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Intramolecular Anodic Olefin Coupling Reactions and the Synthesis of Cyclic Amines

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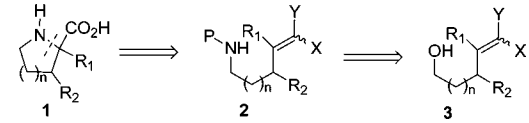
Abstract: Anodic olefin coupling reactions using a tosylamine trapping group have been studied. The cyclizations are favored by the use of a less-polar radical cation and more basic reaction conditions. The most significant factor for obtaining good yields of cyclic product is the use of the more basic reaction conditions. However, a number of factors including the nature of both the solvent and the electrolyte used can influence the yield of the cyclizations. The cyclizations allow for the rapid synthesis of both substituted proline and pipecolic acid type derivatives.

Introduction

The anodic oxidation of an enol ether, vinyl sulfide, or ketene acetal generates a radical cation that can be used to trigger a number of interesting cyclization reactions.[1] Typically, the intermediates are trapped with either an electron-rich olefin, an aromatic ring, or an alcohol nucleophile in order to generate a variety of carbocyclic, tetrahydrofuran, and tetrahydropyran products. In a retrosynthetic analysis, the cyclizations can be recognized by noting that they involve umpolung reactions between the normally nucleophilic carbon alpha to a carbonyl and a second nucleophile.

In principle, anodic cyclization reactions of this type should also be useful for the synthesis of cyclic amino acid derivatives and a variety of peptidomimetics (Scheme 1).[2−6] In this scenario, the target amino acid would be dissected between the carbon alpha to the carboxylic acid and a nitrogen-based nucleophile to afford an acyclic electrolysis substrate **2**.[7] The cyclization would then offer the opportunity to construct the amino acid

Scheme 1



derivative with control over the stereochemistry of the α carbon, even in cases where a tetrasubstituted carbon was needed at this position.[8] The substrates for the electrolyses would be available in an asymmetric fashion by taking advantage of the previous route to alcohol-based substrates like **3**.[8a] With this in

(1) For a recent account, see (a) Moeller, K. D. *Synlett* **2009**, 1208. For reviews of early work, see (b) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (c) Moeller, K. D. *Top. Curr. Chem.* **1997**, *185*, 49.

(2) For a review of cyclic amino acid derivatives, see Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629.

(3) For recent references, see (a) Mitsunaga, S.; Ohbayashi, T.; Sugiyama, S.; Saitou, T.; Tadokoro, M.; Satoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 1697. (b) Wang, Y.-G.; Mii, H.; Kano, T.; Maruoka, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3795. (c) Kaname, M.; Yamada, M.; Yoshifuji, S.; Sashida, H. *Chem. Pharm. Bull.* **2009**, *57*, 49. (d) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 15794. (e) Prazeres, V. F. V.; Castedo, L.; Gonzalez-Bello, C. *Eur. J. Org. Chem.* **2008**, *23*, 3991. (f) Simila, S. T. M.; Martin, S. F. *Tetrahedron Lett.* **2008**, *49*, 4501. (g) Undheim, K. *Amino Acids* **2008**, *34*, 357, and references therein.

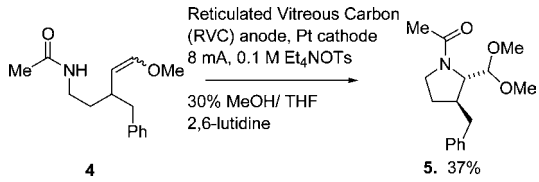
(4) For leading references concerning the use of lactam-based peptidomimetics containing cyclic amino acid derivatives, see (a) Cluzeau, J.; Lubell, W. D. *Biopolymers* **2005**, *80*, 98. (b) I-lalab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers* **2000**, *55*, 101. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. For additional lead references, see (d) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937. (e) Curran, T. P.; Marcaurell, L. A.; O'Sullivan, K. M. *Org. Lett.* **1999**, *1*, 1225. (f) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163. (g) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171. (h) Feng, Z.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1181.

