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Building Functionalized Peptidomimetics: Use of Electroauxiliaries for Introducing *N*-Acyliminium Ions into Peptides

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Abstract: A series of silyl-substituted amino acids have been synthesized, inserted into peptides, and then employed as precursors for oxidatively generating reactive *N*-acyliminium ions. Both electrochemical and chemical oxidation procedures have been employed. *N*-Acyliminium ion generation in a solid-phase substrate as well as application to a small library of functionalized dipeptides has been demonstrated. Limitations in terms of how electron-rich the silyl groups can be as well as the compatibility of multiple silyl groups within a longer peptide are defined.

Introduction

Constrained peptide mimetics are potentially very useful tools for probing the nature of ligand−receptor interactions.[1] This is especially true for the lactam-based analogues that are often suggested as probes for determining if a particular peptide conformation represents the biologically active form of the molecule.[2] In these cases, the peptide mimetic is readily designed by simply replacing spatially close hydrogens in the desired conformation with constraints or bridges. Yet while this design process is easy, introduction of the conformational constraints often leads to a ring skeleton that represents a significant synthetic challenge. The need for these ring skeletons has triggered the development of a number of elegant approaches for their synthesis. Yet while the core scaffolds can often be rapidly synthesized, synthetic strategies that offer control over both the regio- and stereochemistry of various substituents on the rings are less common.[3,4] Further complicating this picture is the growing desire to incorporate conformational probes into diversity-oriented approaches to mapping receptors.[5] In such approaches, the scaffolds made are diversified with the use of protected side chains on the periphery of the structure. To map more than one conformational space, a library with a variety of core scaffolds is needed. Hence, synthetic methodology is needed that allows for not only systematically varying the periphery of a scaffold, but also systematically varying the core scaffold itself.

So how does one rapidly assemble a series of conformationally constrained peptidomimetics in a fashion that allows for systematic variation of both the periphery functional groups and the core scaffold? Furthermore, is the chemistry used compatible with building the molecules on addressable microarrays of

(1) For recent reviews see: (a) Galeazzi, R.; Mobili, G.; Orena, M. *Curr. Org. Chem.* **2004**, *8*, 1799. (b) Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S. *Curr. Med. Chem.* **2004**, *11*, 2799. (c) Maison, W. In *Highlights in Bioorganic Chemistry*; Schmuck, C., Wennemers, H., Eds.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2004; pp 18−29. (d) Patch, J. A.; Kirshenbaum, K.; Seurynck, S. L.; Zuckermann, R. N.; Barron, A. E. In *Pseudo-Peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2004; pp 1−31. (e) Martin-Martinez, M.; Patino-Molina, R.; Garcia-Lopez, M. T.; Gozalez-Muniz, R. *Mini-Rev. Med. Chem.* **2004**, *4*, 229. (f) Davies, J. S. *Amino Acids, Pept., Proteins* **2003**, *34*, 149.

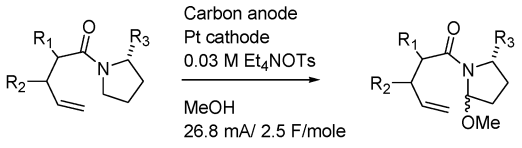
(2) For reviews concerning the use of lactam based peptidomimetics see: (a) Cluzeau, J.; Lubell, W. D. *Biopolymers* **2005**, *80*, 98. (b) I-lalab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers* **2000**, *55*, 101. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **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.

(3) For selected examples see: (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.

(4) For examples using electrochemistry as a tool to functionalize amino acids see: (a) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113 and references 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. *Methods Mol. Med.* **1999**, *23* (Peptidomimetic Protocols), 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.

(5) For a review of diversity-oriented libraries see: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. In addition see: (b) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T. Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740. (c) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312.

Scheme 1



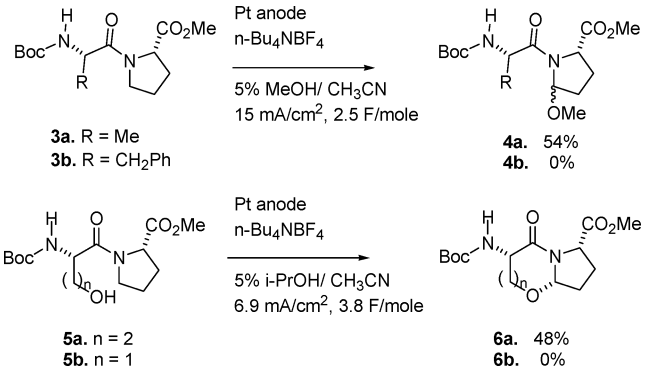
1a. $R_1 = R_2 = H$, $R_3 = CO_2Me$
1b. $R_1 = OBn$, $R_2 = H$, $R_3 = CO_2Me$
1c. $R_1 = H$, $R_2 = Ph$, $R_3 = CH_2OBn$
1d. $R_1 = OBn$, $R_2 = Ph$, $R_3 = CH_2OBn$

2a. 68%
2b. 0%
2c. 60% (34% recovered SM)
2d. 0%

electrodes so that the subsequent behavior of the molecules can be monitored in "real time"?[6−9] Finding answers to these questions motivated our interest in the oxidation of peptide analogues containing electroauxiliaries.[10,11] Yoshida and coworkers have defined electroauxiliaries as groups that aid in either the oxidation or the reduction of a molecule by lowering its oxidation or reduction potential.

For a number of years we have been interested in oxidative routes to the construction of constrained peptidomimetics.[4a−g,12] The key to this work was the use of an amide oxidation reaction that allowed for the selective functionalization of an amino acid derivative. The functionalized amino acid derivative was used to complete a cyclization reaction that introduced a conformational constraint. In this way, the syntheses took advantage of the initial chiral centers in the original amino acids. The work culminated in the synthesis of a variety of constrained peptidomimetics. Unfortunately, while the reaction proved very successful in terms of functionalizing simple amino acid derivatives, it had major limitations when it came to oxidizing more complicated systems. These problems arose because the oxidation potential of an amide is very high and on the order of $E_{P1/2} = +1.95$ to $+2.10$ V vs Ag/AgCl. Hence, the success of reactions with substrates having additional inductively electron-withdrawing groups present is highly dependent on the nature of the substrate. For example, consider the oxidations illustrated in Scheme 1. While the oxidation of simple proline derivatives proceeded in good yields,[12] oxidations with inductively electron-withdrawing groups at position R_1 were problematic. When R_1 was a benzyl ether (**1b** and **1d**), the reactions failed to yield any methoxylated product. The starting material was recovered from these reactions, and it appeared that the

Scheme 2



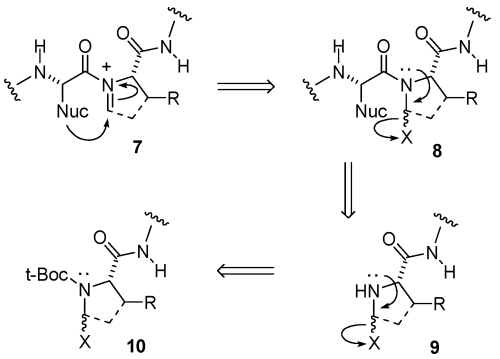
3a. R = Me
3b. R = CH_2Ph

4a. 54%
4b. 0%

5a. n = 2
5b. n = 1

6a. 48%
6b. 0%

Scheme 3



oxidation potential of the substrate was raised to a point where background oxidation of the solvent interfered with its oxidation.

