JOC*Note*

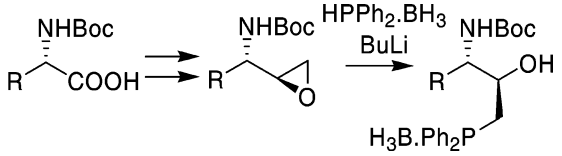
Synthesis of New Enantiomerically Enriched β-Hydroxy-γ-amino Phosphines by Selective Transformation of Naturally Occurring Amino Acids

Chiara Ciardi,[†] Antonio Romerosa,*[,†] Manuel Serrano-Ruiz,[†] Luca Gonsalvi,[‡] Maurizio Peruzzini,[‡] and Gianna Reginato*[,‡]

Area de Química Inorgánica, Facultad de Ciencias Experimentales, Universidad de Almería, 04071 Almería, Spain, and Istituto di Chimica dei Composti Organometallici (ICCOM-CNR), Via Madonna del Piano 10, 50019 Sesto Fiorentino (Firenze), Italy

gianna.reginato@unifi.it

Received May 16, 2007



Ring opening of amino epoxides derived from naturally occurring amino acids with lithium diphenylphosphido borane is reported as an efficient approach to a new family of enantiomerically enriched multifunctional phosphines.

Due to the large variety of catalytic reactions in which they are involved, chiral phosphines can be regarded as the most important class of ligands for transition-metal-catalyzed asymmetric reactions.[1−3] For this reason, the development of new synthetic pathways to increase the complexity of a phosphine skeleton represents a very attractive area of research, leading to higher versatility of the catalysts for wider scope. In particular, the presence of polar groups might enhance selectivity via electrostatic interactions with different substrates[4] and also increase the solubility in polar solvents.

The formation of a P−heteroatom bond is one of the preferred methods for incorporation of phosphorus into highly functionalized ligands,[5−7] although other pathways toward efficient P−C bond forming reactions are known.[8−11]

Stemming from our interest in the use of naturally occurring amino acids as building blocks for organic synthesis,[12−14] we were particularly attracted by the recently described synthesis of monohydroxyphosphines from ring opening reaction of epoxides with phosphorus nucleophiles.[15] Amino epoxides are very versatile synthons, easily accessible from amino acids using standard procedures.[16] In particular, they can be employed to obtain β-substituted amino alcohols by ring opening with different nucleophiles; for instance, a complete regioselective opening of amino epoxides by organolithium reagents has been reported very recently.[17] Modifications of amino acids to obtain chiral amino phosphines[18,19] and phosphines containing amino acids and peptides[20−27] have been described before, but, to our knowledge, amino epoxides have not been employed as starting reagents yet. Consequently, we considered that the extension of the oxirane ring opening to the use of phosphorus nucleophiles could provide an easy and stereoselective access to different β-hydroxy, γ-amino phosphines in which the lateral chain and the configuration of the stereogenic centers can be pivoted by the choice of the suitable starting amino acid. This new class of compounds, bearing simultaneously at least one hydroxy and one amino group, may be of great interest as new potential polydentate ligands for asymmetric reactions[28−30] and for water phase applications.[31]

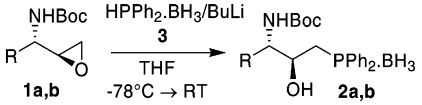
Accordingly, enantiopure *anti*-amino epoxides **1a,b** derived from Boc-protected L-phenylalanine and L-valine, respectively, were prepared by reaction of the corresponding amino aldehydes

[†] Universidad de Almería.
[‡] ICCOM-CNR.