(5) For synthetic routes to peptidomimetics containing cyclic amino acid derivatives: (a) Scott, W. L.; Alsina, J.; Kennedy, J. H.; O'Donnell, M. J. *Org. Lett.* **2004**, *6*, 1629. (b) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin- Santamaria, S.; Linden, A. *J. Am. Chem. Soc.* **2003**, *125*, 16243. (c) Colombo, L.; Di Giacomo, M.; Vinci, V.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 4501. (d) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **2003**, *46*, 727. (e) Khalil, E. M.; Pradhan, A.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 2977. (f) Aube, J. *Adv. Amino Acid Mimetics Peptidomimetics* **1997**, *1*, 193. (g) Tong, Y.; Olczak, J.; Zabrocki, J.; Gershengorn, M. C.; Marshall, G. R.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 9791. (h) Duan, S.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 6407. (i) Liu, B.; Brandt, J. D.; Moeller, K. D. *Tetrahedron* **2003**, *59*, 8515.

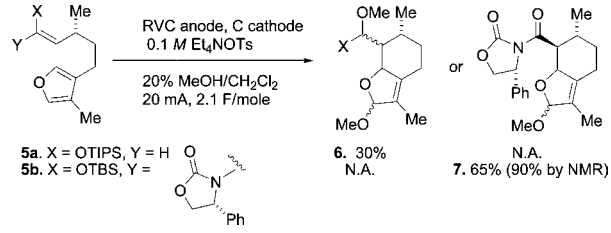
(6) For examples of the use of electrochemistry to functionalize cyclic amino acids, see (a) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113 and references cited therein. (b) Fobian, Y. M.; d'Avignon, D. A.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 315. (c) Fobian, Y. M.; Moeller, K. D. *Peptidomimetic Protocols*; Methods in Molecular Medicine, Vol. 23; Humana Press: Totowa, NJ, 1999; p 259. (d) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484. (e) Cornille, F.; Fobian, Y. M.; Slomczynska, U.; Beusen, D. D.; Marshall, G. R.; Moeller, K. D. *Tetrahedron Lett.* **1994**, *35*, 6989. (f) Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 909. (g) Slomczynska, U.; Chalmers, D. K.; Cornille, F.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Org. Chem.* **1996**, *61*, 1198. (h) Simpson, J. C.; Ho, C.; Shands, E. F. B.; Gershengorn, M. C.; Marshall, G. R.; Moeller, K. D. *Bioorg. Med. Chem.* **2002**, *10*, 291. (i) Li, W.; Hanau, C. E.; d'Avignon, A.; Moeller, K. D. *J. Org. Chem.* **1995**, *60*, 8155.

(7) For a preliminary account of this work, see Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542.

Scheme 2



Scheme 3



mind, the key question was whether or not a nitrogen-based nucleophile would be compatible with the oxidative coupling reaction.

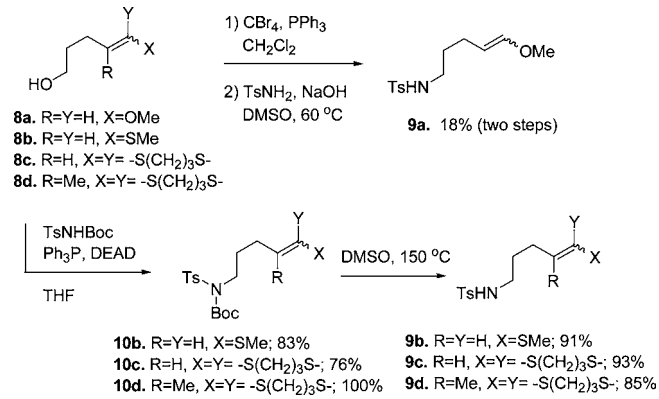
Initial attempts to answer this question were not encouraging. A number of substituent patterns were tried for the reactions, with the most successful being illustrated in Scheme 2. In this case, a methoxyenol ether was tethered to an acylated amine in order to generate a five-membered ring product upon cyclization. A low yield of the desired product was obtained (Scheme 2).

Varying the reaction conditions did not improve the cyclization. Neither did changing the protecting group on the nitrogen. Even the known alternative approach of triggering related cyclizations by oxidizing an amine or hydroxylamine derivative met with failure.[9] Evidently, the enol ether is not compatible with such an approach.

Fortunately, recent efforts have demonstrated that the nature of the substituents on a radical cation intermediate can have a profound influence on its ability to react with various trapping groups.[10] More polarized radical cations tend to favor carbon−carbon bond forming reactions, while less polarized radical cations tend to favor reactions with heteroatomic trapping groups. This observation was used nicely to optimize a coupling reaction between an electron-rich olefin and an electron-rich furan ring during our synthesis of the arteannuin ring system (Scheme 3).[8c] In this case, the use of a more polarized ketene acetal-derived radical cation dramatically improved the yield of the cyclization relative to the use of an enol ether-derived radical cation.

