ORGANIC
LETTERS

2011
Vol. 13, No. 7
1678–1681

Anodic Coupling Reactions: Exploring the Generality of Curtin−Hammett Controlled Reactions

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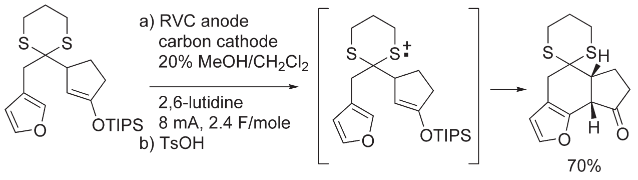
Received January 20, 2011

ABSTRACT



Intramolecular anodic olefin coupling reactions can be compatible with the presence of dithioketal protecting groups even though the dithioketal oxidizes at a lower potential than either of the groups participating in the cyclization. In such cases, product formation is controlled by the Curtin−Hammett Principle. In this study, the generality of such reactions is examined along with the use of alternative reaction conditions to suppress unwanted side reactions.

Anodic olefin coupling reactions provide a unique opportunity for both synthesizing new ring skeletons and probing the chemistry of reactive radical cation intermediates.[1,2] In these reactions, the radical cation formed at the anode can undergo a reversible, intramolecular electron-transfer reaction.[3,4] In such cases, the product formed from the oxidation is governed by the Curtin−Hammett Principle. An example of this behavior is illustrated in Scheme 1.[3] The dithioketal in substrate **1** has an oxidation potential of $E_{p/2} = +1.1$ V vs Ag/AgCl while the enol ether has an oxidation potential of $E_{p/2} = +1.4$ V vs Ag/AgCl. Hence, oxidation of **1** generates radical cation **2**. This radical cation undergoes an electron-transfer reaction to form an enol ether radical cation (**3**) that in turn triggers a cyclization and the formation of **4** in a 70% isolated yield. If the alcohol in the substrate is not present, then the only product observed is derived from radical cation **2**.

Curtin−Hammett controlled reactions of this type are potentially very useful. Consider the retrosynthesis of artemisolide outlined in Scheme 2.[5,6] A Michael reaction−anodic oxidation sequence analogous to the one developed by the Wright and Trauner groups is proposed.[7] In this case, the presence of a dithioketal in **5** would both aid the Michael reaction by stabilizing the anion and serve as a carbonyl equivalent for setting up C$_7$ in the final product. The cyclization would take advantage of an enol ether−furan coupling reaction.[8] The success of this

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(1) For a recent review, see: Moeller, K. D. *Synlett*. **2009**, *8*, 1208.

(2) For reviews covering the use of electrochemical methods in synthesis, 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.

(3) Duan, S.; Moeller, K. D. *J. Am. Chem. Soc*. **2002**, *124*, 9368.

(4) (a) For an intramolecular electron-transfer reaction involving a radical cation and a 4-methoxyphenyl ring as an electron donor, see: Chiba, K.; Miura, T.; Kim, S.; Kitano, Y.; Tada, M. *J. Am. Chem. Soc*. **2001**, *123*, 11314. (b) For an earlier example involving the anodic oxidation of an aromatic ring and an amide as an electron donor, see: Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem*. **1991**, *56*, 1058.

(5) (a) For the isolation of Artemisolide, see: Dim, J. H.; Kim, H.-K.; Jeon, S. B.; Son, K.-H.; Kim, E. H.; Kang, S. K.; Sung, N.-D.; Kwon, B.-M. *Tetrahedron Lett*. **2002**, *43*, 6203. (b) For the isolation of the related Arteminolides, see: Lee, S.-H.; Kim, H.-K.; Seo, J.-M.; Kang, H.-M.; Kim, J. H.; Son, K.-H.; Lee, H.; Kwon, B.-M. *J. Org. Chem*. **2002**, *67*, 7670.

