ORGANIC LETTERS

2006
Vol. 8, No. 5
971−974

A Formal [3,3]-Sigmatropic Rearrangement Route to Quaternary α-Vinyl Amino Acids: Use of Allylic *N*-PMP Trifluoroacetimidates

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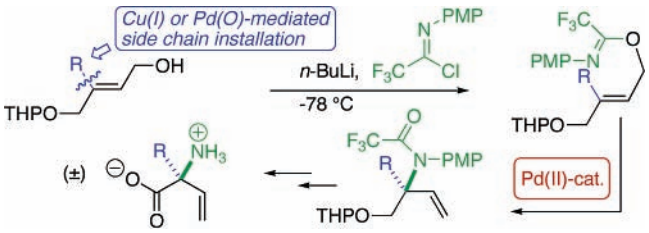
Received January 4, 2006

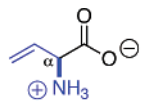
ABSTRACT



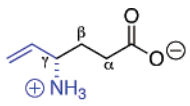
Pd(II)-mediated rearrangement of allylic *N*-PMP (*p*-methoxyphenyl) trifluoroacetimidates provides the first formal sigmatropic route to quaternary, α-vinylic amino acids, potential suicide substrates for PLP enzymes. The amino acid side chains enter via transition-metal-mediated C–C bond constructions, including (i) Cu(I)-mediated conjugate addition (Ala); (ii) Pd(0)/$AsPh_3$-mediated Stille coupling (allyl-Gly, Phe, DOPA, *m*-Tyr); and (iii) Pd(0)/P*t*-Bu_3-mediated Negishi coupling (Leu). In the synthesis of the DOPA decarboxylase inactivator, α-vinyl-*m*-tyrosine, the new *N*-PMP trifluoroacetimidate rearranges much more efficiently than the corresponding trichloroacetimidate.

Placing an unsubstituted vinyl group alpha to the amino group in an amino acid is an effective strategy for the suicide inactivation of some pyridoxal phosphate (PLP) enzymes. Examples include α-vinylglycine (naturally occurring) and vigabatrin (γ-vinyl-GABA), a synthetic antiepileptic drug, with exciting new potential for the treatment of substance abuse.[1] The principal mechanism by which the vinylic trigger is actuated, leading to an active site-directed Michael acceptor, is now established for both vinylglycine[2] and vigabatrin.[3] These precedents continue to motivate the synthesis and testing of quaternary, α-vinyl amino acids as candidates for the inactivation of amino acid decarboxylases (AADC's).[4]

The replacement of the α-hydrogen with a vinyl group builds specificity into the design, as it prevents PLP-dependent racemase, transaminase, and β- or γ-eliminase/replacement enzymes from actuating the trigger, yet allows for inclusion of the usual side chain for AADC recognition. The α-vinyl branch can subsequently be elaborated into halovinyl[5] or oxiranyl[6] groups, as potential triggering functionalities.



α-vinylglycine
(transaminases, ACC synthase)



vigabatrin (γ-vinyl-GABA)
(GABA transaminase)

Quaternary amino acids are also noteworthy targets for their ability to confer stability to proteases,[7] promote helical

(1) (a) Brodie, J. D.; Figueroa, E.; Laska, E. M.; Dewey, S. L. *Synapse* **2005**, *55*, 122−125. (b) Brodie, J. D.; Figueroa, E.; Dewey, S. L. *Synapse* **2003**, *50*, 261−265.

(2) Capitani, G.; Tschopp, M.; Eliot, A. C.; Kirsch, J. F.; Gruetter, M. G. *FEBS Lett.* **2005**, *579*, 2458−2462.