Having used a more polarized radical cation to improve the cyclization highlighted in Scheme 3, we wondered if the use of a less polarized radical cation might improve the cyclizations highlighted in Scheme 2.

Scheme 4



Initial Studies

In order to test this idea and give the study the best chance for success, a *p*-toluenesulfonamide trapping group was selected for the cyclizations. The sulfonamide trapping group was chosen because of its propensity for serving as a nucleophile.[11] Four substrates were synthesized as outlined in Scheme 4.[12] One aspect of this work deserves comment. Initially, the enol ether substrate (**9a**) could not be made via the very effective Mitsunobu reaction−*t*-Boc deprotection strategy used to make substrates **9b,c** because the enol ether group was not stable to the deprotection reaction. For this reason, the alternative low-yielding sequence illustrated in Scheme 4 was used. Recently, this problem has been solved by developing an alternative method for the deprotection. This method involves treatment of the *t*-Boc-protected sulfonamide with methyllithium in ether at −20 °C for 10 min. With these conditions, the *t*-Boc group can be removed from the sulfonamide in 90% yield even in the presence of an enol ether. These conditions are now used for the deprotection reaction in all circumstances.

The initial substrate oxidized was enol ether **9a** (Table 1, entry 1).[7] The reaction was carried out by use of a reticulated vitreous carbon anode, a Pt cathode, 0.1 M tetraethylammonium tosylate in 30% MeOH/tetrahydrofuran (THF) electrolyte solution, 2,6-lutidine as a proton scavenger, and a constant current of 6 mA. The reaction was conducted until 2.2 F/mol current had been passed (10% more than the theoretical amount needed for the two-electron oxidation). As in the previous studies, the cyclization was not very successful, affording the desired product in only 20% yield.

An immediate improvement in the cyclization was observed when the vinyl sulfide substrate **9b** was used. In this case, the reaction afforded a 54% isolated yield of the cyclic product **11b** under reaction conditions identical to those employed for the oxidation of **9a**. The improvement in the yield was ascribed to the decrease in polarization of the radical cation derived from the vinyl sulfide. A feel for the lower polarization of the vinyl sulfide-derived radical cation can be gained by examining the polarity of the substrates by ^{13}C NMR (Figure 1). For example, the presence of the sulfide does not polarize the double bond in the starting material, leaving both olefinic carbons with the same

(8) For selected examples of reactions leading to tetrasubstituted carbons, see ref 7 in addition to (a) Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868. (b) Tang, F.; Moeller, K. D. *J. Am. Chem. Soc.* **2007**, *129*, 12414. (c) Wu, H.; Moeller, K. D. *Org. Lett.* **2007**, *9*, 4599. (d) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106–9111. (e) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101. (f) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183. (g) Frey, D. A.; Reddy, S. H. K.; Wu, N.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805–2813. (h) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381.

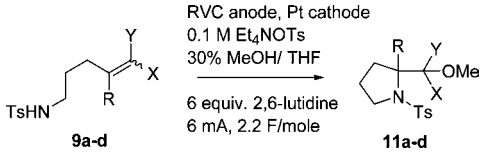
(9) (a) Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747. (b) Tokuda, M.; Fujita, H.; Miyamoto, T.; Suginome, H. *Tetrahedron* **1993**, *49*, 2413. (c) Karady, S.; Corley, E. G.; Abramson, N. L.; Amato, J. S.; Weinstock, L. M. *Tetrahedron* **1991**, *47*, 757. (d) Abou-Elenien, G. M.; El-Anadouli, B. E.; Baraka, R. M. *J. Chem. Soc.; Perkin Trans. 2* **1991**, 1377.

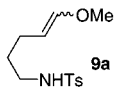
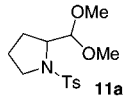
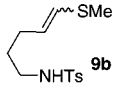
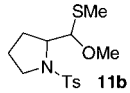
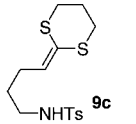
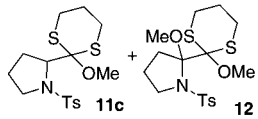
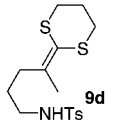
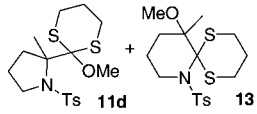
(10) See ref 8b as well as Huang, Y.-T.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536.

(11) (a) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 8328. (b) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164.

(12) For complete experimental details concerning syntheses of the substrates, see the Supporting Information.