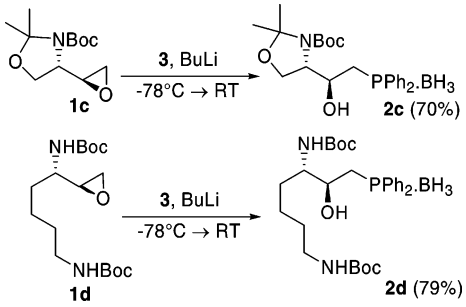
(1) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, Germany, 1993.
(2) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994.
(3) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, 1999.
(4) Hayashi, T.; Yamada, I.; Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1869.
(5) Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811.
(6) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445.
(7) Blanc, C.; Hannedouche, J.; Agbossou-Niedercorn, F. *Tetrahedron Lett.* **2003**, *44*, 6469.
(8) Hartley, F. R. *The Chemistry of Organophoshporous Compounds*; John Wiley & Sons: New York, 1990; Vol. 1.
(9) Schwan, A. L. *Chem. Soc. Rev.* **2004**, *33*, 218.
(10) Bunlaksananursorn, T.; Knochel, P. *Tetrahedron Lett.* **2002**, *43*, 5817.
(11) Join, B.; Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun.* **2006**, 3249 and references cited therein.
(12) Reginato, G.; Mordini, A.; Valacchi, M.; Grandini, E. *J. Org. Chem.* **1999**, *64*, 9211.
(13) Reginato, G.; Meffre, P.; Gaggini, F. *Amino Acids* **2005**, *29*, 81.
(14) Reginato, G.; Gaggini, F.; Mordini, A.; Valacchi, M. *Tetrahedron* **2005**, *61*, 6791.
(15) Fox, D. L.; Robinson, A. A.; Frank, J. B.; Salvatore, R. N. *Tetrahedron Lett.* **2003**, *44*, 7579.
(16) Albeck, A.; Estreicher, G. L. *Tetrahedron* **1997**, *53*, 5325 and references cited therein.
(17) Concellon, J. M.; Bernad, P. L.; Solar, V. d.; Suarez, J. R.; Garcia-Granda, S.; Diaz, M. R. *J. Org. Chem.* **2006**, *71*, 6420.
(18) Saitoh, A.; Achiwa, K.; TAnaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227.
(19) Malkov, A. V.; Hand, J. B.; Kocovsky, P. *Chem. Commun*. **2003**, 1948.
(20) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481.
(21) Gilbertson, S. R.; Starkey, G. W. *J. Org. Chem.* **1996**, *61*, 2922.
(22) Gilbertson, S. R.; Wang, X. *J. Org. Chem.* **1996**, *61*, 434.
(23) Tepper, M.; Stelzer, O.; Hausler, T.; Sheldrick, W. S. *Tetrahedron Lett.* **1997**, *38*, 2257.
(24) Porte, A. M.; van der Donk, W. A.; Burgess, K. *J. Org. Chem.* **1998**, *63*, 5262.
(25) Brauer, D. J.; Schenk, S.; Rossenbach, S.; Tepper, M.; Stelzer, O.; Hausler, Y.; Sheldrick, W. S. *J. Organomet. Chem.* **2000**, *598*, 116.
(26) Greenfield, S. J.; Gilbertson, S. R. *Synthesis* **2001**, 2337.
(27) Agarkov, A.; Greenfield, S. J.; Ohishi, T.; Collibee, S. E.; Gilbertson, S. R. *J. Org. Chem.* **2004**, *69*, 8077.
(28) Leautey, M.; Castelot-Deliencourt, G.; Jubault, P.; Pannecoucke, X.; Quirion, J.-C. *Tetrahedron Lett.* **2002**, *43*, 9237.
(29) Yamagishi, T.; Suemune, K.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2002**, *58*, 2577.
(30) Cheng, X.; Hornton, P. N.; Hursthouse, M. B.; Hii, K. K. *Tetrahedron: Asymmetry* **2004**, *15*, 2241.
(31) Condom, M.; Suades, J. In. *Chem. Commun.* **2005**, *8*, 355.

10.1021/jo070915x CCC: $37.00
Published on Web 09/05/2007

SCHEME 1



SCHEME 2



with methylsulphonium methylide.[32] These were then reacted with diphenylphosphido borane **3** in the presence of BuLi (Scheme 1).