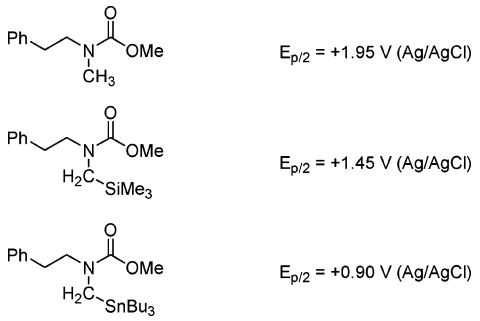
Related reactions with substrates having a less inductively electron-withdrawing nitrogen group in position R_1 were possible, but these reactions were very sensitive to the nature of the amino acid side chain used (Scheme 2). For example, the anodic oxidation of substrate **3a** led to a 56% isolated yield of product. However, even the addition of a remote phenyl ring (substrate **3b**) stopped the reaction.[4b−d] In a similar fashion, the anodic oxidation of **5a** led to a 48% yield of the functionalized product, while the anodic oxidation of **5b** led to none of the desired product.[4e−g] Instead, the reaction of **5b** led to oxidation of the serine moiety followed by a subsequent loss of formaldehyde.

Because of these limitations, it was clear that the initial oxidation had to be accomplished before the dipeptide was synthesized. However, for many peptidomimetics this approach is also problematic. As an example, consider the general reaction plan outlined in Scheme 3. If the monoamino acid substrate **10** was functionalized in typical fashion (X = OMe, OAc, etc.), then an elimination of the X group would be expected following deprotection to form the amine **9** required for making dipeptide **8**. In fact, any group that would serve as a good leaving group for the conversion of an amide into the *N*-acyliminium ion **7** would leave faster from amine **9** than **8**. What was needed was an X group that could serve as a protecting group for the *N*-acyliminium ion but was not a leaving group.

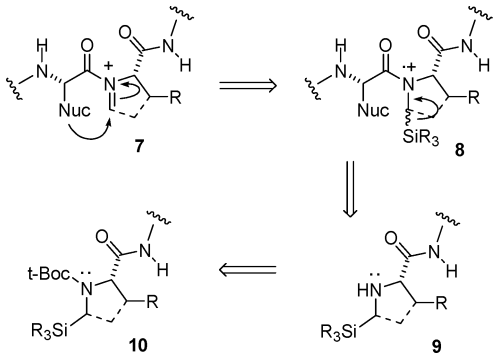
It was with this in mind that we first became interested in the very intriguing electroauxiliary chemistry being developed by the Yoshida group.[10,11c−e] In these efforts, the Yoshida group reported that placing a silyl group on the carbon α to an amide nitrogen lowered the oxidation potential of the nitrogen by approximately 1/2 V (Scheme 4). A corresponding stannyl group

(6) For the use of Pd(0) catalysts on an addressable electrode microarray see: Tian, J.; Maurer, K.; Tesfu, E.; Moeller, K. D. *J. Am. Chem. Soc.* **2005**, *127*, 1392.
(7) For the use of Pd(II) on an addressable electrode microarray see: (a) Tesfu, E.; Maurer, K.; Ragsdale, S. R.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 6212. (b) Tesfu, E.; Maurer, K.; Moeller, K. D. *J. Am. Chem. Soc.* **2006**, *128*, 70.
(8) For the lead patent on DNA-related work involving addressable electrode microarrays see: Montgomery, D. D. PCT Int. Appl. WO 9801221, 1998, 91 pp; CODEN: PIXXD2 WO 9801221 Al 19980115.
(9) For peptide-based libraries on addressable electrode microarrays see: Rossi, F. M.; Montgomery, D. D. PCT Int. Appl. WO 0053625, 2000, 52 pp; CODEN: PIXXD2 WO 0053625 A2 20000914. For recent work see: Oleinikov, A. V.; Gray, M. D.; Zhao, J.; Montgomery, D. D.; Ghindilis, A. L.; Dill, K. J. *Proteome Res.* **2003**, *2*, 313.
(10) (a) Yoshida J.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 6621. (b) For a review see: Yoshida, J. *Top. Curr. Chem.* **1994**, *170*, 39. (c) Yoshida, J.; Wtanabe, M.; Toshioka, H.; Imagawa, M.; Suga, S. In *Novel Trends in Electroorganic Synthesis*; Torii, S., Ed.; Springer: Tokyo, 1998; p 99. (d) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589.
(11) For several recent applications see: (a) Kamada, T.; Oku, A. *J. Chem. Soc., Perkin Trans 1* **1998**, 3381. (b) Cao, Y.; Hidaka, A.; Tajima, T.; Fuchigami, T. *J. Org. Chem.* **2005**, *70*, 9614. (c) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (d) Yoshida, J.; Suga, S.; Fuke, K.; Watanabe, M. *Chem. Lett.* **1999**, 251. (e) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755.
(12) In addition to ref 4a−g see: Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 10106.

Scheme 4



Scheme 5

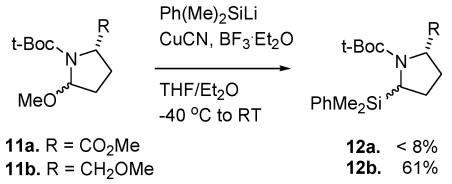


lowered the oxidation potential of the amide by almost 1 V. Hence, if a silyl group were placed into a peptide, it would lower the oxidation potential of the neighboring amide by 1/2 V relative to that of the rest of the peptide backbone. Since in a constant-current electrolysis the oxidation potential at the anode climbs to a point matching the functional group in solution with the lowest oxidation potential and then remains there for the bulk of the experiment, even a simple electrolysis reaction would chemoselectively oxidize the silylated amino acid. Furthermore, the oxidation of such a group reverses the polarity of *N*-acyliminium ion formation. In normal circumstances, *N*-acyliminium ions are generated by having the lone pair on the nitrogen of an amide "drive out" a leaving group (Scheme 3). However, in the Yoshida chemistry oxidation of the amide lone pair leads to a radical cation that then induces elimination of the silyl group (Scheme 5). The carbon−silicon bond serves to *donate* electron density to the system. For this reason, it was easy to imagine functionalizing a monoamino acid with a silyl substituent and then carrying the group through the deprotection and coupling steps needed to build a peptide (Scheme 5). Since the silyl group is not a leaving group, no elimination from **9** would be possible. But can a silyl electroauxiliary really be used to introduce *N*-acyliminium ions into a peptide?

Initial Experiments

Because of a long-standing interest in bicyclic peptidomimetics, efforts to answer this question began with the development of a route for annulating rings onto proline derivatives. To this end, we sought to substitute the 5-position of a proline by taking advantage of the anodic oxidation−cuprate addition sequence used to build other 5-substituted proline derivatives.[4a−d] However, despite the success of the earlier cuprate additions to *N*-acyliminium ions and the success of reactions adding silyl-based cuprate reagents[13] to enones, the addition of a silyl cuprate to a methoxylated proline derivative (**11a**)[4a] led to only minor