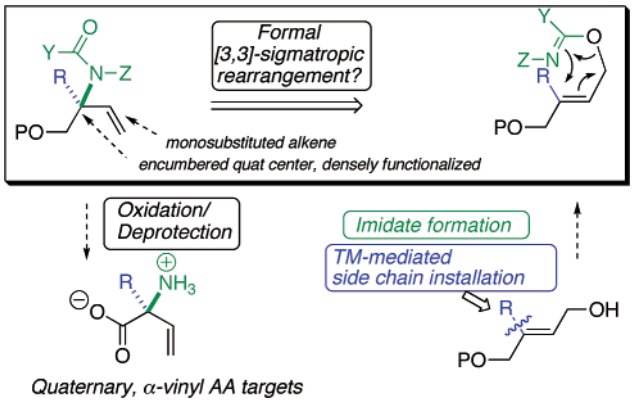
(3) (a) Czapinski, P.; Blaszczyk, B.; Czuczwar, S. J. *Curr. Top. Med. Chem.* **2005**, *5*, 3−14. (b) Storici, P.; De Biase, D.; Bossa, F.; Bruno, S.; Mozzarelli, A.; Peneff, C.; Silverman, R. B.; Schirmer, T. *J. Biol. Chem.* **2004**, *279*, 363−373. (c) Nanavati, S. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 9341−9349. (d) De Biase, D.; Barra, D.; Bossa, F.; Pucci, P.; John, R. A. *J. Biol. Chem.* **1991**, *266*, 20056−20061.

10.1021/ol060019s CCC: $33.50
Published on Web 02/10/2006

structure,[8] and serve as substrates for unnatural amino acid mutagenesis.[9] The incorporation of unsaturation adds synthetic value.[10] Given this, several synthetic approaches to quaternary, α-vinyl AA's have appeared, most using alkylative disconnections at the C_α-vinylic[11] or C_α-side chain[12] junctions.

We describe here a new entry into this unnatural AA class; namely, we disconnect at the C_α−N bond via a formal [3,3]-sigmatropic process (Scheme 1). To our knowledge, no

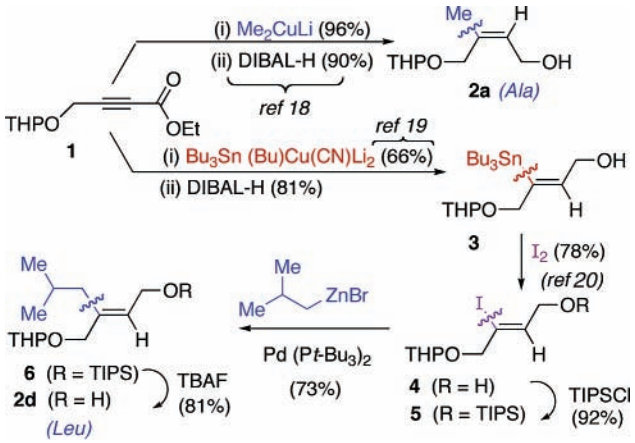
Scheme 1. New Disconnection toward Quaternary, α-Vinyl AA's



examples of sigmatropic routes to quaternary α-vinyl AA's have previously appeared, though a high temperature, thermal allylic imidate rearrangement gives vinylglycinol.[13,14] We had hoped to tap into the favorable O−C═N to O═C−N enthalpics to overcome the transformation of a trisubstituted olefin to a monosubstituted and sterically encumbered, quaternary vinyl group. Specifically, the Pd(II)-mediated allylic imidate rearrangement appeared attractive, as it proceeds under mild conditions and asymmetric variants have appeared, largely through the work of Overman.[15] We are pleased to report that the *N*-PMP (*p*-methoxyphenyl) trifluoroacetimidate is particularly well suited for this transformation.[16,17]

One distinguishing feature of a sigmatropic rearrangement approach to these unnatural AA's lies in the mode of side chain attachment. Previous approaches from our laboratory[12a−c] and others[12d,e] have used vinylglycine-derived AA enolates as the vehicles for side chain introduction. This chemistry usually requires strictly anhydrous conditions and low temperature.

Scheme 2. Introduction of the Ala and Leu Side Chains via Cuprate and Negishi Couplings



As is illustrated in Schemes 2 and 3, the formal sigmatropic approach exploits transition-metal-mediated C−C

(4) Berkowitz, D. B.; Jahng, W.-J.; Pedersen, M. L. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2151−2156 and references therein.

(5) (a) Berkowitz, D. B.; de la Salud-Bea, R.; Jahng, W.-J. *Org. Lett.* **2004**, *6*, 1821−1824. (b) Berkowitz, D. B.; Pedersen, M. L.; Jahng, W.-J. *Tetrahedron Lett.* **1996**, *37*, 4309−4312.

(6) Berkowitz, D. B.; Pedersen, M. L. *J. Org. Chem.* **1995**, *60*, 5368−5369.