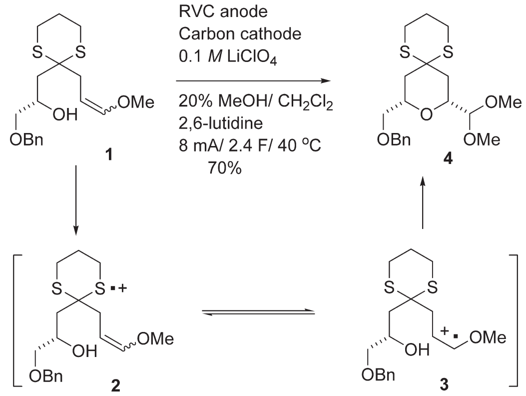
(6) For synthetic studies targeting the related Arteminolides, see: (a) Sohn, J.-H. *Bull. Korean Chem. Soc*. **2010**, *31*, 1841. (b) Sohn, J.-H. *Bull. Korean Chem. Soc*. **2009**, *30*, 2517. (c) Lee, H.-Y.; Sohn, J.-H.; Kim, H. Y. *Tetrahedron Lett*. **2001**, *42*, 1695.

(7) For lead references, see: (a) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett*. **1999**, *1*, 1535. (b) Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc*. **2006**, *128*, 17057.

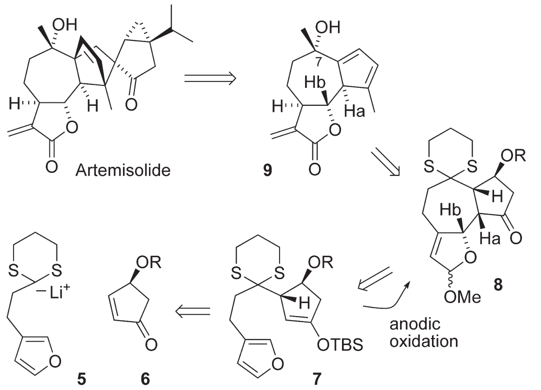
(8) Please see: Wu, Honghui; Moeller, Kevin D. *Org. Lett*. **2007**, *9*, 4599 and references therein.

10.1021/ol200182f © 2011 American Chemical Society
Published on Web 03/04/2011

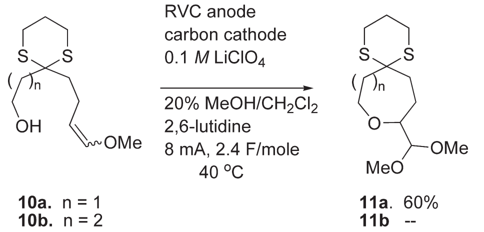
Scheme 1



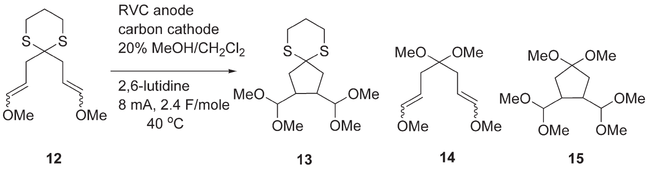
Scheme 2



Scheme 3



Scheme 4



Electrolyte:	13	14	15
0.1 M $LiClO_4$:	21%	16%	19%
0.1 M Et_4NOTs:	51%	6%	10%
0.5 M Et_4NOTs:	60%	2%	7%

cyclization would require a Curtin−Hammett type scenario since the oxidation potential of the dithioketal is significantly lower than that of either the enol ether or the furan ring.

But will the oxidation of **7** really give rise to a reaction consistent with the Curtin−Hammett Principle? Anodic coupling reactions forming carbon−carbon bonds are typically slower than reactions leading to carbon−oxygen bonds,[9] and the formation of the seven-membered ring proposed in Scheme 2 should be significantly slower than formation of the six-membered ring generated from the oxidation of **1**. Is the proposed cyclization still fast enough to drain the reaction toward the formation of **8**? How general is the conclusion reached for the oxidation of **1**?

Initially, this question was addressed for the formation of medium-size rings. To this end, both seven- and eight-membered ring substrates (Scheme 3) were synthesized in a fashion directly analogous to **1**.[10] When the seven-membered ring substrate **10a** was oxidized using conditions identical to those employed for the oxidation of **1** (a reticulated vitreous carbon (RVC) anode, a carbon cathode, lithium perchlorate electrolyte, 20% MeOH/CH_2Cl_2 solvent, 2,6-lutidine as a proton scavenger, and a constant current of 8 mA), a 60% isolated yield of the cyclic product **11a** was obtained. A ^1H NMR of the crude reaction material showed only the desired product suggesting that the lower isolated yield for the reaction resulted from instability of the product to chromatography. Clearly, formation of the seven-membered ring did not interfere with Curtin−Hammett control of the oxidation. An oxidation of the eight-membered ring substrate **10b** did not lead to the same conclusion. In this case, the reaction led to a mixture of products, none of which were consistent with cyclized material.