Table 1



entry	substrate	product(s)	yield(s)
1	 **9a**	 **11a**	20%
2	 **9b**	 **11b**	54%
3	 **9c**	 **11c** + **12**	14% + 4%
4	 **9d**	 **11d** + **13**	19% + 24%

chemical shift. For comparison, oxygen serves as a clear electron donor to the π-system. The improvement in the cyclization observed with **9b** suggested that the use of the vinyl sulfide might allow for the development of a synthetically useful oxidative approach to cyclic amino acids.

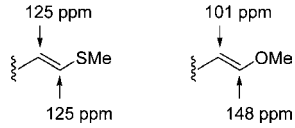
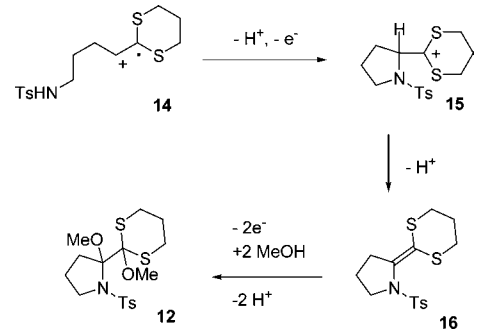


Figure 1

A suggestion for how the reactions could be further optimized arose from the study of ketene dithioacetal substrates **9c** and **9d**. Ketene dithioacetals have proven to be very effective coupling partners for alcohol nucleophiles in anodic olefin coupling reactions.[13] However, the anodic oxidation of **9c** under the same conditions described above led to only a 14% yield of cyclic product **11c** along with 4% of an overoxidized product. The overoxidized product appeared to arise from the elimination of proton from the initial cyclization product (**15**) competing with the desired methanol trapping reaction. The elimination was followed by oxidation of the resulting ketene acetal (**16**) and subsequent methanol trapping of the radical cation generated (Scheme 5).

In order to avoid the elimination reaction, the oxidation of substrate **9d** was examined. In this case, a methyl group replaced the proton on the β-carbon of the electron-rich olefin. The reaction again gave rise to a poor yield (19%) of the desired cyclic product. The reaction led to a six-membered ring product (**13**) formed by competitive trapping of the radical cation with methanol solvent. The formation of the six-membered ring

Scheme 5



product meant that the toluenesulfonamide group was not nearly as good a nucleophile for trapping the radical cation as was an alcohol.

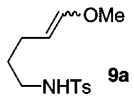
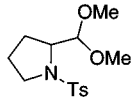
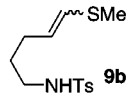
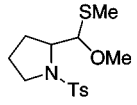
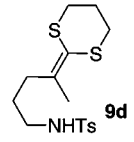
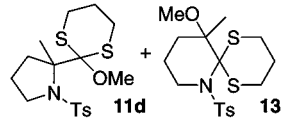
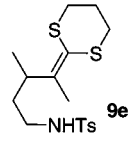
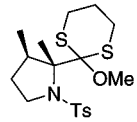
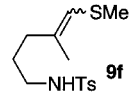
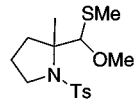
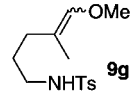
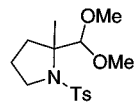
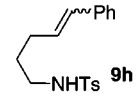
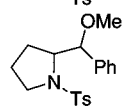
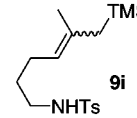
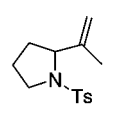
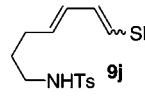
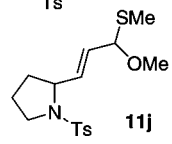
Electrolyses under More Basic Conditions

The intramolecular reaction was not competing effectively with the intermolecular trapping group. One method for solving this problem would be to increase the nucleophilicity of the nitrogen trapping group. In order to accomplish this goal, the reactions were repeated under more basic reaction conditions. The idea was to take advantage of the acidity of the sulfonamide relative to that of the methanol solvent. To this end, the 2,6-lutidine used in the initial reactions was replaced with lithium methoxide. For an electrolysis reaction in an undivided cell, acid is produced at the anode and equal amount of base produced at the cathode by the reduction of methanol. The electrolysis remains at the same pH throughout the entire course of the reaction. Hence, the use of lithium methoxide in place of 2,6-lutidine raises the pH of the reaction medium used for the electrolysis from start to finish. The lithium methoxide was either produced in situ by adding *n*-BuLi to the methanol-based solvent mixture or introduced as a THF solution (available from Aldrich).

