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Anodic Coupling Reactions: The Use of *N*,*O*-Ketene Acetal Coupling Partners

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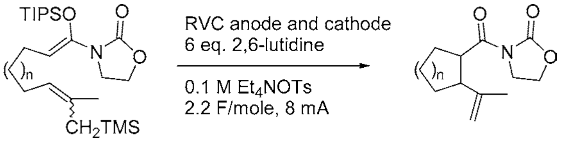
ABSTRACT

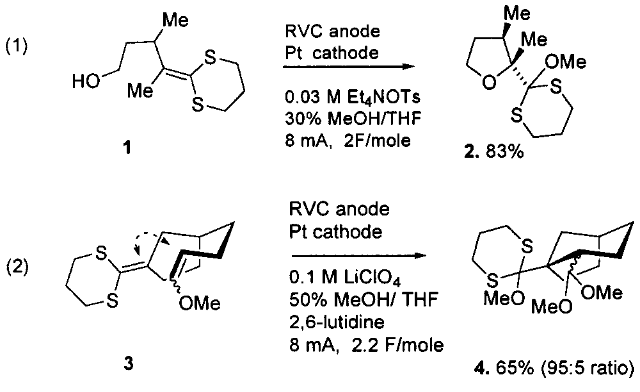


Intramolecular anodic olefin coupling reactions utilizing *N*,*O*-ketene acetals have been studied. Coupling reactions with both enol ether and allylsilane terminating groups were examined. The reactions involving the coupling of the *N*,*O*-ketene acetals with allylsilane groups were found to be much more efficient than corresponding reactions utilizing dithioketene acetal groups and allylsilanes. The reactions were also more efficient than the intramolecular coupling reactions between enol ethers and allylsilanes studied earlier.

The anodic oxidation of electron-rich olefins can lead to a variety of interesting new umpolung reactions.[1−3] Recently, this family of synthetic transformations was extended to include cyclization reactions triggered by the oxidation of dithioketene acetals (Scheme 1).[4,5] These reactions were important because they led to the formal equivalent of bond formation between a nucleophile and the carbon α to a carboxylic acid derivative.

However, while initial experiments to establish the viability of dithioketene acetals as substrates for the oxidation were very successful, efforts to expand the scope of the reactions to include substrates with allylsilane trapping groups suggested that the reactions are not as general as reactions originating from the oxidation of an enol ether.[1−3] For example, consider the reactions illustrated in Scheme 2. Cyclizations originating from enol ether substrates **5a** and **5b** proceed well,[6] while cyclizations originating from dithioketene acetal substrates **5c** and **5d** are less successful.[4a] This is especially true for the cyclization using the trisubstituted allylsilane (**5d**), where only a 20−30% yield of crude product can be obtained. Pure product could not be isolated from this reaction mixture. While disappointing from a

Scheme 1



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[1] (a) For a review, see: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. For recent examples, see: (b) Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. *J. Am. Chem. Soc.* **2001**, *123*, 11314. (c) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726. (d) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106 and references therein.

[2] For related chemical oxidations to form enol ether radical cations, see: (a) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786. (b) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399. (c) Fujii, T.; Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1992**, *33*, 5823. (d) Heidbreder, A.; Mattay, J. *Tetrahedron Lett.* **1992**, *33*, 1973. (e) Ryter, K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658. (f) Schmittel, M.; Burghart, A.; Werner, H.; Laubender, M.; Söllner, R. *J. Org. Chem.* **1999**, *64*, 3077.

[3] For an alternative approach to enol ether radical cations, see: (a) Crich, D.; Suk, D. H.; Sun, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2861. (b) Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402 and references therein.

[4] (a) Sun, Y.; Liu, B.; Kao, J.; d'Avignon, D. A.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 1729. (b) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101. (c) Sun, Y.; Moeller, K. D. *Tetrahedron Lett.* **2002**, *43*, 7159.