Attention was then turned toward probing the compatibility of the cyclizations with less reactive carbon-based nucleophiles. This work began by examining bis-enol ether substrate **12**.[10] When **12** was oxidized using the same conditions described above (Scheme 4), the reaction led to cyclic product **13** in a 21% yield along with 16% of the acyclic dimethoxyketal product **14** (derived from oxidation of the dithioketal) and 19% of the overoxidized cyclic product **15**. The formation of the acyclic product **14** highlighted how much slower the C−C bond forming reaction is relative to alcohol trapping of the radical cation. For the carbon−carbon bond forming reaction, trapping of the dithioketal radical cation by methanol competed with the cyclization even when the cyclization afforded a five-membered ring instead of the seven-membered ring generated from the oxidation of **10a**.

Cyclic voltammetry data suggested a method for aiding the cyclization originating from **12** (Figure 1).[11] The $E_{p/2}$-value measured for an isolated methoxy enol ether (compound **16**) was +1.40 V vs a Ag/AgCl reference

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[9] For an example, see: Frey, D. a.; Reddy, S. H. K.; Wu, N.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805.

[10] Synthetic details are contained in the Supporting Information.

[11] $E_{p/2}$ values were measured using a Ag/AgCl reference electrode, a Pt anode, a 0.1 N $LiClO_4$ in CH_3CN electrolyte solution, and a sweep rate of 25 mV/s.

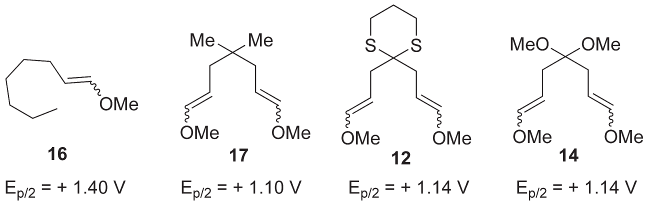
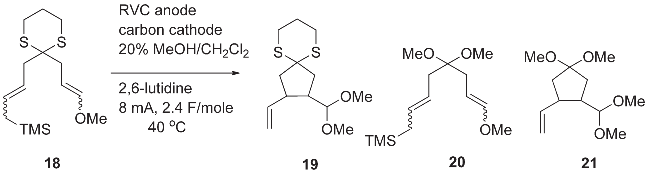


Figure 1. Potentials measured by CV relative to a Ag/AgCl reference electrode.

Scheme 5



	19	20	21
Electrolyte: 0.2 *M* $LiClO_4$:	15%	30%	16%
0.2 *M* Et_4NOTs:	53%	6%	8%

electrode. For a substrate leading to a fast cyclization, a lower oxidation potential would be expected.[12] This occurs because fast radical cation initiated cyclizations happen at or near the electrode surface. Hence, the cyclization removes the radical cation intermediate from the surface of the anode resulting in a shift in the equilibrium at the electrode surface toward the product. The shift in equilibrium lowers the potential measured for the substrate. The faster the cyclization reaction, the lower the potential measured. For example, consider substrate **17** in Figure 1. In this case, the formation of a five-membered ring and a gem-dialkyl effect afford a fast cyclization and a 300 mV drop in the oxidation potential measured for the substrate. For comparison, the potential measured for a similar substrate without the gem methyls is +1.2 V vs Ag/AgCl (a drop of only 200 mV relative to the enol ether).[13] The faster cyclization (gem methyls present) has a lower observed potential. As expected, the oxidation potential measure for **14** shows a drop similar to that measured for **17**. In the case of **12**, a lower potential is observed, but this potential reflects oxidation of the dithioketal and not simply the cyclization. Nevertheless, the oxidative cyclization arising from **12** should proceed in a fashion very similar to that of both **17** and **14**. In other words, it should also occur at or near the electrode surface.