The more basic reaction conditions had a dramatic influence on the reactions (Table 2). For example, the oxidation of substrate **9a** (entry 1) led to the formation of cyclic product **11a** in a 70% isolated yield when 30% MeOH/THF was used as the solvent for the reaction. When the solvent was changed to methanol, the isolated yield of **11a** climbed to 82%. Once again, the reaction utilizing the thioenol ether (**9b**) led to a higher yield of product (entry 2) than did the reaction using the methoxyenol ether. In this case, the yield of the reaction was 85% when 30% MeOH/THF was used as solvent and 90% when methanol was used.

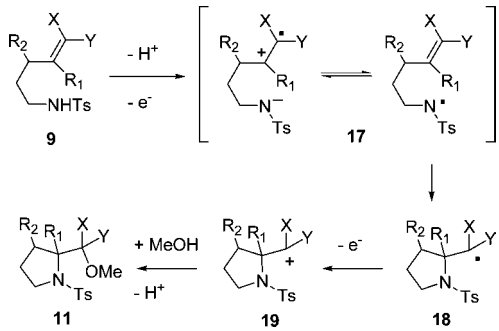
The role of LiOMe in these reactions is thought to be deprotonation of the toluenesulfonamide in order to make a better coupling partner for the reaction. This can occur either by the anion of the sulfonamide serving as a better nucleophile for the electrochemically generated radical cation, or by the oxidation taking place at the nitrogen in order to form a nitrogen-based radical that then adds to the olefin (Scheme 6). These two pathways cannot be readily distinguished from the oxidation potentials of the two coupling partners because they have the potential to equilibrate through a fast intramolecular electron transfer.[14] Both pathways lead to the same cyclic radical product **18**. Radical **18** is then oxidized to form a stabilized cation **19** that is trapped with methanol solvent to form the final cyclic product. It is thought that the reactions benefit from the use of pure methanol as solvent because of a need to trap cation **19**

Table 2

entry	substrate	product(s)	yield(s)
1	 **9a**	 **11a**	(70%)[a] (82%)[b]
2	 **9b**	 **11b**	(85%)[a] (90%)[b] (91%)[c]
3	 **9d**	 **11d** **13**	(72% + 0%)[a] (73% + 7%)[b]
4	 **9e**	 **11e**	(28%)[a] (83%)[b]
5	 **9f**	 **11f**	(89%)[b]
6	 **9g**	 **11g**	(77%)[b]
7	 **9h**	 **11h**	(88%)[b]
8	 **9i**	 **11i**	(90%)[b]
9	 **9j**	 **11j**	(70%)[c]

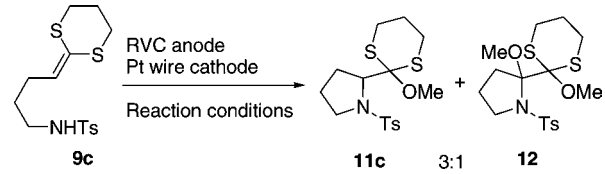
[a] Reaction conditions: RVC anode, Pt wire cathode, 0.5 equiv of LiOMe, 30% MeOH/THF, 0.1 M Et_4NOTs, 6 mA, 2.0−2.4 F/mol. [b] MeOH as solvent. [c] 0.7 equiv of LiOMe (no additional electrolyte was used), MeOH.

Scheme 6



before subsequent rearrangement can take place. In this way, the reactions require a balance between having the cyclization occur faster than methanol trapping of the original radical cation while still having methanol present in sufficient quantity to efficiently form the final product.

Table 3



entry	reaction conditions	yield (%)
1	0.5 equiv of *n*-BuLi, MeOH, 0.1 M Et_4NOTs, 6 mA, 9.4 F/mol	39
2	0.5 equiv of *n*-BuLi, 30% MeOH/THF, 0.1 M Et_4NOTs, 6 mA, 2.4 F/mol	33
3	0.5 equiv of *n*-BuLi, 60% MeOH-THF, 0.1 M Et_4NOTs, 6 mA, 2.4 F/mol	34
4	0.5 equiv of *n*-BuLi, MeOH, 0.03 M Et_4NOTs, 6 mA, 3.3 F/mol	66
5	0.5 equiv of *n*-BuLi, MeOH, 0.003 M Et_4NOTs, 6 mA, 3.8 F/mol	47
6	0.5 equiv of *n*-BuLi, MeOH, 0.03 M $LiClO_4$ 6 mA, 4 F/mol	10
7	2,6-lutidine, MeOH, 0.03 M $LiClO_4$, 6 mA, 4 F/mol	18

Even with the more basic reaction conditions and the use of methanol solvent to accelerate the trapping of the cyclic cation **19**, the cyclization originating from **9c** remained problematic (Table 3). While the overall yield of cyclic product could be raised to 66% by reducing the concentration of the electrolyte to further increase the concentration of MeOH close to the surface of the anode, the elimination reaction leading to overoxidation of the product could not be avoided.