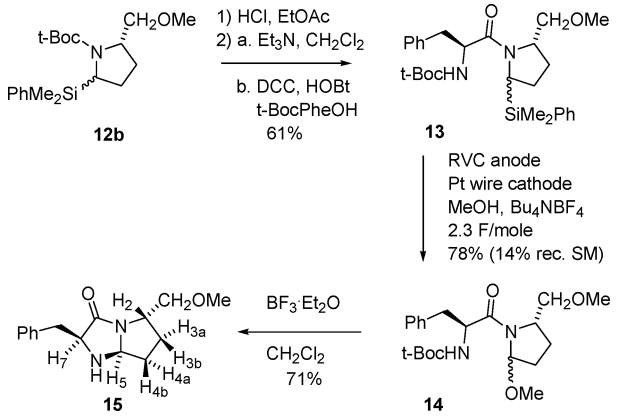
Scheme 6



11a. R = CO_2Me
11b. R = CH_2OMe

12a. < 8%
12b. 61%

Scheme 7



12b **13** **15** **14**

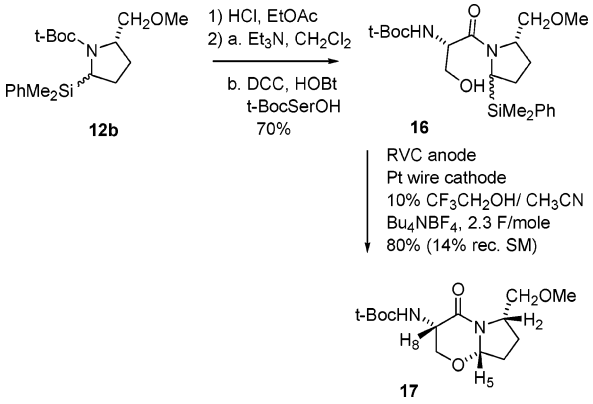
amounts of product (Scheme 6). NMR analysis of the crude reaction mixture indicated that the silyl cuprate underwent addition reactions to the methyl ester of **11a**. This suspicion was confirmed when the silyl cuprate proved compatible with addition to a proline derivative lacking the methyl ester functionality (Scheme 6, **11b**).[14,15]

While this second reaction did not solve the problems associated with synthesizing a silylamino acid with all of the functionality required for peptide synthesis, it did enable a first look at the use of an electroauxiliary in a dipeptide analogue (Scheme 7). The first example selected (**13**, Scheme 7) was chosen because of the difficulties it presented for the earlier oxidation (Scheme 2). The substrate **13** was synthesized by deprotection of product **12b** followed by a standard peptide coupling reaction. A constant-current (21 mA, 2.3 faradays/mol) oxidation of the substrate at a carbon anode using an undivided cell, methanol solvent, tetrabutylammonium tetrafluoroborate as the electrolyte, and a Pt wire counter electrode led to a 78% yield of product along with 14% recovered starting material. The initial methoxylated product was readily converted into a bicyclic peptidomimetic in a 71% yield. The stereochemistry of the bicyclic product was determined using an NOESY experiment that showed cross-peaks for H_7 and H_5, H_5 and H_{3a}, and H_2 and H_{4b}. These longer range interactions combined with the interaction integrals obtained for vicinal protons (H_5, H_{4a} > H_5, H_{4b}, for example) made the assignment straightforward. In addition to the two-step process illustrated, the bicyclic product could be formed directly in the oxidation reaction, albeit in low (20%) yield. Clearly, the presence of the electroauxiliary did have the desired effect and allowed for selective oxidation of the dipeptide analogue.

The influence of the electroauxiliary was also prevalent in the oxidation of substrate **16**. In this case, the oxidation reaction

(13) (a) For a review see: Fleming, I. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, U.K., 1994; pp 257−292. (b) See also: Lee, T. W.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3337.
(14) Sun, H. Ph.D. Thesis, Washington University, St. Louis, July 2003.
(15) For a similar observation see: Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905.

Scheme 8



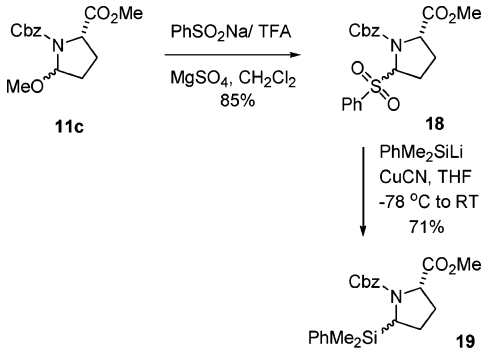
could be used to directly afford the desired bicyclic product (Scheme 8). The oxidation was conducted in 10% trifluoroethanol in acetonitrile to avoid solvent trapping of the *N*-acyliminium ion intermediate. An 80% isolated yield of product **17** was obtained along with 14% recovered starting material. No observation of serine oxidation or the elimination of formaldehyde from the substrate was observed. The relative stereochemistry of **17** was determined with the use of a NOESY experiment that showed cross-peaks for H_8 and H_5 as well as H_5 and H_2. The stereochemistry of the reaction was consistent with that obtained for earlier seven-membered ring cyclizations.[12g] In this case, the *cis* stereochemistry about the five-membered ring can be rationalized using a transition state for the six-membered ring cyclization having the protected N-terminus in a pseudoequatorial position.

Changing the Synthesis. Dipeptide Mimetics

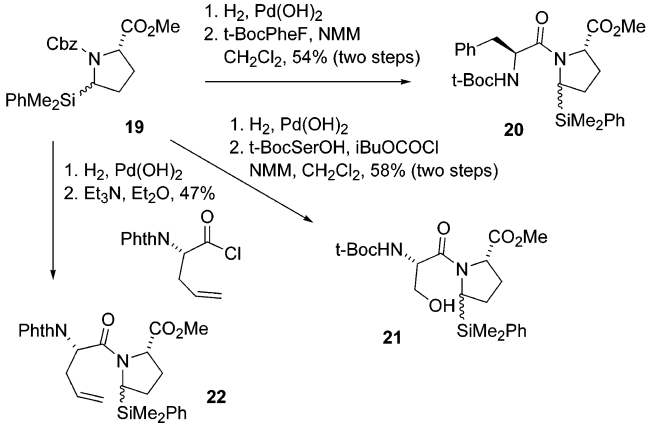
Having shown that an electroauxiliary can dramatically improve the selectivity of a dipeptide oxidation, attention was turned toward synthesizing a 5-silyl-substituted proline derivative having the correct oxidation state at the C-terminus. Since an *N*-acyliminium ion should be more reactive toward a cuprate reagent than a methyl ester, it appeared that in the attempted cuprate addition to the methyl ester **11a** (Scheme 6) there must not have been a high enough concentration of the *N*-acyliminium ion. For this reason, it was decided that the methoxy group in **11c** should be exchanged for a better leaving group. To this end, methoxylated proline **11c** was treated with sodium phenylsulfinate in the presence of TFA and magnesium sulfate in dichloromethane solvent to afford an 85% isolated yield of the 5-phenylsulfonyl-substituted proline **18** (Scheme 9).[16] Treatment of **18** with the silyl cuprate led to a 71% isolated yield of the desired 5-silyl-substituted proline **19**. Interestingly, this reaction generated the product even in the absence of additional Lewis acid. Either the copper in the reaction served as a strong enough Lewis acid to trigger formation of a transient *N*-acyliminium ion or the reaction proceeded through an S_N2 mechanism.