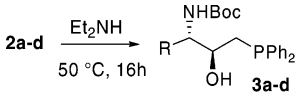
Boranes are very convenient precursors for phosphine ligands because they are air stable and easily cleaved. Furthermore, the borane moiety acts both as protecting and as activating group, yielding smoothly lithium diphenylphosphide by treatment with BuLi under mild conditions.[33] The reaction was carried out in THF. Lithium diphenylphosphide was generated with Bu−Li at −78 °C, then reacted with the suitable epoxides **1a,b** at room temperature to afford smoothly the expected compounds **2a,b**. ^{1}H and ^{31}P NMR analysis of the crude mixtures showed that the ring opening was in both cases totally regioselective, leading to the only isomer (**2**) derived from nucleophilic attack at the C-3 position. Moreover, in the course of the ring opening, absolute configuration of the oxirane was preserved as only one diastereoisomer was recovered. Thus, in analogy with previously reported results,[32] we assigned the (2*S*,3*S*) *anti*-stereochemistry to the final compounds **2a,b**.

It is noteworthy that, although the reaction was performed in THF at room temperature, no elimination to give the corresponding allylamines was observed according to the high nucleophilicity of lithium diphenylphosphide, which is enhanced by coordination with BH_3.[34] This might account also for the higher regioselectivity compared with the ring opening of styrene oxide with $LiPPh_2$.[35]

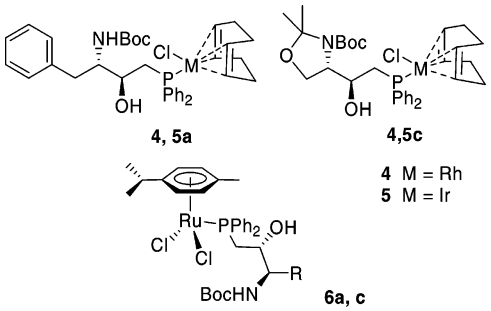
This optimized reaction protocol was then extended to more functionalized amino epoxides, namely, to the epoxy oxazolidine **1c**,[36] derived from naturally occurring L-serine and to the novel *tert*-Boc-protected epoxy L-lysine **1d** (Scheme 2).

In both cases, the corresponding phosphino boranes **2c,d**, bearing, respectively, one additional hydroxy and one additional amino functional group on the lateral chain, were obtained in good yields and with high selectivity. All compounds **2a**−**d** were obtained as air-stable solids, which could be purified by column chromatography and stored in the refrigerator without decomposition.

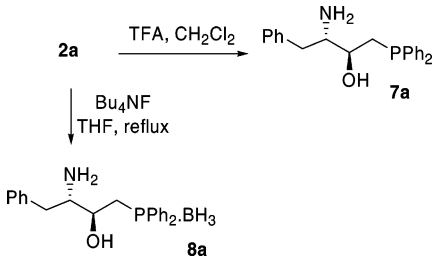
SCHEME 3



SCHEME 4



SCHEME 5



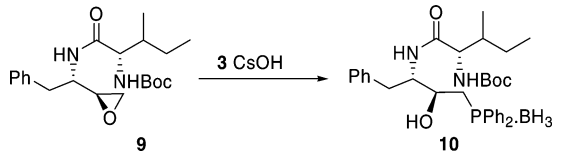
The deprotection of phosphines **2a**−**d** was performed by simple treatment with an excess of diethylamine, without solvent, at 50 °C for several hours (Scheme 3).[34] The final *N*-*tert*-Boc-protected amino hydroxyphosphines **3a**−**d** were obtained quantitatively as air-sensitive microcrystalline solids and characterized by ^{1}H and ^{31}P NMR spectra.