[5] Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183.

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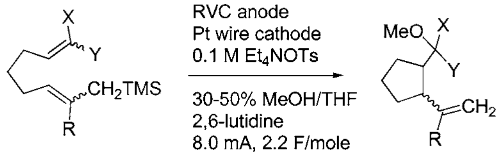
Scheme 2

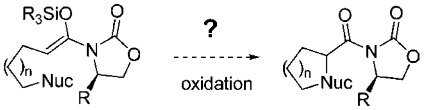


5a. X=H, Y=OMe, R=H	**6a.** X=H, Y=OMe, R=H, 86%
5b. X=H, Y=OMe, R=CH$_3$	**6b.** X=H, Y=OMe, R=CH$_3$, 66%
5c. X=Y= S(CH$_2$)$_3$S, R=H	**6c.** X=Y= S(CH$_2$)$_3$S, R=H, 55%
5d. X=Y= S(CH$_2$)$_3$S, R=CH$_3$	**6d.** X=Y= S(CH$_2$)$_3$S, R=CH$_3$, (20-30%)

synthetic standpoint, these observations did indicate that the efficiency of an intramolecular anodic olefin coupling reaction might be tunable by adjusting the nature of the olefin being oxidized. But would the oxidation of all ketene acetal substrates lead to cyclization reactions that are less efficient than those originating from an enol ether, or is this observation limited to the use of dithioketene acetal substrates? We report here that oxidation of an *N*,*O*-ketene acetal leads to more efficient intramolecular carbon−carbon bond formation than either the oxidation of a dithioketene acetal or the oxidation of an enol ether.

Because of their known synthetic utility,[7] we chose to extend our studies involving ketene acetal substrates to include oxazolidinone-substituted enolate equivalents (Scheme 3). Two aspects of these reactions were particularly enticing.

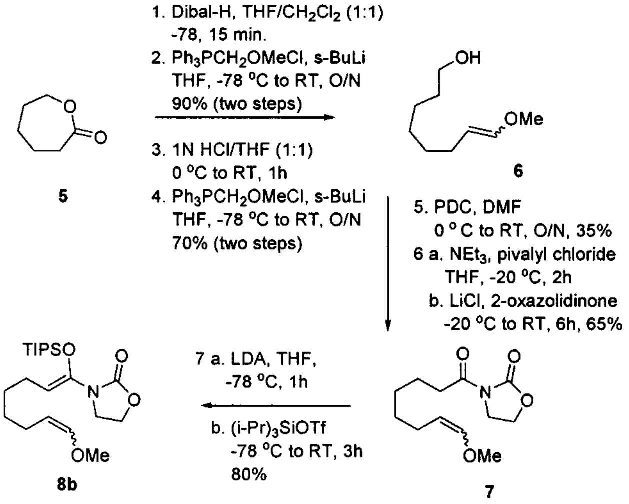
Scheme 3



First, the silyl enol ether derivatives are known to be stable. This meant that we could isolate the ketene acetal substrates and then carefully study their oxidation. Second, we were intrigued by the possibility of reversing the polarity of an enolate equivalent known for its effectiveness as a nucleophile in asymmetric aldol condensations and asymmetric alkylation reactions.

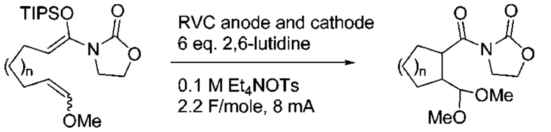
With this in mind, we turned our attention toward the synthesis and oxidation of two substrates (**8a**, **8b**) having an enol ether for trapping the intermediate radical cations. The synthesis of **8b** is illustrated in Scheme 4. The five-membered ring precursor **8a** was made in a nearly identical fashion by omitting steps three and four (chain extension).

