159. (d) Tang, F.; Moeller, K. D. *Tetrahedron* **2009**, *65*, 10863. (e) Redden, A.; Moeller, K. D. *Org. Lett.* **2011**, *13*, 1678. (f) Campbell, J. M.; Xu, H. -C.; Moeller, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 18388.
- (7) Sun, Y.; Liu, B.; Kao, J.; d'Avignon, D. A.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 1729.
- (8) (a) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381. (b) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183.
- (9) Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536.
- (10) (a) Smith, J. A.; Moeller, K. D. *Org. Lett.* **2013**, *15*, 5818. (b) Perkins, R. J.; Xu, H. -C.; Campbell, J. M.; Moeller, K. D. *Beilstein J. Org. Chem.* **2013**, *9*, 1630.
- (11) For previous chemical clock-type competition experiments for measuring the rate of an enol ether radical cation derived cyclizations see: (a) Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **2001**, *123*, 4364. (b) Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402.
- (12) Please see the supporting information for synthetic details.
- (13) For oxidations of dithioketals see: Porter, G. N.; Utley, J. H. P. *J. Chem. Soc., Perkin. Trans. 1* **1984**, 973.
- (14) Hai-Chao Xu and Kevin D. Moeller *Angew. Chem. Int. Ed. Eng.* **2010**, *49*, 8004.
- (15) For examples see: a) K. D. Moeller, L. V. Tinao, *J. Am. Chem. Soc.* **1992**, *114*, 1033-1041; b) S. H. K. Reddy, K. Chiba, Y. Sun, K. D. Moeller, *Tetrahedron* **2001**, *57*, 5183-5197