The use of the more basic reaction conditions did solve the problems initially encountered with substrate **9d** (Table 2, entry 3). In this case, the reaction utilizing the 30% MeOH/THF conditions formed the desired cyclization product in 72% isolated yield without any of the methanol trapping product. The use of MeOH as the solvent did lead to some of the competing six-membered ring MeOH trapping product but did not lower the yield of the desired five-membered ring product obtained. Evidently, the loss of product through trapping of the radical cation with methanol solvent was counteracted by the improved yield of the cyclic product by methanol trapping of **19**.

The need for having sufficient methanol present to trap the cyclic cation **19** was acutely observed when substrate **9e** was oxidized (Table 2, entry 4).[12,15] The oxidation of **9e** in 30% MeOH/THF led to only a 28% yield of the desired cyclic product. The isolated yield of the reaction was raised to 80% by switching to MeOH solvent. The product was formed as a single diastereomer whose stereochemistry was assigned with the use of a nuclear Overhauser effect spectroscopy (NOESY) experiment. Formation of the major diastereomer can be rationalized by the preference for the transition state in which steric interactions between the methyl and dithiane groups are

(13) In addition to refs 8a and 8e, please see (a) Brandt, J. D.; Moeller, K. D. *Heterocycles* **2006**, *67*, 621. (b) Brandt, J. D.; Moeller, K. D. *Org. Lett.* **2005**, *7*, 3553. (c) Sun, Y.; Liu, B.; Kao, J.; d'Avignon, A.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 1729.

(14) For examples of intramolecular electron transfers in anodic oxidations, see (a) Duan, D.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 9368. (b) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058.

(15) For a previous example of the final trapping step playing a large role in the yield of an anodic olefin coupling reaction, see ref 13c.

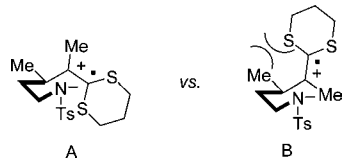
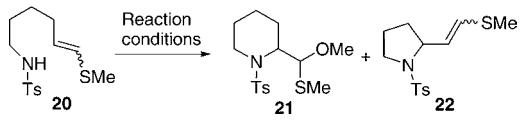


Figure 2

Table 4



entry	reaction conditions	yield (%) 21	22
1	0.5 equiv of *n*-BuLi, MeOH, 0.1 M Et_4NOTs, 6 mA, 2.3 F/mol	20	9
2	0.5 equiv of *n*-BuLi, 30% MeOH/THF, 0.1 M Et_4NOTs, 6 mA, 2.3 F/mol	27	8
3	$c = 0.006$ M, 0.5 equiv of *n*-BuLi, MeOH, 0.1 M Et_4NOTs, 6 mA, 14 F/mol	17	5

minimized (Figure 2). The stereochemistry of the reaction is consistent with earlier cyclizations using oxygen nucleophiles.[16]

Reactions originating from thioenol ether (Table 2, entry 5) and methoxyenol ether (Table 2, entry 6) sustrates were also compatible with the generation of tetrasubstituted carbons. These reactions again benefited from the use of methanol as the solvent and the less polar thioenol ether substrate.

The observation that the cyclizations proceed well with less-polarized radical cations suggested that they may be compatible with the use of a variety of olefins. To test this idea, substrates **9h** and **9i** were studied.[12] In both cases, anodic oxidation of the substrate led smoothly to the cyclized product. With the styrene-based substrate (Table 2, entry 7), an 88% isolated yield of product was obtained. Oxidation of the allylsilane-based substrate (Table 2, entry 8) led to a 90% isolated yield of product.

Finally, the cyclizations were compatible with the use of a diene substrate (**9j**). In this reaction, 0.7 equiv of LiOMe was used. No additional electrolyte was employed. The reaction led to a 70% isolated yield of the desired five-membered ring product. Conditions with LiOMe and no additional electrolyte were also used for the oxidation of **9b**. In this case, a 91% isolated yield of the cyclic product was obtained. It appears the LiOMe used in the reaction can fulfill the role of both the 2,6-lutidine base scavenger and the tetraethylammonium tosylate electrolyte used in the earlier examples.