Once the silylated proline derivative was obtained, it was deprotected and coupled to a second amino acid to make the substrates for the electrochemical studies (Scheme 10). In each case, the coupling reaction required stronger conditions than the corresponding proline coupling reactions, most likely due to the steric bulk of the silyl group. The coupling reactions were

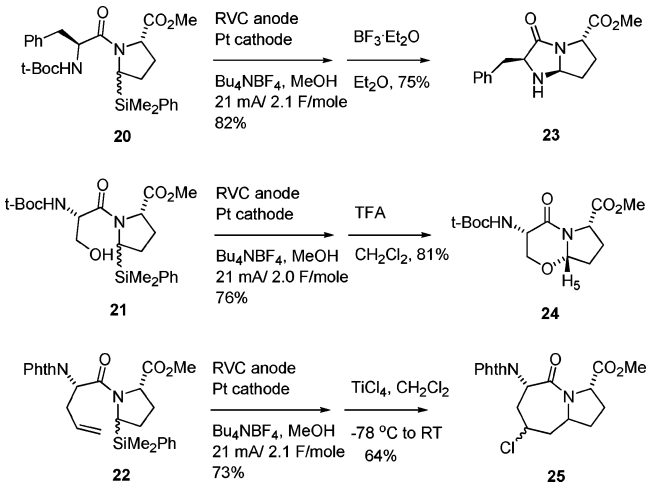
Scheme 9



Scheme 10



Scheme 11

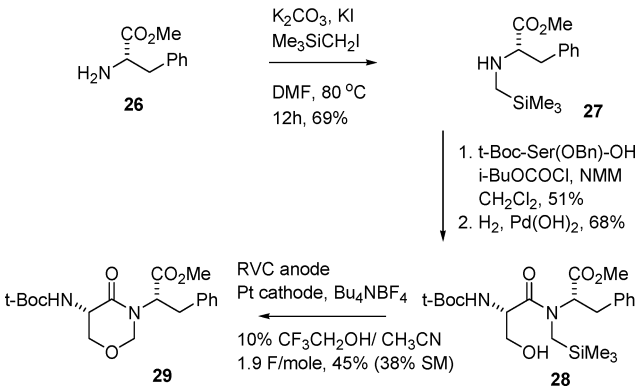


not optimized since it was not clear that the dimethylphenylsilyl group would be the best electroauxiliary.

With the substrates in hand, the electrochemical studies were undertaken (Scheme 11). In each case, both the electrolysis reaction and the cyclization proceeded as before. Several aspects of the electrolysis reaction deserve further comment. First, the electrolyses proceeded better when pure methanol was used as solvent and cosolvents were avoided. Second, the yields of the reaction were approximately 10−25% higher when Bu_4NBF_4 was used as the electrolyte instead of Et_4NOTs. While the reason for this increase in yield is not clear, it is tempting to suggest that a small amount of fluoride ion is in equilibrium with the Bu_4NBF_4 electrolyte and helps to cleave the electroauxiliary from the radical cation intermediate formed at the anode. The

(16) For the previous use of a phenylsulfonyl leaving group for *N*-acyliminium ion formation see: Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.

Scheme 12



use of a tetrafluoroborate electrolyte has led to the addition of fluoride to electrochemically generated electrophiles.[17] Third, the use of a reticulated vitreous carbon (RVC) electrode afforded cleaner products than did a simple carbon rod anode. Finally, the reactions were stopped when 2.1−2.3 faradays/mol of charge had been passed to reduce the risk of oxidizing the methoxylated proline product. For this reason, a small amount of starting material was recovered.

Of course, the cyclization reactions in this case did run the risk of epimerization, and minor amounts of the epimerized product were obtained in each case. Fortunately, the amount of this material could be minimized by carefully controlling the concentration of the Lewis acid used in the reaction. As in the earlier model studies, the stereochemistry of the bicyclic products was assigned by NOESY spectroscopy.

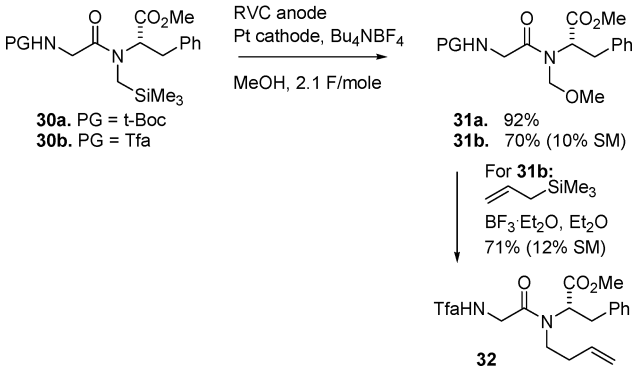
Acyclic Amino Acids. Moncyclic Peptidomimetics

The use of the silyl electroauxiliary was not limited to the use of proline derivatives (Scheme 12). The synthesis of the substrate involved a simple alkylation of the monoamino acid starting material followed by coupling to a second peptide. Once available, silylated dipeptide **28** was oxidized at a carbon anode using the reaction conditions described above. The oxidation of **28** led to both formation of an acyclic *N*-acyliminium ion intermediate and the subsequent cyclization. A 45% yield of the product was obtained along with a 38% yield of the recovered starting material. The reaction was allowed to proceed until 1.9 faradays/mol of charge was passed and then stopped to avoid the formation of unwanted side products.

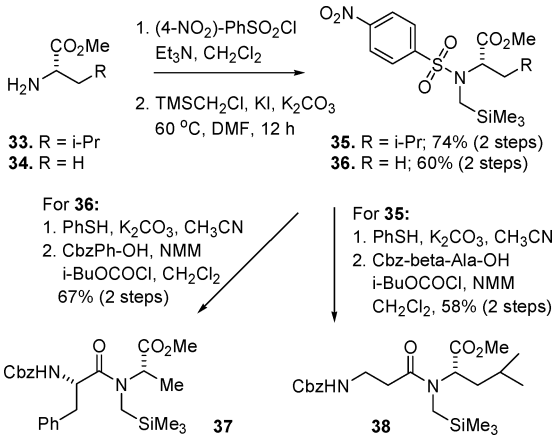
The moderate yield obtained for the oxidation−cyclization reaction illustrated in Scheme 12 was not a result of the oxidation step. For example, the anodic oxidation of dipeptide **30a** led to a 92% yield of the methoxylated product (Scheme 13). The methoxylated product could be used to add nucleophiles to the peptide, as illustrated for the addition of an allyl group to the substrate having a trifluoroacetate-protected N-terminus. The change in protecting group for this reaction was made because the *t*-Boc group was not stable to the alkylation conditions. All of these initial studies used a silylated phenylalanine as the initial amino acid. This was done because the unprotected phenylalanine could be successfully alkylated with (iodomethyl)trialkylsilane derivatives to directly add the electroauxiliary. Unfortunately, this alkylation reaction was not compatible with the use of other amino acid starting materials.

(17) Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434.

Scheme 13



Scheme 14



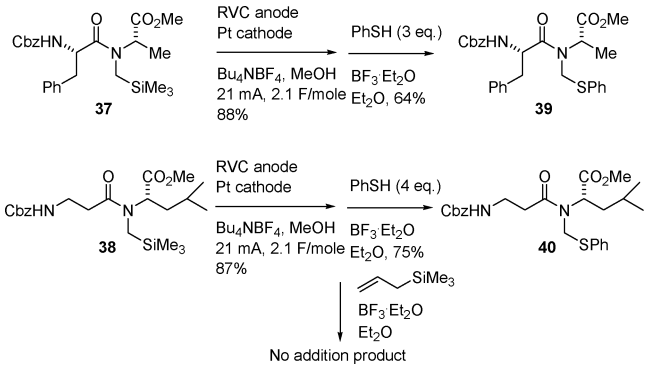
For example, the reaction between the glycine methyl ester and (iodomethyl)trimethylsilane led to the formation of no product. Instead, only the unalkylated starting material was obtained. The use of the *t*-Boc-protected glycine methyl ester led to a complex mixture of products. It appeared that the (iodomethyl)trimethylsilane was not an effective enough electrophile. The result was a need for harsh reaction conditions that led to decomposition of the protected amino acid starting material.

At this point, it was clear that a change in strategy was needed, and the alkylation procedure developed by Fukuyama was adopted (Scheme 14).[18] To this end, the 2-nitrophenylsulfonamide was synthesized, treated with base, and then alkylated with the (trimethylsilyl)methyl iodide. The sulfonamide was then cleaved with the use of phenylthiolate and a nucleophilic aromatic substitution reaction to afford the desired amino acid derivative. Once the amino acid was available, it could be carried forward in a fashion identical to that described previously.