Scheme 4



Once synthesized, the substrates were oxidized in an undivided cell using constant current electrolysis conditions (8 mA/2.2 F/mole), a reticulated vitreous carbon (RVC anode, RVC cathode), 2,6-lutidine as a proton scavenger, and a 0.1 M tetraethylammonium tosylate electrolyte solution. The solvent for the reaction was either methanol or a mixture of methanol and THF as indicated in Scheme 5. The overall process was neutral since acid is generated at the anode and base (from the reduction of methanol) is generated at the cathode. Hence, the added proton scavenger played no net role in the reaction. However, due to the acid sensitivity of the ketene acetal, the presence of 2,6-lutidine was important for maintaining the neutrality of the reaction in the region immediately surrounding the anode. Using these conditions led to reactions with good yields of cyclized products. In addition, a small amount (ca. 5%) of the imide product derived from methanolysis of the ketene acetal prior to oxidation was typically obtained. The rest of the mass balance for the reactions was apparently lost to trapping of the radical cation intermediate by methanol solvent (the major decomposition pathway for the radical cation in the absence of an intramolecular trapping group). Although no uncyclized products other than the imide were isolated, several minor methoxylated products were observed in the NMR of the crude reaction mixtures. While the cyclization to form the five-membered ring product **9a** did benefit from the presence of THF (added to reduce the effective concentration of MeOH at the electrode surface), both cyclizations formed good yields of the product even when methanol was used as

Scheme 5



Substrate	Solvent	Product (yield)
8a. n = 1	MeOH	**9a** (74%/ 2:1 isomer ratio)
8a. n = 1	4:1 MeOH/THF	**9a** (87%/ 3:2 isomer ratio)
8b. n = 2	MeOH	**9b** (63%/ 2:1 isomer ratio)
8b. n = 2	4:1 MeOH/THF	**9b** (65%/ 2:1 isomer ratio)

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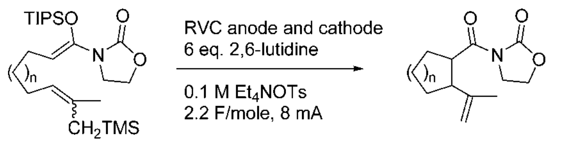
(6) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372.

(7) Ager, D. J. Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3.

Scheme 6



Substrate	Solvent	Product (yield)
10a. n = 1	MeOH	**11a** (51%/ 3:2 isomer ratio)
10a. n = 1	4:1 MeOH/THF	**11a** (70%/ 3:2 isomer ratio)
10a. n = 1	1:4 MeOH/CH$_2$Cl$_2$	**11a** (74%/ 3:2 isomer ratio)
10b. n = 2	MeOH	**11b** (57%/ trans isomer)
10b. n = 2	4:1 MeOH/THF	**11b** (71%/ trans isomer)
10b. n = 2	1:4 MeOH/CH$_2$Cl$_2$	**11b** (54% - 10.5 F/mole)
10c. n = 2, TBS enol ether	4:1 MeOH/THF	**11b** (60%/ trans isomer)

the solvent. In this way, the cyclizations behaved like the best of the previously studied anodic cyclizations such as the coupling of two enol ethers[8] or the coupling of an enol ether and a furan.[9] Like earlier enol ether−enol ether coupling reactions, the cyclizations do not lead to the formation of products in a stereoselective fashion.[8] In this case, ratio of stereoisomers about the newly formed C−C bond ranged from 3:2 to 1:1. The major isomer for the five-membered ring-forming cyclization was not assigned since the isomers could not be separated and the NMR signals for the methine protons overlap.