These phosphines can be used as ligands for transition-metal complexation without further purification. For instance, compounds **3a** and **3c** have been tested as ligands toward Rh(I), Ir(I), and Ru(II) metal centers. The reactions were performed in CH_2Cl_2 at room temperature with the corresponding precursors $[Rh(cod)Cl]_2$, $[Ir(cod)Cl]_2$, and $[RuCl_2(p\text{-cymene})]_2$, yielding complexes **4a**, **4c**, **5a**, **5c**, **6a**, and **6c** in which the phosphines coordinate to the metals in a monodentate fashion (Scheme 4). All of the six new complexes were isolated as microcrystalline solids and characterized by standard NMR analyses (see Supporting Information for details).

The *tert*-Boc protective group could also be removed in order to obtain the free primary amine residue; hence treatment of **2a** with an excess of TFA gave the fully deprotected amino phosphine **7a** in high yield (Scheme 5). When deprotection was performed using Bu_4NF in THF,[37] phosphino borane **8a** was instead obtained as the only reaction product (Scheme 5), thus proving that the borane and the *tert*-Boc can be used as orthogonal protective groups in the synthesis of amino phosphines.

(32) Evans, E. B.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615.
(33) Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *178*−*180*, 665.
(34) Imamoto, T. *Pure Appl. Chem.* **1993**, *65*, 655 and references cited therein.
(35) Muller, G.; Sainz, D. *J. Organomet. Chem.* **1995**, *495*, 103.
(36) Moore, W. J.; Luzzio, F. A. *Tetrahedron Lett.* **1995**, *36*, 6599.
(37) Routier, S.; Sauge, L.; Ayerbe, N.; Coudert, G.; Merour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589.

SCHEME 6



Finally, dipeptido epoxide **9** was prepared according to a reported procedure.[38] When it was reacted with lithium diphenylphosphido borane, only decomposition of the starting material was observed; however, by reaction with $HPPh_2{\cdot}BH_3$ and CsOH as base, in the presence of molecular sieves and with DMF as solvent, epoxide ring opening occurred and the corresponding dipeptide-derived phosphino borane **10** was recovered after chromatographic purification, albeit in low yield (Scheme 6).

Although the whole procedure would need optimization, it is remarkable that ^{1}H and ^{13}C NMR spectra of compound **10** showed no peaks due to epimerization at the γ-carbon of the amino phosphine, thus suggesting that no racemization of the starting material occurred.

It is worth mentioning that this kind of phosphine-containing small peptides, allowing easy modification of the chiral ligand, might influence the development of screening strategies to accelerate and increase the efficiency of catalysts.[39−41]

In summary, we have shown that amino epoxides derived from naturally occurring amino acids or dipeptides undergo selective opening with diphenylphosphido borane to give a new class of enantiomerically enriched multifunctional phosphines which can be used as ligands for transition-metal complexation. Work is in progress to test the activity of such complexes as catalysts in enantioselective hydrogenation of prochiral aryl and alkyl ketones and for water phase application.

Experimental Section

General Procedure for Epoxide Ring Opening with Diphenylphosphido Borane. Epoxides **1a**−**d** (1 equiv) and diphenylphosphide borane **3** (1 equiv) were dissolved in THF. The mixture was cooled at −78 °C, then BuLi (1.6 M in hexane, 1 equiv) was added dropwise. The reaction was left at low temperature for 1 h, then the mixture was warmed up to room temperature and stirred overnight. After cooling at 0 °C, a 10% NH_4Cl aqueous solution was added, the aqueous layer was extracted with Et_2O, and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude was purified by silica gel flash chromatography.