(7) Khosla, M. C.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 757−60.

(8) (a) Yokum, T. S.; Gauthier, T. J.; Hammer, R. P.; McLaughlin, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1167−1168. (b) Jaun, B.; Tanaka, M.; Seiler, P.; Kuhnle, F. N. M.; Braun, C.; Seebach, D. *Liebigs Annalen/Recueil* **1997**, 1697−1710. (c) Aubry, A.; Bayeul, D.; Precigoux, G.; Pantano, M.; Formaggio, F.; Crisma, M.; Toniolo, C.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 525−529.

(9) Mendel, D.; Ellman, J.; Schultz, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 4359−4360.

(10) Kaiser, J.; Kinderman, S. S.; van Esseveldt, B. C. J.; van Delft, F. L.; Schoemaker, H. E.; Blaauw, R. H.; Rutjes, F. P. J. T. *Org. Biomol. Chem.* **2005**, *3*, 3435−3467.

(11) (a) Ma, D.; Zhu, W. *J. Org. Chem.* **2001**, *66*, 348−350. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445−446. (c) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966−6975. (d) Groth, U.; Schoellkopf, U.; Chiang, Y. C. *Synthesis* **1982**, 864−866.

(12) (a) Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329−6343. (b) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907−2918. (c) Berkowitz, D. B.; McFadden, J. M.; Chisowa, E.; Semerad, C. L. *J. Am. Chem. Soc.* **2000**, *122*, 11031−11032. (d) Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918−5924. (e) Seebach, D.; Buerger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669−684.

(13) Vyas, D. M.; Chiang, Y.; Doyle, T. W. *J. Org. Chem.* **1984**, *49*, 2037−2039.

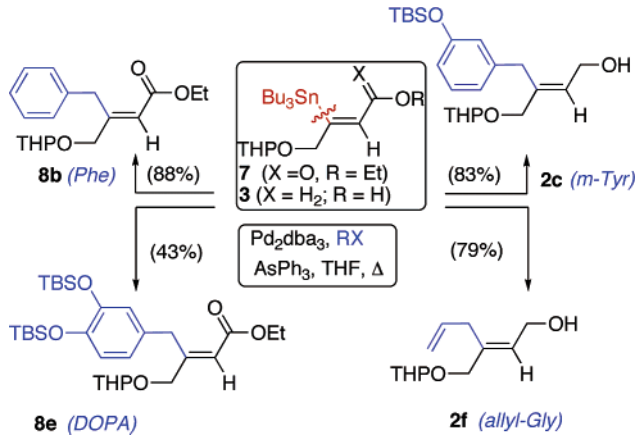
(14) For examples of thermal rearrangements (typically refluxing toluene for days) of allylic trichloroacetimidates to access quaternary centers in the lactacystin class of natural products, see: (a) Sato, H.; Maeba, T.; Yanase, R.; Yamaji-Hasegawa, A.; Kobayashi, T.; Chida, N. *J. Antibiot.* **2005**, *58*, 37−49. (b) Oishi, T.; Ando, K.; Inomiya, K.; Sato, H.; Iida, M.; Chida, N. *Org. Lett.* **2002**, *4*, 151−154. (c) Chida, N.; Takeoka, J.; Ando, K.; Tsutsumi, N.; Ogawa, S. *Tetrahedron* **1997**, *53*, 16287−16298.

(15) (a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (b) Kang, J.; Yew, K. H.; Kim, T. H.; Choi, D. H. *Tetrahedron Lett.* **2002**, *43*, 9509−9512. (c) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933−2934. (d) Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1065−1072. (e) Calter, M.; Hollis; Keith, T.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449−1456.

(16) For preliminary descriptions of the behavior of the new allylic *N*-PMP trifluoroacetimidates and their application to the synthesis of quaternary, α-vinyl AA's via Pd(II)-mediated rearrangement, see: (a) Berkowitz, D. B. Abstract No. 68, 36th Midwest Regional American Chemical Society Meeting, 2001. (b) Li, H. A New Approach to Quaternary Beta,Gamma-Unsaturated Amino Acids via a Formal [3,3]-Sigmatropic Rearrangement. M.S. Thesis, University of Nebraska, 2001.