The oxidation potential ($E_{p/2}$ by cyclic voltammetry) for both **8a** and **8b** was measured to be +1.07 V vs Ag/AgCl.[10] This potential is consistent with initial oxidation of the ketene acetal moiety. The oxidation potential ($E_{p/2}$) for the enol ether trapping group is +1.40 V vs Ag/AgCl.[8] In the case of **8a** and **8b**, the $E_{p/2}$ value of +1.07 V vs Ag/AgCl is slightly lower than that measured for the ketene acetal in the absence of a trapping group ($E_{p/2} = +1.11$ V vs Ag/AgCl).[11] This slight shift in potential is consistent with an electrochemical process in which oxidation to form a radical cation intermediate is followed by a rapid chemical step.[12] The equivalence of the potentials measured for **8a** and **8b** suggests that five- and six-membered ring formation occurs at roughly the same rate. Neither cyclization was as fast as those of bis enol ether substrates, where shifts of 200 mV for a five-membered ring-forming reaction and 100 mV for a six-membered ring-forming reaction were observed.[8]

Having demonstrated that the N,O-based ketene acetals were good substrates for the reactions, we next focused our attention on probing the utility of these groups in cyclization reactions utilizing the less reactive allylsilane moieties (Scheme 6). Again both five- and six-membered ring precursors **10a−c** were synthesized in a fashion directly analogous to the route outlined in Scheme 4. As with substrates **8a** and **8b**, the anodic oxidation reactions of **10a−c** were run in an undivided cell equipped with RVC electrodes using a constant current of 8 mA until 2.2 F/mole of charge had been passed. A 0.1 M tetraethylammonium tosylate electrolyte solution was again used along with 2,6-lutidine as the proton scavenger.

Both five- and six-membered ring-forming reactions proceeded well, indicating that olefin coupling reactions originating from the oxidation of *N*,*O*-ketene acetals are much more efficient than those originating from the oxidation of dithioketene acetals. The overall appearance of these reactions (formation of minor amounts of imide and unidentified methoxylated products) was the same as that of the earlier oxidations of **8a** and **8b**. The use of a triisopropylsilyl enol ether proved to be most effective for the cyclizations. When a *tert*-butyldimethyl silyl enol ether was employed (**10c**), more of the substrate was lost due to cleavage of the silyl group prior to the oxidation. However, the oxidation of **10c** in 4:1 MeOH/THF solvent still led to a 60% yield of the trans six-membered ring product.

Initially, the cyclizations were run using either THF or dichloromethane as a cosolvent. The five-membered ring-forming cyclizations in both solvent systems occurred in nearly identical yield. The 3:2 ratio of cis and trans products generated was analogous to the mixture observed earlier for the methyl enol ether−allylsilane coupling reactions.[6] The six-membered ring-forming cyclization reactions benefited from the use of THF as the cosolvent, where a 71% isolated yield of product was observed. When dichloromethane was used as the cosolvent, the reaction proceeded in a 54% isolated yield and required the passage of 10.5 F/mole of charge in order to reach completion (TLC). In both solvent systems, the oxidation of **10b** led to the stereoselective formation of trans product. Only a small amount (<5%) of a second cyclic product was observed (^{1}H NMR). At this time, we assume that this minor product is the cis isomer. The stereochemistry of the major product was assigned by examining the coupling pattern observed for the two methine protons on the ring. Each was a triplet of doublets, indicating that the methine protons were both axial and hence trans to each other.

Surprisingly, the oxidative cyclization of both substrates **10a** and **10b** took place in over 50% yield even when no cosolvent was used. The success of these reactions indicates that the cyclizations utilizing the *N*,*O*-ketene acetal initiating group are significantly more efficient than not only the troublesome dithioketene acetal−allylsilane coupling reactions but also the very successful methyl enol ether−allylsilane coupling reactions studied earlier. Enol ether−allylsilane coupling reactions do require the use of a cosolvent.[6] The yields of the *N*,*O*-ketene acetal−allylsilane reactions in pure methanol solvent are lower than the yields obtained from corresponding cyclizations utilizing an enol ether trapping group (Scheme 5), confirming the greater trapping efficiency of the enol ether moiety for the *N*,*O*-ketene acetal-derived radical cation.