[(2*S*,3*S*)-2-Hydroxy-3-*tert*-butoxycarbonylamino-4-phenyl]butyldiphenylphosphino Borane 2a: eluent, petroleum ether/AcOEt = 2:1 (yield 87%); ^{31}P NMR (81.01 MHz, $CDCl_3$) δ 12.78 (br m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.61 (m, 4H), 7.51−7.41 (m, 6H), 7.28−7.26 (m, 5H), 4.63 (br d, 1H, ^3J = 8.0 Hz), 3.89−3.84 (m, 1H), 3.84−3.71 (m, 1H), 2.95 (dd, 1H, ^2J = 14.2 Hz, ^3J = 4.6 Hz), 2.78−2.63 (m, 1H), 2.50−2.47 (m, 1H), 2.39−2.32 (m, 1H), 1.24 (s, 9H), 1.47−0.82 (br m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.7, 137.8, 132.3 (d, $^2J_{C-P}$ = 9.1 Hz), 131.9 (d, $^2J_{C-P}$ = 9.1 Hz), 131.5 (d, $^4J_{C-P}$ = 2.3 Hz), 131.3 (d, $^4J_{C-P}$ = 2.3 Hz), 129.4, 129.0 (d, $^3J_{C-P}$ = 9.9 Hz), 128.9 (d, $^3J_{C-P}$ = 9.9 Hz), 128.4, 126.4, 79.6, 69.6, 56.7, 35.7, 31.4 (d, $^1J_{C-P}$ = 37.6 Hz), 28.2. Anal. Calcd for $C_{27}H_{35}BNO_3P$: C, 69.99; H, 7.61; N, 3.02. Found: C, 69.92; H, 7.63; N, 3.00. $[\alpha]^{26}_D$ = +2.58 (*c* = 0.98, $CHCl_3$).

[(2*S*,3*S*)-2-Hydroxy-3-*tert*-butoxycarbonylamino-3-methyl]butyldiphenylphosphino Borane 2b: eluent, petroleum ether/AcOEt = 2:1 (yield 81%); ^{31}P NMR (81.01 MHz, $CDCl_3$) δ 11.22 (br m); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74−7.63 (m, 4H), 7.53−7.43 (m, 6H), 4.91 (br d, 1H, ^3J = 10.4 Hz), 4.17−4.06 (m, 1H), 3.20−3.10 (m, 1H), 2.62−2.38 (m, 2H), 1.88−1.72 (m, 1H), 1.45 (s, 9H), 0.91 (d, 3H, ^3J = 6.6 Hz), 0.85 (d, 3H, ^3J = 6.6 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 156.6, 132.8 (d, $^1J_{C-P}$ = 15.0 Hz), 132.6 (d, $^1J_{C-P}$ = 15.3 Hz), 132.2 (d, $^2J_{C-P}$ = 9.1 Hz), 131.7 (d, $^2J_{C-P}$ = 9.1 Hz), 131.5 (d, $^4J_{C-P}$ = 2.3 Hz), 131.2 (d, $^4J_{C-P}$ = 2.3 Hz), 129.0 (d, $^3J_{C-P}$ = 10.7 Hz), 128.8 (d, $^3J_{C-P}$ = 8.4 Hz), 79.3, 66.3, 62.0 (d, $^2J_{C-P}$ = 11.5 Hz), 32.4 (d, $^1J_{C-P}$ = 36.7 Hz), 30.5, 28.5, 19.8, 19.7. Anal. Calcd for $C_{23}H_{35}BNO_3P$: C, 66.52; H, 8.49; N, 3.37. Found: C, 66.45; H, 8.51; N, 3.36. $[\alpha]^{26}_D$ = +0.25 (*c* = 0.60, $CHCl_3$).