(17) Subsequently, Overman and co-workers reported asymmetric, Pd(II) rearrangements of *N*-PMP trifluoroacetimidates in nonquaternary model systems: (a) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809−1812. (b) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648−657. (c) Prasad, R. S.; Anderson, C. E.; Richards, C. J.; Overman, L. E. *Organometallics* **2005**, *24*, 77−81.

Scheme 3. Side Chain Introduction via Modified Stille Couplings

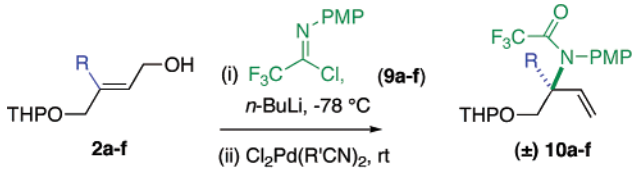


bond forming processes, at sp^2- or sp-centers, for side chain installation. On one hand, for α-vinylalanine, the side chain (Me) is carried in directly as part of a cuprate, thereby adding to the activated sp-center in **1**, under conditions described recently by Joullié.[18] Alternatively, advantage was taken of higher order stannylcuprate chemistry pioneered by Lipshutz,[19] again emanating from **1**, to access vinylstannanes **3** and **7** and lay the foundation for Stille-based chemistry.

Stannane **3** also serves to provide a complementary vinyl iodide **4**,[20] for cross-couplings with the opposite sense of polarity. Indeed, the leucine side chain, as the isobutylzinc reagent, enters efficiently (73%) via Negishi-type coupling on this system. Best results were obtained with the Pd(P*t*-$Bu_3)_2$ catalyst, under the Fu conditions.[21] Cl_2Pd(dppf) was much less effective. Formation of the isobutylzinc reagent, via halogen−metal exchange from *i*-BuI, under the conditions recently disclosed by Smith (3 equiv of *t*-BuLi, $ZnCl_2$),[22] led to successful Negishi coupling, albeit in lower yields (30−35%). For benzylic and allylic side chains, a modified Pd-mediated Stille cross-coupling reaction[23] on ester **7** or alcohol **3** proceeded smoothly. In our hands, use of the $AsPh_3$ ligand generally gave very good results, though the DOPA system proved to be more difficult to handle.

With all six targeted AA side chains installed, the desired imidate rearrangement could be investigated. *N*-PMP-trifluoroacetimidoyl chloride is readily accessible[24] and provides for an exceedingly mild and efficient method for the introduction of the title imidate at −78 °C (Table 1).

Table 1. Allylic *N*-PMP Trifluoroacetimidate Installation/Rearrangement[a]



entry	R	AA	yield of **9/10**[b]
a	Me	Ala	88/92%[c]
b	CH_2Ph	Phe	95/98%[d]
c	$CH_2(3'\text{-OTBS})C_6H_4$	*m*-Tyr	95/83%[d,e]
d	CH_2CHMe_2	Leu	98/83%[c]
e	$CH_2(3',4'\text{-bis-OTBS})C_6H_3$	DOPA	82/96%[d]
f	$CH_2CH{=}CH_2$	All-Gly	82/(70%)[c,f]

[a] Procedure: Imidate installations were initiated at −78 °C in dry THF. Rearrangements were run in PhH at room temperature, until complete conversion to **10** was evident by TLC. **9a**−**f** designate the *N*-PMP allylic trifluoroacetimidates. [b] Isolated yields of purified rearrangement products [as THP diastereomers]. [c] R′ = Ph. [d] R′ = Me. [e] In this case, the reaction is more rapid for the benzonitrile-based catalyst (see Figure 1). [f] This yield is corrected for recovery of starting imidate (27%). Product **10f** itself was isolated in 51% yield.