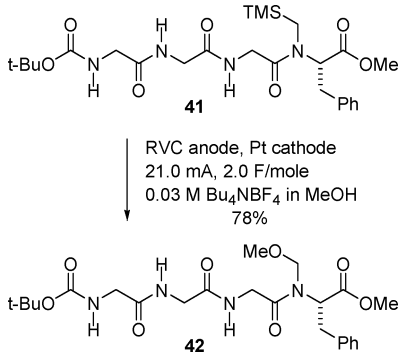
As illustrated in Scheme 15, both of the substrates synthesized smoothly underwent the oxidation to form good yields of methoxylated products that could be carried forward in subsequent alkylation reactions. As a side note, the oxidation of **37** was also carried out using a 6 V lantern battery as a power supply.[19] Using this very simple setup, a 74% yield of the oxidized product was obtained along with 14% recovered starting material. The methoxylated product from the oxidation was then treated with a Lewis acid in the presence of a trapping

(18) (a) Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *46*, 15787.
(19) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317. The reaction was monitored by TLC for the disappearance of substrate.

Scheme 15



Scheme 16



nucleophile. In most cases, the reactions proceeded in a fashion directly analogous to that of earlier studies. Interestingly, however, reactions using a b-N-terminal amino acid (**38**) turned out to be dependent on the nature of the trapping nucleophile. When a thiol nucleophile was used for the reaction, the yield of the addition product was high. However, only a small amount of product was obtained when a less reactive allylsilane nucleophile was used. The reaction led to multiple products, and it appeared that an intramolecular cyclization might be interfering with the desired intermolecular trap of the *N*-acyliminium ion. Intramolecular cyclization reactions typically did not interfere with the reactions when a normal amino acid was used. In these cases, the cyclization required a 5-*endo*-trig cyclization, a scenario that apparently slowed the cyclization to a point where it was not seen.

Having established the compatibility of the reactions with acyclic systems, we turned our attention toward demonstrating the compatibility of the reaction with longer peptide chains. This was accomplished by taking the (trimethylsilyl)methyl-substituted phenylalanine **27** synthesized earlier and converting it into tetrapeptide **41** using a standard *t*-Boc protecting group based strategy. The tetrapeptide was oxidized using exactly the same electrolysis conditions reported above to afford a 78% isolated yield of the methoxylated amide (Scheme 16).

Parallel Synthesis Approaches

The success of these first examples suggested that it might be possible to extend the anodic oxidation chemistry previously reported for making small libraries of amide derivatives to the synthesis of peptide derivatives.[20] In the previous work, Yudin and co-workers took advantage of a computer-controlled, automated platform that they had developed for running electrochemical reactions in a parallel fashion.[21] They oxidized

Scheme 17

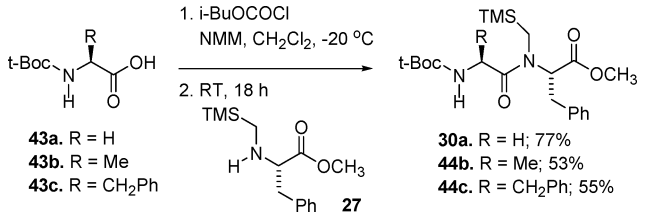
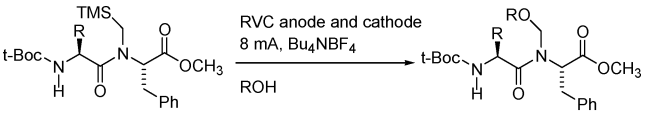


Table 1. Yields for the Parallel Electrolysis



30a. R = H; 77%
44b. R = Me; 53%
44c. R = CH_2Ph; 55%

cell	SM[a]	solvent	charge, faradays/mol	internal standard	HPLC yield, %	isolated yield, %
1	**30a**	MeOH	2.2	toluene	96	
2	**30a**	EtOH	2.2	toluene	95	
3	**30a**	PrOH	2.2	toluene	78	
4	**30a**	BuOH	2.2	n/a		48
5	**44b**	MeOH	2.2	benzene	97	88
6	**44b**	EtOH	2.2	toluene	95	
7	**44b**	PrOH	2.2	benzene	85	
8	**44b**	BuOH	1.6	n/a		52
9	**44c**	MeOH	2.2	benzene	101 (94)[b]	
10	**44c**	EtOH	2.2	toluene	96	
11	**44c**	PrOH	2.2	toluene	75	
12	**44c**	BuOH	2.2	n/a		34

[a] SM = starting material. [b] Assay of this product using benzene as an internal standard indicated an inflated yield due to overlap of the product and a small amount of recovered starting material. The yield given in parentheses accounts for the amount of starting material observed.

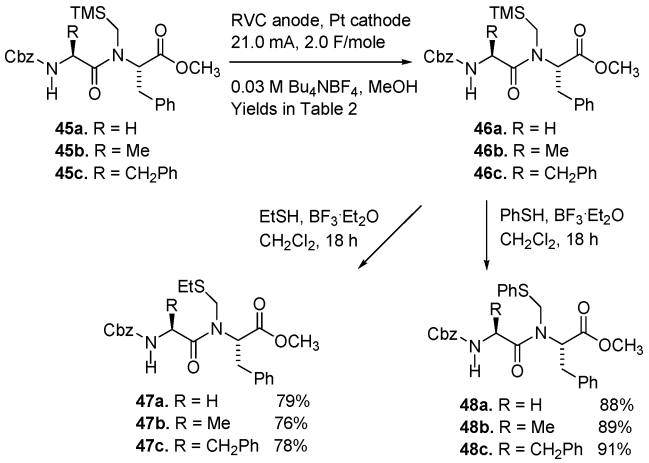
a series of amides to yield *N*-acyliminium ions that were in turn converted into nucleophilic substitution products.

With the use of electroauxiliaries to lower the oxidation potential of amino acid derivatives, it should be possible to functionalize peptides in a similar parallel fashion. To test the feasibility of this idea, a set of three peptide substrates was synthesized starting from the [(trimethylsilyl)methyl]phenylalanine derivative **27** (Scheme 17). Each one of the substrates was then added to four different reaction cells. Along with the substrate, to each reaction cell was added a tetra-*n*-butylammonium tetrafluoroborate in anhydrous alcohol solution. A different alcohol was used for each of the four vials containing any one of the three substrates (Table 1). Each electrolysis cell was then connected to an independent potentiostat that was part of a commercially available Arbin power supply. This allowed for the 12 electrolyses to be run independently in a parallel fashion. Accordingly, 8 mA of current was passed through each of the reactions until 2.2 faradays/mol of charge had been passed. The only exception was cell number 8. In this case, the resistance of the cell was great enough to exceed the voltage limit of the potentiostat. As a result, the current flow in this cell was only 6 mA and a total of 1.6 faradays/mol of charge was passed.

Yields for the reactions were determined by HPLC. The product from cell 5 was isolated and the yield compared with

(20) For the parallel synthesis of amide derivatives see: Siu, T.; Li, W.; Yudin, A. K. *J. Comb. Chem.* **2000**, *2*, 545.
(21) For a review see: (a) Yudin, A. K.; Siu, T. *Curr. Opin. Chem. Biol.* **2001**, *5*, 269. See also: (b) Yudin, A. K.; Siu, T.; Li, W. Patent WO 2001094666.

Scheme 18



that obtained by HPLC to make sure that a high HPLC yield corresponded to a high isolated yield. It was clear from this first pass that the reactions could be run in parallel. All of the reactions utilizing methanol or ethanol solvent proceeded in high yield under nearly identical conditions. The reactions utilizing propanol and butanol were less efficient, with the yield of the reaction dropping with each additional carbon. This effect on the reaction was also observed for single preparative reactions that utilized propanol or butanol solvent.