[(2*S*,4′*S*)-2-Hydroxy-2-(2′,2′-dimethyl-3′-*tert*-butoxycarbonyloxazolidin-4′-yl)]ethyldiphenylphosphino Borane 2c: eluent, petroleum ether/AcOEt = 2:1 (yield 70%); ^{31}P NMR (81.01 MHz, $CDCl_3$) δ 12.25 (br m); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.38 (m, 2H), 7.63 (m, 2H), 7.45−7.26 (m, 6H), 4.45−4.40 (m, 1H), 4.17 (m, 1H), 3.91 (dd, 1H, ^3J = 2.7 Hz, ^3J = 5.7 Hz), 3.66 (m, 1H), 3.51 (m, 1H), 2.72−2.63 (m, 1H), 1.43 (s, 9H), 1.26 (s, 6H), 1.55−0.62 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 50 °C) δ 154.7, 132.3 (d, $^3J_{C-P}$ = 9.2 Hz), 132.0 (d, $^3J_{C-P}$ = 10.8 Hz), 131.3, 131.2, 129.6 (d, $^1J_{C-P}$ = 56.9 Hz), 128.8 (d, $^2J_{C-P}$ = 12.5 Hz), 128.7 (d, $^2J_{C-P}$ = 10.5 Hz), 94.3, 80.7, 68.3, 64.9, 62.1 (d, $^2J_{C-P}$ = 12.3 Hz), 31.5 (d, $^1J_{C-P}$ = 49.0 Hz), 28.3, 27.0, 24.0. Anal. Calcd for $C_{24}H_{35}BNO_4P$: C, 65.02; H, 7.96; N, 3.16. Found: C, 64.95; H, 8.01; N, 3.14. $[\alpha]^{26}_D$ = −0.44 (*c* = 1.28, $CHCl_3$).

[(2*S*,3*S*)-2-Hydroxy-3,7-di-*tert*-butoxycarbonylamino]heptyldiphenylphosphino Borane 2d: eluent, petroleum ether/AcOEt = 3:2 (yield 79%); ^{31}P NMR (81.01 MHz, $CDCl_3$) δ 11.63 (br m); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73−7.51 (m, 4H), 7.42−7.27 (m, 6H), 4.87 (d, 1H, ^3J = 10.1 Hz), 4.57 (m, 1H), 3.93−3.75 (m, 1H), 3.54−3.42 (m, 1H), 3.07−2.96 (m, 2H), 2.54−2.27 (m, 2H), 1.43−1.10 (m, 9H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 156.4, 156.0, 132.2 (d, $^3J_{C-P}$ = 9.2 Hz), 131.9 (d, $^3J_{C-P}$ = 9.4 Hz), 131.5 (d, $^4J_{C-P}$ = 2.3 Hz), 131.2 (d, $^4J_{C-P}$ = 2.4 Hz), 128.9 (d, $^2J_{C-P}$ = 10.5 Hz), 128.7 (d, $^2J_{C-P}$ = 9.0 Hz), 79.4, 79.1, 68.3, 56.0 (d, $^2J_{C-P}$ = 11.4 Hz), 40.4, 32.3, 31.4 (d, $^1J_{C-P}$ = 37.4 Hz), 29.9, 28.6, 28.5, 23.3. Anal. Calcd for $C_{29}H_{46}BN_2O_5P$: C, 63.97; H, 8.52; N, 5.15. Found: C, 63.91; H, 8.54; N, 5.13. $[\alpha]^{26}_D$ = +0.81 (*c* = 1.00, $CHCl_3$).

Acknowledgment. The authors thank Junta de Andalucía (PAI and Consejería de la Presidencia) for FQM-317 and MCYT for project PPQ2003-01339. We thank also ECRF through project FIRENZE HYDROLAB for allowing access to high field NMR spectrometers, the MCRTN program AQUACHEM (MRTN-CT-2003-503864), the COST Actions D17 and D29. C.C., MEC for a F.P.U. grant (2003−2006) and CNR (Short Term Mobility Program 2006) for granting the visit of A.R. to ICCOM CNR.

Supporting Information Available: Experimental procedures and spectroscopic data of new compounds, ^{1}H and ^{13}C NMR spectra of **1d**, **2a**−**d**, **3a**−**d**, **7a**, **8a**, and **10**, and ^{1}H, ^{13}C, and ^{31}P NMR spectra of complexes **4a**,**c**, **5a**,**c**, and **6a**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070915X

(38) Albeck, A.; Fluss, S.; Persky, R. *J. Am. Chem. Soc.* **1996**, *118*, 3591.
(39) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180.
(40) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779.
(41) Agarkov, A.; Greenfield, S.; Xie, D.; Pawlick, R.; Starkey, G.; Gilbertson, S. R. *Pept. Sci.* **2006**, *84*, 48.