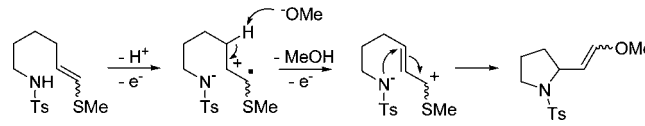
Cyclizations Affording Six-Membered Rings

With the success of the cyclizations leading to five-membered rings, attention was turned toward the more difficult to generate six-membered ring products.[17] Initially, a thioenol ether substrate (**20**) was used along with the optimized conditions developed above (Table 4). The reaction led to only a 20% isolated yield of the six-membered ring product **21**. In addition, a five-membered ring product (**22**) resulting from an elimination reaction involving the initial radical cation intermediate was

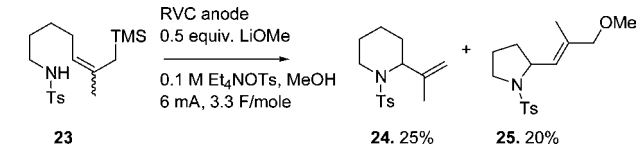
(16) See ref 13 in addition to Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685.

(17) For evidence showing slower anodic olefin coupling reactions leading to six-membered ring products, see refs 8f and 8h.

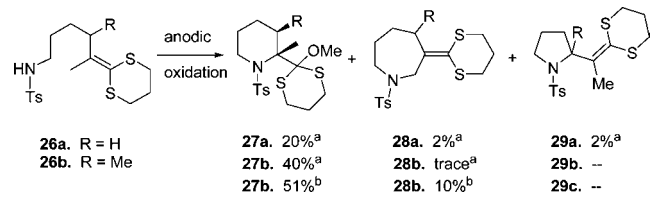
Scheme 7



Scheme 8



Scheme 9[a]



[a] Reaction conditions: (a) RVC anode, 0.5 equiv of LiOMe, 0.1 M Et_4NOTs, MeOH, 6 mA, 2.4 F/mol. (b) RVC anode, 0.5 equiv of LiOMe, 0.1 M $LiClO_4$, MeOH, 6 mA, 2.4 F/mol.

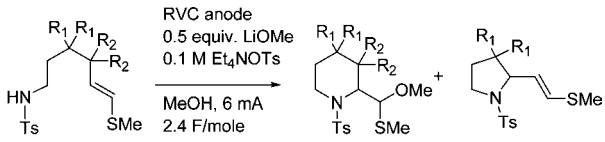
generated. A suggested mechanism for the formation of **22** is shown in Scheme 7. Alternatively, the elimination reaction might arise from either an intramolecular deprotonation of the radical cation by the toluenesulfonamide anion or an intramolecular hydrogen atom abstraction by a nitrogen-based radical.

The elimination reaction was also a problem when attempts were made to use the oxidation of other nonpolar, electron-rich olefins to trigger the formation of six-membered ring pipecolic acid derivatives. For example, the use of an allylsilane coupling partner for the toluenesulfonamide led to a 25% yield of the desired six-membered ring product along with 20% of a product derived from the elimination reaction (Scheme 8).

Insight into the nature of the elimination reaction was gained from examining the electrolyses of substrates **26a** and **26b** (Scheme 9).[12] In these substrates, a methyl group was added to the electron-rich olefin in an attempt to make a tetrasubstituted carbon. In both cases, a low yield of the desired product **27** was obtained along with a product (**28**) derived from the elimination. In these cases, the elimination occurred from both allylic positions, leading to both a seven- and a five-membered ring product. The elimination of a proton from the methyl group suggests that the elimination reaction involves an intermolecular deprotonation (Scheme 7). An intramolecular deprotonation with the toluenesulfonamide anion serving as the base would lead to a five-membered ring product.

The cyclization reaction originating from the oxidation of **26b** formed the six-membered ring product as a single diastereomer with the bulky dithio methylorthoester trans to the neighboring methyl group. The yield of this product could be raised to 51% (along with 10% of the product derived from elimination) by changing the electrolyte to lithium perchlorate. The change to lithium perchlorate electrolyte from the tetraethylammonium tosylate allows for a higher concentration of methanol close to the surface of the anode. The dependence of the isolated yield of product on this change supports the earlier observation that the final methanol trapping step is important for optimizing the yield of the reaction.