The efficiencies of the allylsilane-terminated reactions shown in Scheme 6 suggest either that the *N*,*O*-ketene acetal-

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[8] Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033.

[9] New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578.

[10] Potentials were measured using Pt working and auxiliary electrodes, a Ag/AgCl reference electrode, a 0.1 M LiClO$_4$ in acetonitrile electrolyte solution, a sweep rate of 25 mV/sec, and a substrate concentration of 0.025 M. The reference electrode was calibrated using ferrocene as a standard.

[11] In this case, the ketene acetal was synthesized from 10-undecenoic acid.

[12] For previous examples and a brief discussion, see ref 8.

based radical cation intermediate is more reactive toward the allylsilane than the radical cation intermediates derived from methyl enol ethers and dithioketene acetals or that the *N*,*O*-ketene acetal-based radical cation is more stable to solvent trapping than its counterparts. Initial cyclic voltammetry studies are most consistent with this second explanation. As discussed earlier, the shifts in potentials measured for substrates **8a** and **8b** were significantly smaller than the shift in potentials measured for the bis enol ether substrates studied earlier.[8] This suggests that the *N*,*O*-ketene acetal radical cations cyclize slower than enol ether-based radical cations. The half-wave potentials measured for **10a** and **10b** lead to a similar conclusion. For **10a**, an $E_{p/2} = +1.07$ V vs Ag/AgCl was obtained. Once again, this value is consistent with initial oxidation of the ketene acetal. The $E_{p/2}$ for the allylsilane group is $+1.35$ V vs Ag/AgCl.[13] The potential measured for **10a** is 40 mV lower than the $E_{p/2} = +1.11$ V vs Ag/AgCl measured for the *N*,*O*-ketene acetal in the absence of a trapping group.[11] This shift in potential is only half the magnitude of the shift in potential (80 mV) observed for a five-membered ring precursor having a methyl enol ether and a trisubstituted olefin coupling partner relative to an enol ether in the absence of a trapping group.[8] Again, the reaction of the *N*,*O*-ketene acetal radical cation appears to be slower than the reaction of the enol ether radical cation. For **10b**, an $E_{p/2} = +1.11$ V vs Ag/ AgCl was measured, a value that is the same as that measured for the *N*,*O*-ketene acetal without a trapping group.[11]

While a more thorough mechanistic study is certainly warranted, two conclusions can be reached at this time. First, *N*,*O*-ketene acetals are good substrates for intramolecular olefin coupling reactions leading to both five- and six-membered rings and utilizing both enol ether and allylsilane terminating groups. Second, changing the nature of the olefin used to initiate an intramolecular anodic olefin coupling reaction can have a dramatic effect on the relative efficiency of various trapping groups for the resulting radical cation. Cyclizations involving dithioketene acetal radical cations undergo efficient reactions with enol ether terminating groups, while related reactions utilizing allylsilane terminating groups lead to poor yields of product. In contrast, *N*,*O*-ketene acetal radical cations lead to efficient cyclizations with both olefin terminating groups. The efficiency of cyclization reactions originating from methyl enol ether radical cations is between that observed for the two ketene acetal-derived reactions. The greater efficiency of the *N*,*O*-ketene acetal–allylsilane coupling reaction relative to the enol ether–allylsilane reaction does not appear to be due to the greater reactivity of the *N*,*O*-ketene acetal radical cation toward the allylsilane, but rather the greater stability of the *N*,*O*-ketene acetal radical cation toward trapping by methanol. Clearly, the design of future intramolecular anodic olefin coupling reactions will need to take into account not only the suitability of new initiating groups as substrates for the oxidation reaction but also how their use alters the relative efficiency of subsequent trapping reactions with various nucleophiles.

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Supporting Information Available: Sample experimental procedure is included for the oxidation reaction along with characterization data for all new electrolysis substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Potential for the allylsilane trapping group was measured using an allylsilane derived from octanal.