While the use of different solvents for the oxidation reaction did influence the outcome of this first "proof of principle" experiment, the observation has no long-term implications for the use of the strategy to make substituted peptide derivatives. Building a library of peptide derivatives involves an oxidation step to convert the substrates into *N*-acyliminium ions for use as cation pools[22] or alkoxyalkyl amides for use in subsequent alkylation reactions. In either case, the diversification step for each substrate involves the subsequent alkylation reaction. Hence, even for cases where an alkoxylalkyl amide intermediate is needed the best solvent can be used for the oxidation.

Series Synthesis Approaches

This concept was illustrated by taking three silylated peptide derivatives and converting them into six different thiol-derivatized dipeptides (Scheme 18). Two changes were made to the strategy described above. First, the reactions utilized a Cbz-protected dipeptide to prevent deprotection of the N-terminal end during the acid-catalyzed substitution reaction. Second, we wanted a method for conducting multiple oxidations without the need for specialized equipment. While the computer-driven multichannel power supply used for the parallel electrochemical reactions above is commercially available, it is not common. Hence, the number of groups that can readily make use of the chemistry being developed is limited.

In principle, a parallel approach for running the multiple oxidations described above is not needed. The oxidation involves an electroauxiliary that is the same for each substrate. In the absence of a competing oxidation, all of the electroauxiliary-substituted substrates should undergo identical oxidation reactions. In addition, each individual oxidation reaction is matched by a reduction reaction at the counter electrode. Hence, one should be able to wire the oxidations in a series format where the cathode of one cell is wired to the anode of the next cell (see the Supporting Information for details). In this way, the electrons removed during the oxidation in one reaction would be used to conduct the reduction reaction at the counter electrode in a second electrolysis cell. The electrons removed during the anodic oxidation in the second cell would then be used for the reduction at the counter electrode in a third electrolysis cell, and so on. Hence, a single power supply could be used to run multiple reactions at the same time. Keeping in mind that amide oxidations can be conducted with a battery as the power supply,[19] such a setup would make the rapid functionalization of a series of peptides available to anyone.

(22) For a review see: (a) Yoshida, J.; Suga, S. *Chem.—Eur. J.* **2002**, *8*, 2650. For recent examples see reference 11e and references therein.

Table 2. Yields for the Series Electrolysis

cell	SM[a]	product	conversion, %	yield, %
1	**45a**	**46a**	84	79
2	**45a**	**46a**	85	74
3	**45b**	**46b**	>99	90
4	**45b**	**46b**	83	77
5	**45c**	**46c**	>99	91
6	**45c**	**46c**	92	82

[a] SM = starting material.

To test the feasibility of this idea, the three starting materials illustrated in Scheme 20 were each placed into two electrochemical reaction cells. All of the reactions were then wired to a single potentiostat of the Arbin power supply using a series format. A constant current of 8 mA was then applied to the circuit until 2.6 faradays/mol of charge had been passed through the reaction cells (Table 2). The proton NMR spectrum for each reaction showed only the desired product along with residual starting material.

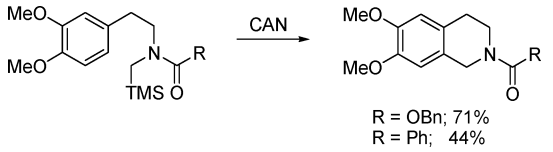
While the reactions were not identical, all of the reactions proceeded very well and the variations observed were within the normal range observed for preparative amide oxidation reactions performed with such a crude reaction setup. In such reactions, it is easy to maintain consistency with respect to solvents, reagents, and concentrations. However, it is not easy to maintain the exact electrode size and surface area. This leads to variations in the current density, a change that can alter the efficiency of the electron-transfer reaction and hence the percent conversion of the reaction. Nevertheless, the high yield of product obtained in each of the reactions indicates that the use of a series electrolysis can be employed to generate a number of *N*-acyliminium ion precursors in a rapid fashion.

As mentioned in the previous section, the real opportunity for diversification of the molecules occurs not in the oxidation step, but rather in the subsequent alkylation. For example, each of the products obtained from the series experiment above was divided into two separate flasks, diluted with dichloromethane, and then treated with BF_3/Et_2O and a thiol. In one flask, thiol phenol was used, and in the other, ethanethiol was used. All other reaction conditions were identical (Scheme 18). In each case, the reaction led to a high yield of product. Clearly, such an approach can be readily expanded by increasing the number of nucleophiles used to make a variety of thiol-substituted dipeptide derivatives.

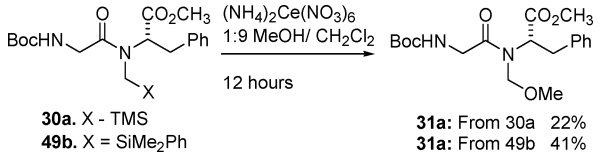
Chemical Oxidation. New Electroauxiliaries

While the electrochemical oxidations work very well and have many advantages, two main factors motivated a move toward

Scheme 19



Scheme 20



also studying chemical oxidation strategies for generating *N*-acyliminium ions. First, the synthesis and purification of peptide libraries is greatly aided by the use of solid-phase synthesis techniques. Such techniques are not readily compatible with electrochemical approaches because they would involve both a solid-phase substrate and a solid-phase reagent (the electrode). A solution-phase chemical oxidant would have no such problem. Second, our interest in building molecular libraries on chips containing arrays of addressable microelectrodes meant that a chemical oxidation route was also needed. Electrode-microarray-based syntheses require the use of a chemical reagent that is recycled at the electrode surface.[6−9]

Routes to *N*-acyliminium ion precursors that capitalize on the chemical oxidation of amides are typically limited in scope because of a lack of selectivity between oxidation of the substrate and oxidation of the product generated. For example, the difference in oxidation potential between an amide and its methoxylated product is only about 150 mV. If a chemical oxidant is found that oxidizes a particular substrate but not the product, then the addition of an electron-withdrawing group to the substrate will stop the oxidation. The addition of an electron-donating group will lead to overoxidation of the product. Electrochemical oxidations do not suffer from this problem because the potential at the electrode surface adjusts to the potential of the substrate. The use of an electroauxiliary on the carbon α to the amide nitrogen also has the potential to solve this problem since the electroauxiliary dramatically lowers the oxidation potential of the starting material but is then eliminated during product formation.

Mariano and co-workers demonstrated that such reactions were feasible (Scheme 19).[23] They studied the chemical oxidation of trimethylsilyl (TMS)-substituted amides and used the subsequent *N*-acyliminium ions in the synthesis of alkaloid ring skeletons. While these reactions were successful, the yields of the oxidations were sensitive to the nature of the substrate. The examples presented in the original paper vary in yield from 25% to 86%. This variation in yield suggests that the oxidation potential of the substrate lies very close to that of the chemical oxidant. Would a similar strategy be effective for oxidizing a dipeptide substrate with an even higher oxidation potential?

Initial studies with dipeptide substrates and ceric ammonium nitrate (CAN) as the chemical oxidant confirmed that dipeptide

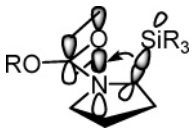
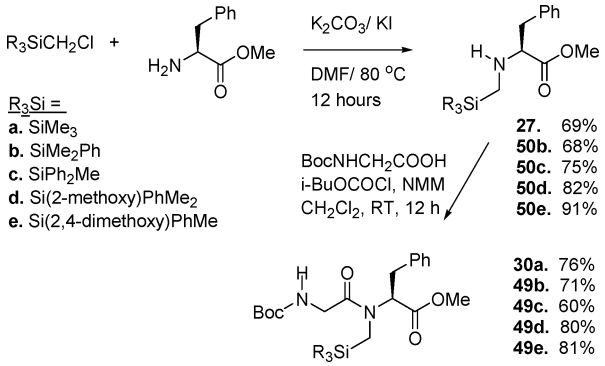


Figure 1.