In such reactions, decreasing the amount of methanol close to the anode should favor the cyclization. A lower concentration of methanol by the anode means slower competitive trapping of the dithioketal radical cation. However, decreasing the concentration of methanol in the electrolysis is not necessarily an option. Methanol is needed in sufficient concentration to serve as both the substrate reduced at the cathode and as the nucleophile to trap the oxonium ions resulting from the cyclization. Fortunately, methanol can serve both of these purposes while having its effective concentration selectively lowered near the surface of the anode by employing a less-polar electrolyte. The electrolyte forms a double layer at the anode thereby controlling the nature of the solution surrounding the electrode.[14] Double layers formed by hydrophobic electrolytes exclude methanol from the surface of the anode. The more hydrophobic the electrolyte used, the more methanol excluded. The oxidation of **12** provides a nice example of this situation. When **12** was oxidized using a 0.1 M tetraethylammonium tosylate solution in place of the lithium perchlorate solution used in the initial experiment, a 51% isolated yield of the cyclic dithioketal product **13** was obtained along with only 6% of the acyclic dithioketal product **14** and 10% of the cyclic overoxidized material **15** (Scheme 4). The use of a 0.5 M Et_4NOTs electrolyte solution improved the reaction even further producing a 60% isolated yield of **13**. Only 2% of **14** was formed along with 7% of **15**. While the oxidation potentials given in Figure 1 suggest that the overoxidized product **15** can be produced from either the oxidation of the dithioketal in **13** or an oxidative cyclization of **14**, the observation that the yield of **14** drops off faster than the yield of **15** is consistent with **15** arising primarily from overoxidation of **13**. In either case, the oxidation leads to a 67% isolated yield of the cyclic product.

The influence of the electrolyte on the reaction was also observed using a less reactive allylsilane trapping group for the enol ether radical cation (Scheme 5).[15] Once again, the yield of cyclized product dramatically improved with the use of tetraethylammonium tosylate as the electrolyte. Using the quaternary ammonium salt, a 61% combined yield of cyclic product was isolated.

Because furan rings are among the most reactive anodic olefin coupling partners studied to date,[8] the success of the cyclizations arising from **12** and **18** bode well for the proposed enol ether−furan coupling reaction highlighted in Scheme 2. With this in mind, six-membered ring substrate **22** was synthesized[10] and oxidized (Scheme 6).

The reactivity of the furan ring was immediately evident when the reaction led to a good yield of cyclic product even with lithium perchlorate as the electrolyte. No evidence was observed for methanol trapping of the dithioketal radical cation **25**. The initial cyclization product **23** was not isolated but instead treated with toluenesulfonic acid to directly obtain the tricyclic furan.[7,10] Like previous Curtin−Hammett controlled cyclizations, the reaction

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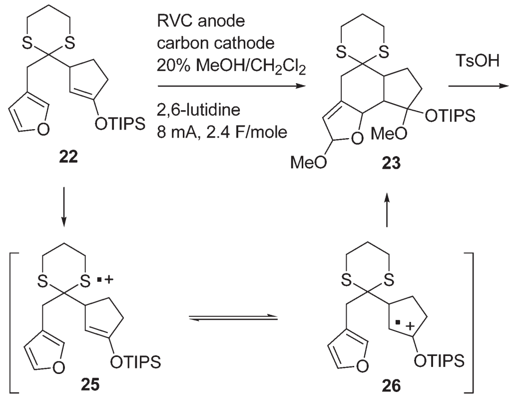
[12] For examples, please see: Xu, H.; Moeller, K. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8004 and references therein.

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

[14] (a) For general discussions of how the adsorption of a substrate and an electrolyte onto an electrode surface can exclude solvent and protect a reactive intermediate, see: *Organic Electrochemistry: 4th ed., Revised and Expanded*; Lund, H., Hemmerich, O., Eds.; Marcel Dekker: New York-Basel, 2001; p 802. *Synthetic Organic Electrochemistry*, 2nd ed.; Fry, A. J., Ed.; John Wiley and Sons: New York, 1989; p 126. (b) For a detailed example, see: Fry, A. J.; Reed, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 8475.