This is to be contrasted with the typical procedure for imidate installation by alcohol condensation with a nitrile in the presence of base (e.g., NaH, DBU) at room temperature.[14]

The *N*-PMP trifluoroacetimidate functionality was found to lead to clean rearrangement to the desired quaternary, protected α-amino alcohols, under Pd(II) catalysis, with all AA side chains examined (Table 1). Among Pd(II) catalyst candidates examined, phosphine-coordinated complexes, such as $Cl_2Pd(PPh_3)_2$ or Cl_2Pd(dppf), gave little to no product. Provided that reactions were carried out in MeCN, $Pd(OAc)_2$ and $PdCl_2$ catalysts gave the desired formal [3,3]-sigmatropic rearrangement products. However, best results were obtained by starting from the preformed nitrile complex, either $Cl_2Pd(NCMe)_2$ or $Cl_2Pd(NCPh)_2$, in benzene solvent, whereby the latter complex generally produced more rapid conversion. The title imidate appears especially well suited to the construction of these hindered quaternary centers. Thus, in the important *m*-tyrosine system, direct NMR comparison (benzene-d_6) revealed that the allylic *N*-PMP trifluoroacetimidate rearranges completely within 1 h, whereas the corresponding trichloroacetimidate gives little to no product (Figure 1).

In these transformations, it proved auspicious to mask the latent α-carboxyl group as a THP ether. This protecting group is stable to the cuprate, Negishi or Stille side chain-couplings employed early, and leads to successful Pd(II) rearrangement.

(18) Leonard, M. S.; Carroll, P. J.; Joullie, M. M. *J. Org. Chem.* **2004**, *69*, 2526−2531.
(19) (a) Reginato, G.; Capperucci, A.; Degl'Innocenti, A.; Mordini, A.; Pecchi, S. *Tetrahedron* **1995**, *51*, 2129−2136. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065−2068.
(20) Thibonnet, J.; Launay, V.; Abarbri, M.; Duchene, A.; Parrain, J.-L. *Tetrahedron Lett.* **1998**, *39*, 4277−4280.
(21) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.
(22) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664.
(23) (a) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833−4840. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992−4998.
(24) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32−35.

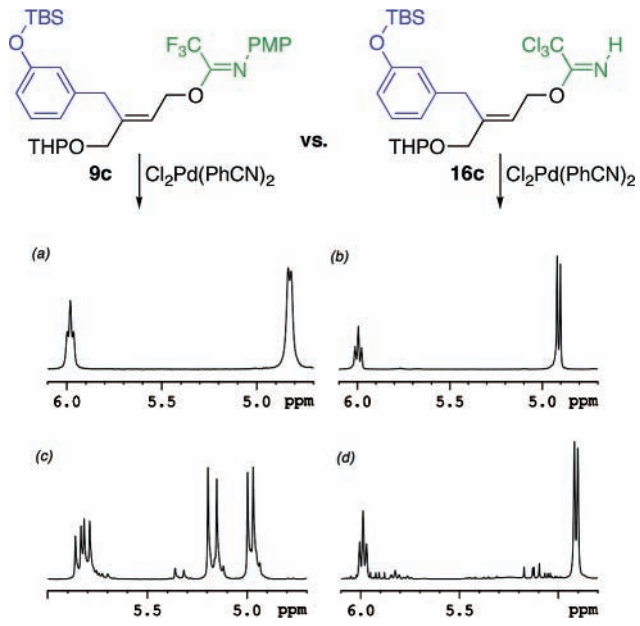
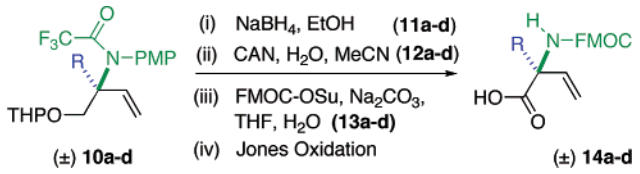


Figure 1. Allylic imidate rearrangement, as monitored by ^{1}H NMR (benzene-d_6). Panels a and b show allylic *N*-PMP trifluoroacetimidate **9c** and trichloroacetimidate **16c**, respectively, at $t = 0$. Panels c and d show NMR spectra of the same samples at $t = 1$ h, after exposure to 10 mol % of $PdCl_2(PhCN)_2$. In going from panel a to c, the imidate methine proton in **9c** (br t, 6.0 ppm) is converted to the methine proton of the emerging vinyl group (dd, 5.8 ppm) in **10c**. Simultaneously, the allylic ether methylene in **9c** (2 H, 4.8 ppm) splits out into the *cis* (d, 1 H, 4.95 ppm) and *trans* (d, 1 H, 5.16 ppm) terminal vinylic protons of **10c**. These spectral snapshots attest to the efficiency with which the new quaternary center in the α-vinyl-*m*-tyrosine system is assembled, when the *N*-PMP trifluoroacetimidate is employed.