Scheme 21



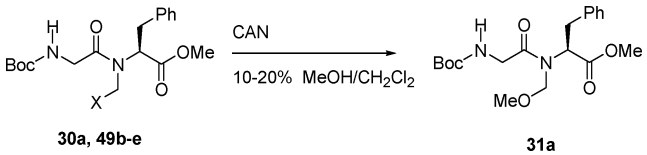
oxidations would indeed be more difficult. For example, the chemical oxidation of the TMS-substituted dipeptide **49a** led to only a 22% isolated yield of the methoxylated product (Scheme 20). The yield could be raised to 41% with the use of a dimethylphenylsilyl electroauxiliary (**49b**), an observation that first suggested that the yield of the chemical reaction was dependent on the nature of the electroauxiliary. As with the earlier Mariano example, the variation in yield based on structure suggested that the low yields might be due to the oxidation potential of the substrate being too close to that of the chemical oxidant. The low yield of the reaction was not a result of the substrate not being able to undergo the reaction. The electrochemical oxidation, which adjusts to the oxidation potential of **30a**, led to a 92% isolated yield of product.

Since using a stronger chemical oxidant would mean greater limitations on the number of functional groups compatible with the oxidation reaction, attention was turned toward lowering the oxidation potential of the substrate with a more effective electroauxiliary. Electroauxiliaries that aid oxidation reactions are thought to work by donating electron density to the neighboring functional group. In the case of a silyl-substituted amide, this means electron density from the C−Si bond is donated to the neighboring π-system, thereby raising the energy of the amide lone pair and decreasing its oxidation potential (Figure 1).[10c] If this were the case, then increasing the electron-donating ability of groups on the silicon would increase the ability of the electroauxiliary to donate electrons and further lower the oxidation potential of the functional group as a whole. This was at least the first explanation for why the oxidation of **49b** led to a higher yield of product than the oxidation of **30a**. With this in mind, a trio of new substrates was prepared using the same chemistry used to synthesize **30a** and **49b** (Scheme 21). While the strategy to lower the oxidation potential of the substrate seemed obvious, it should be noted that the simple addition of alkoxy substituents to the aryl ring on the silicon was worrisome on the basis of earlier synthetic efforts to capitalize on the fragmentation of radical cation intermediates in systems lacking the silyl group.[24] In these experiments,

(23) (a) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (b) Kim, H.-J.; Yoon, U.-C.; Jung, Y.-S.; Park, N. S.; Cederstrom, E. M.; Mariano, P. S. J. *Org. Chem.* **1998**, *63*, 860.

(24) Wang, L.; Seiders, J. R., II.; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596.

Table 3. Chemical Oxidation



30a, 49b-e **31a**

	X	$E_{p/2}$,[a] V	time	temp, °C	yield, %
30a	Me_3Si	+1.63	12 h	25	22[b]
30a	Me_3Si	+1.63	30 min	0	0
49b	$PhMe_2Si$	+1.67	12 h	25	41[c]
49c	Ph_2MeSi		12 h	25	0[d]
49d	(2-MeOPh)Me_2Si	+1.64	30 min	25	87
49d	(2-MeOPh)Me_2Si	+1.64	90 min	−40	0[d]
49e	(2,4-dimethoxyphenyl)Me_2Si	+1.38	15 min	25	80
49e	(2,4-dimethoxyphenyl)Me_2Si	+1.38	35 min	0	82
49e	(2,4-dimethoxyphenyl)Me_2Si	+1.38	90 min	−40	86

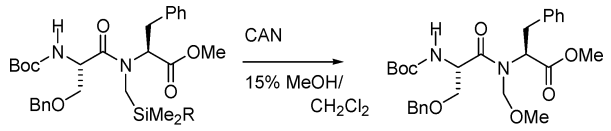
[a] Measured by cyclic voltammetry using a silver/silver chloride reference electrode, a tetrabutylammonium perchlorate in acetonitrile electrolyte solution, and Pt electrodes. [b] The preparative electrolysis of this substrate led to a 92% yield of **44**. [c] The product was isolated along with 15% recovered starting material. [d] No reaction was observed for this substrate using the conditions indicated.

Floreancig and co-workers synthesized both oxonium and iminium ions by oxidizing and fragmenting amines and ethers having β-aromatic rings. They found that when the oxidation potential of the aromatic ring was lowered by adding an oxygen substituent, the fragmentation step failed. This problem was nicely resolved by adding a second aryl substituent to the carbon β to the heteroatom, an observation that led us to design substrate **49c**. But would the silyl-substituted cases behave the same as the all-carbon systems?

To address this question, the substrates were oxidized using CAN (Table 3). For comparison purposes, the first two entries in the table include the data from Scheme 20. The first observation made was that the addition of a second phenyl ring to the electroauxiliary (**49c)** did not improve the oxidation. However, in contrast to the all-carbon systems the addition of an alkoxy group to the aromatic ring on the silyl electroauxiliary (**49d)** did improve the oxidation reaction. After 30 min at room temperature, the oxidation of **49d** led to an 87% yield of the desired methoxylated compound. For comparison, oxidation of the TMS substrate **30a** did not afford any product under these conditions. Interestingly, the cyclic voltammogram of the methoxylated substrate **49d** suggested that the initial mechanistic premise was not correct. It was thought that the use of a more electron-rich aryl ring on the electroauxiliary would decrease the oxidation potential of the substrate and lead to a higher yield of product. While the yield of the reaction did improve, there was no perceptible change in the oxidation potential of the substrate. The addition of the methoxy group must have influenced the second step of the reaction. In other words, since the more electron-rich electroauxiliary did not influence the oxidation step, it must have accelerated the subsequent elimination reaction. This conclusion was consistent with the second step (elimination of the silyl group from the initial radical cation) being the rate-limiting step.

The addition of a second methoxy group to the phenyl ring on the electroauxiliary (**49e)** improved the reaction even further. In this case, the room temperature oxidation led to an 80% yield of product after only 15 min. The reaction temperature could be lowered to −40 °C, although it took 90 min to reach

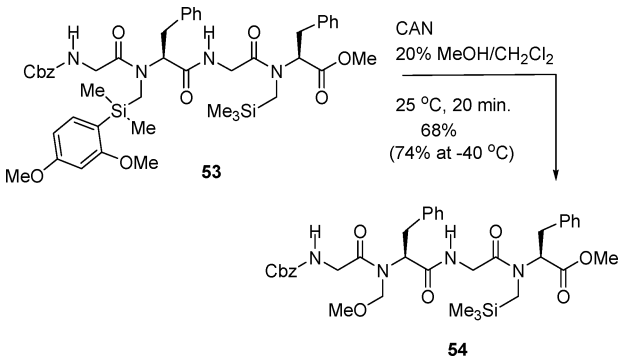
Scheme 22



51a. R = Me
51b. R = 2-methoxyphenyl
51c. R = 2,4-dimethoxyphenyl

52. From **51a** at RT: 45%
From **51b** at RT: 72%
From **51c** at RT: 70%
From **51c** at 0°C: 80%

Scheme 23



53 **54**

completion at this lower temperature. For comparison, no product was obtained at −40 °C when the monomethyoxyphenyl-substituted electroauxiliary **49d** was used. Once again, a cyclic voltammogram of the substrate was informative. While all of the other silylated amino acid starting materials led to roughly the same oxidation potential irrespective of the substituents on the silyl group, the oxidation potential measured for **49e** was over 0.25 V lower. This shift in potential was consistent with a shift in mechanism from oxidation of the amide to oxidation of the aryl ring on the silicon. Fortunately, this change did not alter the outcome of the reaction. Instead, the oxidation reaction served to reverse the polarity of the silyl group, turning it from an electron-donating moiety into a leaving group.