Scheme 10

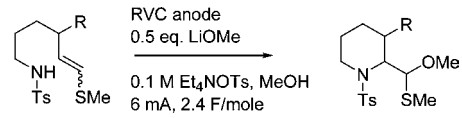


29a. R_1 = H, R_2 = Me
29b. R_1 = Me, R_2 = H

30a. 81%
30b. 35%

31a. --
31b. 8%

Scheme 11



32a. R = Me
32b. R = OTBDPS

33a. 44%
33b. 62%

The oxidation of substrates **29a** and **29b** was examined in order to elucidate the success of six-membered ring formation in the absence of the elimination reaction (Scheme 10).[12]

The oxidation of **29a** proceeded well and led to an 81% isolated yield of the six-membered ring product. The oxidation of **29b** provided a control experiment to determine whether the success of the cyclization resulting from **29a** was really due to the *gem*-methyl groups stopping the elimination reaction or if it was the result of a faster cyclization due to the *gem*-dialkyl effect.[18] While the presence of the *gem*-methyl groups in **29b** improved the cyclization relative to the reaction originating from **20** (Table 4), it was clear that the 81% yield of product **30a** was mainly due to the *gem*-methyls in **29a** preventing the elimination reaction.

With the knowledge that the six-membered ring cyclizations can be successful, attention was turned toward developing a strategy for the synthesis of 3-substituted pipecolic acid derivatives. The plan was to take advantage of sterics to slow down the elimination reaction and increase the time available for the cyclization. It was hoped that a single substituent on the allylic carbon of the substrate would accomplish this task (Scheme 11).[12] Since substrates like **32a** and **32b** can be synthesized in an asymmetric fashion, a successful cyclization would allow access to the chiral amino acid derivatives.

The cyclizations met with limited success. When a methyl group was placed on the allylic carbon of the substrate, the yield of cyclized product improved to 44%. The yield could be improved to 62% by placing a larger *t*-butyldiphenylsiloxy group on the allylic carbon of the substrate.

While the reaction with the *t*-butyldiphenylsiloxy group was successful, the need for such a large group limited the types of pipecolic acid derivatives that could be made with the cyclizations. What was needed was a method for increasing the effective steric size of any group used at the allylic position of the substrate. One strategy for accomplishing this goal would be to take advantage of the earlier observation that allylsilanes

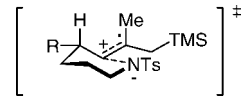
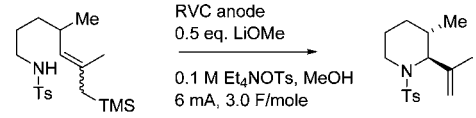


Figure 3

Scheme 12



34

35. 71%

are effective olefin coupling partners for the reactions. If a trisubstituted allylsilane were employed in the cyclization, then an $A^{1,3}$-interaction in the transition state for the reaction would force the allylic R group into a pseudoequatorial position and the allylic proton into a pseudoaxial position perpendicular to the π-system of the radical cation (Figure 3). The poor overlap between the allylic proton and the radical cation would be expected to lead to a slow elimination reaction and more time for the desired cyclization.

In practice, this idea worked very nicely (Scheme 12). When a substrate having an trisubstituted allylsilane coupling partner and an allylic methyl group (**34)** was oxidized, a 71% isolated yield of the cyclized product was obtained as a single diastereomer. Clearly, the use of the larger allylsilane group pushed the reaction toward the cyclized product.

Conclusions

We have found that anodic olefin coupling reactions can be used to generate new carbon−nitrogen bonds and synthesize substituted pyrrolidine and piperidine rings. The cyclization reactions benefit from the use of LiOMe as a base and methanol solvent. For the synthesis of five-membered ring products, the cyclizations proceed well with methoxyenol ether-, thioenol ether-, and dithioketene acetal-derived substrates. Reactions using a less polar olefin as a coupling partner afford higher yields of cyclized product.

Coupling reactions leading to six-membered rings are more difficult because of the competing elimination of a proton from the carbon alpha to the radical cation intermediate. This problem can be minimized by manipulating the sterics of the reactions, an observation that suggests the use of a trisubstituted allylsilane as an optimized olefin coupling partner for the reactions.

Overall, the cyclizations hold promise as a new method for constructing both proline and pipecolic acid-based amino acid derivatives. Work along these lines is continuing.

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Supporting Information Available: Full experimental and characterization data for all substrates and products, including copies of proton and carbon NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

JA910586V

(18) For examples, see (a) Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 8034. (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (c) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789. (d) Parrill, A. L.; Dolata, D. P. *J. Mol. Struct. (THEOCHEM)* **1996**, *370*, 187. (e) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183. For early references, see (f) Eliel, E. L.; Allinger, J. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley−Interscience: New York, 1967; p 191. (g) Allinger, J. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.