Moreover, immediately thereafter, we find that one can simultaneously cleave both the THP ether and the *N*-PMP group (CAN, MeCN, H_2O), following reductive ($NaBH_4$) removal of the trifluoroacetamide functionality (Table 2). This quickly yields α-vinyl amino alcohols, good vehicles for the introduction of FMOC functionality. To our knowledge, this is first synthesis of quaternary α-vinyl AA's that outfits them with FMOC protection.

Finally, Jones oxidation serves to complete the synthesis of the targeted *N*-FMOC α-vinyl AA's, in a form appropriate for future peptide synthesis. Alternatively, should one wish to unveil the corresponding free α-vinyl AA's for study with PLP enzymes, one can cleave the FMOC groups, by subjection to mildly basic conditions (TBAF at room temperature). We were particularly pleased to find that, for **14c**, both the side chain OTIPS protecting group and the *N*-FMOC group could be cleaved simultaneously in this way (Scheme 4), providing a novel synthesis of the known DOPA decarboxylase suicide substrate, **15c**. This work serves as proof of principle for a new allylic imidate rearrangement entry into quaternary α-vinyl amino acids, in the racemic series, and sets the stage for potential asymmetric variants of the approach, as well as for further applications of the interesting *N*-PMP trifluoroacetimidate to the installation of quaternary centers bearing nitrogen.

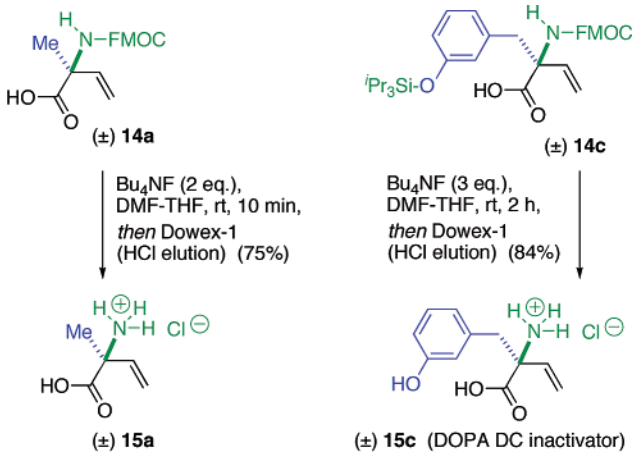
Table 2. Protecting Group Interchange/Oxidation[a]



entry	R	AA	11[b]	12[c]	13	14
a	Me	Ala	83%		51%[d]	79%
b	CH_2Ph	Phe	96%	63%	41%	90%
c	$CH_2(3'\text{-OTBS})C_6H_4$	*m*-Tyr	87%[e]	67%	78%	76%
d	CH_2CHMe_2	Leu	67%		54%[d]	73%

[a] Isolated yields of purified products are reported. **11a**−**d** denote the products of trifluoroacetamide deprotection. **12a**−**d** are the products of simultaneous *N*-PMP and THP deprotection. **13a**−**d** designate the *N*-FMOC-protected amino alcohols. [b] These reactions typically involve addition of 5 equiv of $NaBH_4$ in EtOH, at 0 °C, in portions, followed by warming to room temperature. [c] Yields here reflect cleavage of both the OTHP and *N*-PMP protecting groups. [d] In these cases, the crude amino alcohol was protected with FMOC−OSu, so a two-step yield is given. [e] This yield reflects the installation of a more robust TIPS silyl protecting group (TBAF, then TIPSCl, imidazole), following rearrangement, in addition to trifluoroacetamide cleavage.

Scheme 4. Joint FMOC/TIPS Deprotection to α-Vinyl-*m*-Tyr



Acknowledgment. We thank the NSF (CHE-0317083) and NIH (CA 62034) for support of our research program. Assistance from Kannan Karukurichi, Weijun Shen, Xiang Shi, and Sonia Bironneau-Gouault is acknowledged. This research was facilitated by shared instrumentation grants (NIH SIG-1-510-RR-06301, NSF CHE-0091975, NSF MRI-0079750).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra, as well as experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060019S