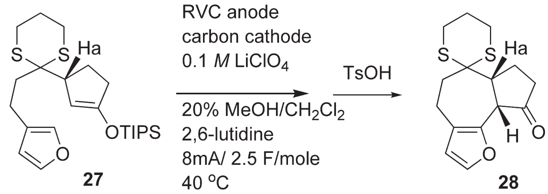
[15] For evidence showing the lower reactivity of allylsilane trapping groups, see: (a) Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536. (b) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372. (c) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381.

Scheme 6

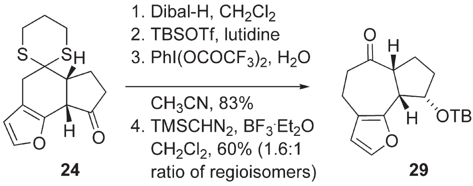


electrolyte	t (°C)	F/mol	NMR yield (**23**)	isolated yield (**24**)
0.2 *M* LiClO$_4$	rt	2.5	66%	51%
0.2 *M* LiClO$_4$	40	2.4	71%	55%
0.2 *M* Et$_4$NOTs	40	4	51%	--
0.5 *M* LiClO$_4$	40	2.4	88%	70%

Scheme 7



Scheme 8



benefited from elevated temperature, presumably by favoring the intramolecular cyclization over bimolecular methanol trapping.[3] Surprisingly, the reaction did not proceed as well when tetraethylammonium tosylate was used as the electrolyte. It appears that the use of the less polar electrolyte did too good of a job excluding methanol from the reaction medium surrounding the anode. Reactions involving furan rings require sufficient methanol to be present in order to trap the initial cyclic cation leading to **23**. If this trapping reaction does not occur, then the elimination of a proton regenerates an electron-rich furan ring with a lower oxidation potential than the substrate. Eventually, it was found that the use of a 0.5 M LiClO$_4$ electrolyte solution and elevated temperature afforded a 70% isolated yield of the tricyclic furan after treatment of the initial product with acid.

The reaction could not be extended to the formation of a seven-membered ring (Scheme 7).[10] The reaction again benefited from the use of LiClO$_4$ as the electrolyte, but under the optimal conditions (in this case 0.1 M electrolyte) only a 9% isolated yield of the tricyclic product **28** was obtained. None of the product derived from simple oxidation of the dithioketal was observed. Instead, the reaction led to a complex mixture of products. Related experiments suggest that an elimination of H$_a$ from the enol ether radical cation can compete with the cyclization. However, no evidence for any one alternative product was obtained from the oxidation of **27**.

The failure of the seven-membered ring cyclization suggested that the synthesis of artemisolide would best take advantage of the six-membered ring cyclization followed by a ring expansion (Scheme 8). To this end, the tricyclic electrolysis product was reduced, the resulting alcohol protected, and the dithioketal cleaved to deprotect the six-membered ring ketone. The ketone was then treated with trimethylsilyldiazomethane and BF$_3$·Et$_2$O in dichloromethane to expand the central ring in the desired direction.[16] The reaction led to a 60% isolated yield of two seven-membered ring products in a 1.6:1 ratio. A HMQC-TOCSY experiment was used to assign the connectivity of the two products showing that the major isomer was the desired **29** and the minor isomer the product of ring expansion in the opposite direction. Clearly, the Curtin–Hammet controlled anodic cyclization can provide access to the ring skeleton needed for the synthesis of artemisolide, but work is still needed to improve the yield and regioselectivity of the ring-expansion reaction.

In conclusion, we have extended the scope of Curtin–Hammett controlled anodic cyclizations by examining the compatibility of coupling reactions conducted in the presence of a dithioketal protecting group with both the formation of medium-size rings and the generation of carbon–carbon bonds. Cyclizations utilizing an alcohol trapping group are fast and show no signs of competitive trapping of the dithioketal radical cation even when forming a seven-membered ring. Carbon–carbon bond forming reactions utilizing reactive furan trapping groups are also fast, although not fast enough to allow for seven-membered ring formation. Slower carbon–carbon bond forming reactions benefit strongly from the use of less polar electrolytes that selectively lower the concentration of methanol in the region of the reaction surrounding the anode. Applications of these reactions to total syntheses efforts are underway.

Acknowledgment. We thank the National Science Foundation (CHE-0809142) for their generous support of this work.

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

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[16] Saito, T.; Nakata, T. *Org. Lett.* **2009**, *11* (1), 113.