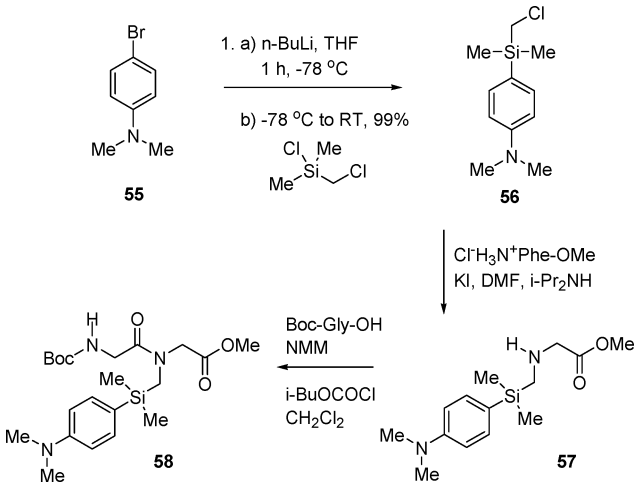
The effectiveness of the dimethoxyphenyl-substituted silyl electroauxiliary was also observed with a second substrate containing a masked nucleophile on the N-terminal amino acid (Scheme 22). In this case, the dimethoxyphenyl- and the monomethoxyphenyl-substituted silyl groups were equally effective at facilitating the room temperature oxidation. A slightly higher yield of product could be obtained by conducting the oxidation utilizing the dimethoxyphenyl-substituted electroauxiliary at a lower temperature. For comparison, the oxidation of **51a** with CAN at the lower temperature led to less than 15% methoxylated product.

The difference in potential measured for substrate **49e** suggested that it might be possible to differentiate two electroauxiliaries in the same molecule.[25] With this in mind, substrate **53** was synthesized using the alkylation and coupling procedures described above (Scheme 23).

Once synthesized, the substrate was oxidized at room temperature using CAN to afford a 68% isolated yield of the methoxylated product having the TMS electroauxiliary intact. Lowering the temperature to a point where it was known that oxidation of a TMS-functionalized amino acid would be even

(25) Yoshida, J.-i.; Watanabe, M.; Toshioka, H.; Imagawa, M.; Suga, S. *J. Electroanal. Chem.* **2001**, *507* (1−2), 55−65.

Scheme 24



slower raised the yield of the product **54** to 74%. Clearly, selective functionalization reactions were possible.

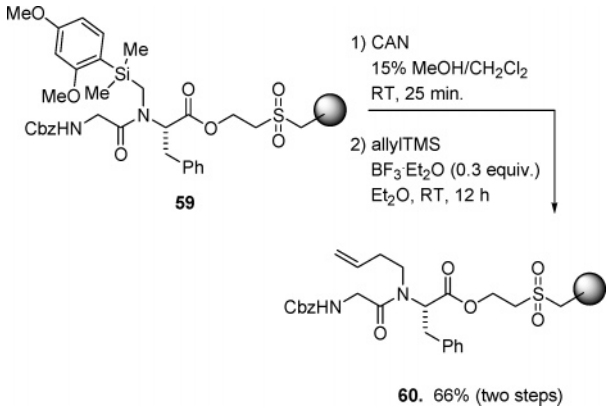
The shift in mechanism for the oxidation of substrate **49e** also suggested that formation of an *N*-acyliminium ion might occur at an even lower potential if an amine substituent was added to the aryl ring on the electroauxiliary. To test this idea, substrate **58** was synthesized (Scheme 24).[26] The synthesis was straightforward but needed to be done with care to avoid protodesilylation reactions. Cyclic voltammetry indicated that the presence of the amine on the aryl ring did have the desired effect on the oxidation potential of the substrate. The $E_{p/2}$ value measured for substrate **58** was +0.83 V vs a Ag/AgCl reference electrode. Unfortunately, neither the preparative oxidation of **58** using CAN nor the preparative oxidation of **58** employing electrochemical conditions afforded any of the desired methoxyalkyl amide product. In each case, the reaction led to a complex mixture of products.

Attempts to solve this problem by placing a second (dimethylamino)phenyl onto the silyl electroauxiliary were not successful. Again complex mixtures of products were obtained. In this case it was clear that the oxidation reaction failed to fragment the molecule in a manner that cleaved the silyl electroauxiliary from the dipeptide starting material. In analogy to the earlier studies of Floreancig and co-workers with systems lacking the silyl group, the potential of the electroauxiliary can be lowered to a point where the fragmentation no longer occurs. The presence of the silyl group simply lowers the oxidation potential for when this situation arises.

Solid-Phase Reactions

With a chemical oxidation strategy in hand, attention was turned toward demonstrating the utility of the reaction for placing an *N*-acyliminium ion into a solid-phase peptide substrate. To this end, Merrifield resin-based substrate **59** was synthesized and oxidized using CAN (Scheme 25). In this case, the methoxylated product was converted into a second product by treatment with BF_3/Et_2O and allyltrimethylsilane. This was done so that the product could be characterized following cleavage from the resin. The reaction was run by dividing the solid-phase substrate into two portions. The first was oxidized,

Scheme 25



the resulting product treated with the Lewis acid and allylsilane, and then the peptide cleaved from the resin. The second was simply treated under the reaction conditions for cleavage of the peptide from the resin. The yield for the oxidation−alkylation sequence was then determined by comparing the amount of material obtained from the two portions and found to be 66%. Since yields for the allylsilane reaction are typically on the order of 80%,[1a,e] it was concluded that the yield for the oxidation reaction must also be around 80%. In other words, the oxidation reaction utilizing the solid-phase substrate proceeded in a manner very similar to that of the oxidation of a solution-phase substrate.

Conclusions

We have found that the use of silyl electroauxiliaries overcomes the difficulties associated with oxidizing simple peptides and hence enables oxidative routes for the placement of *N*-acyliminium ions into peptide substrates. The oxidations can be accomplished using a variety of electrochemical techniques including both parallel- and series-type electrolyses. If the silyl electroauxiliary bears an alkoxy-substituted phenyl ring, then the oxidation can be performed on a solid-phase substrate using CAN as the oxidant. At present, the oxidations can be done using an electroauxiliary having an oxidation potential of +1.38 V vs Ag/AgCl. This oxidation potential should allow for the construction of peptide mimetics containing a wide variety of protected functional groups. For example, esters, alkyl, silyl, and benzyl ethers, amides, and carbamates, as well as a wide variety of aromatic rings and olefins, should all be compatible with cleavage of an electroauxiliary that oxidizes at +1.38 V. Hence, the chemistry should be applicable to the construction of core scaffolds for use in diversity-oriented synthesis approaches.

Attempts to develop an electroauxiliary with an even lower oxidation potential were not successful. This will limit application of the chemistry for placing *N*-acyliminium ions into larger peptides that may contain thiol, thioether, amine, or unprotected tyrosine side chains.

Having established the methodology needed for both electrochemically and chemically oxidizing dipeptide substrates, efforts are now under way to exploit the chemistry for the synthesis of core peptide scaffolds and the release of *N*-acyliminium ion intermediates at preselected sites on an addressable electrode microarray.

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(26) For the literature synthesis of **56** please see: Ankianiec, B. C.; Young, G. B. *Polyhedron* **1995**, *14*, 249.

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Supporting Information Available: Full experimental details along with both proton and carbon spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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