A Novel Linking-Protecting Group Strategy for Solid-Phase Organic Chemistry with Configurationally Stable α-[*N*-(Phenylfluorenyl)]amino Carbonyl Compounds: Synthesis of Enantiopure Norephedrines on Solid Support

Francis Gosselin, Jo Van Betsbrugge, Mostafa Hatam, and William D. Lubell*

Département de chimie, Université de Montréal, C. P. 6128, Succursale Centre Ville, Montréal, Québec H3C 3J7, Canada

Received December 10, 1998

A novel linking strategy has been developed for synthesizing configurationally stable α-amino aldehyde on polymeric supports. Alkylation of L-alanine methyl ester with 9-bromo-9-*p*-bromophenylfluorenene, followed by ester hydrolysis and coupling to isoxazolidine, provided *N*-(9-*p*-bromophenylfluoren-9-yl)alanine isoxazolidide (**5**), which was transformed into its corresponding boronate **2** by a palladium-catalyzed cross-coupling reaction with diboron pinacol ester. Boronate **2** was anchored to four different polymeric aryl halides **6**−**9** in 70−99% yields. Polymer-bound alaninal **1b** was then synthesized on non-cross-linked polystyrene by hydride reduction of isoxazolidide **10b**. Treatment of alaninal **1b** with phenylmagnesium bromide, cleavage of the resulting amino alcohol in a 1:2:2 TFA/CH_2Cl_2/anisole cocktail, and acylation with di-*tert*-butyl dicarbonate furnished *N*-(BOC)norephedrines **14** that were demonstrated to be enantiopure by conversion to diastereomeric thioureas **15** and analysis by HPLC. In summary, we have developed a process by which the 9-phenylfluoren-9-yl protecting group has been converted into a new linker for the solid-phase synthesis and manipulation of α-amino carbonyl compounds.

Introduction

The development of novel strategies for effectively linking organic compounds to solid supports has become essential as solid-phase chemistry and combinatorial technology have evolved into fundamental tools for drug discovery.[1] In principle, the ideal linker should provide effective loading onto the support, stability under a diverse variety of reaction conditions, and easy product removal without contamination from the linker.[2] Although several strategies have emerged for attaching amines to solid supports,[3−5] many of these linkers are not stable under strong base, strong acid, or organometallic reaction conditions. Furthermore, because such linkers often require amine attachment to the support early in the synthesis, multiple reactions may be necessary prior to steps for generating molecular diversity. Solution-phase amine protection that converts into a solid-phase amine linker anytime during synthesis may offer advantages over conventional support-bound protecting groups because penultimate intermediates could be initially synthesized in solution on large scale and then attached to supports for transformation via molecular diversification chemistry.

The 9-phenylfluoren-9-yl (PhF) amine protecting group has ensured configurational stability in the preparation and manipulation of α-amino carbonyl compounds during solution-phase syntheses of enantiopure alkaloids,[6,7] heterocycles,[8] and amino acids.[9,10] The PhF group prevents the racemization of α-amino carbonyl compounds by sterically shielding the α-proton and by positioning the α-proton and carbonyl in a planar geometry in which deprotonation is stereoelectronically disfavored.[10,11] Relative to the trityl group,[5,12] the PhF group is also significantly more stable to solvolysis in acid because of the

(1) Recently reviewed: Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293 and refs 1−27 therein.

(2) Examples include the following. Germanium- and silicon-based traceless linkers: (a) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885. Safety-catch linkers: (b) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171. For additional examples see ref 1.

(3) Urethane linkers that comprise the elements of their solution-phase counterparts include the following. BOC linker: (a) Hernández, A. S.; Hodges, J. C. *J. Org. Chem.* **1997**, *62*, 3153. Fmoc linker: (b) Rabanal, F.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **1992**, *33*, 1775. Cbz linker: (c) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937. (d) Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589.

(4) Dimethoxybenzylamine linker: (a) Jensen, K. J.; Songster, M. F.; Vágner, J.; Alsina, J.; Albericio, F.; Barany, G. In *Peptides: Chemistry, Structure and Biology*; Kaumaya, P. T. P., Hodges, R. S., Eds.; ESCOM Sci. Pub. B.V.: Leiden, The Netherlands, 1996; p 30. (b) Sharma, S. K.; Songster, M. F.; Colpitts, T. L.; Hegyes, P.; Barany, G.; Castellino, F. J. *J. Org. Chem.* **1993**, *58*, 4993. ADCC linker: (c) Bannwarth, W.; Huebscher, J.; Barner, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1525.

(5) Trityl linkers: (a) Barlos, K.; Gatos, D.; Kallitsis, I.; Papaioannou, D.; Sotiriou, P. *Liebigs Ann. Chem.* **1988**, 1079. (b) Zikos, C. C.; Ferderigos, N. G. *Tetrahedron Lett.* **1994**, *35*, 1767. (c) Bidaine, A.; Berens, C.; Sonveaux, E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1167.

(6) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239.

(7) Examples include (a) (+)-vincamine [Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068] and (b) (+)-castanospermine and (+)-6-epicastanospermine: Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700.

(8) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748.

(9) Examples include: (a) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511. (b) Beausoleil, E.; L'Archevêque, B.; Bélec, L.; Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9447. (c) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463. (d) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937. (e) Koskinen, A. M. P.; Schwerdtfeger, J.; Edmonds, M. *Tetrahedron Lett.* **1997**, *38*, 5399.

(10) (a) Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467. (b) Atfani, M.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 3184.

(11) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(12) The acid lability of the trityl group is described: Sieber, P.; Riniker, B. In *Peptides: Chemistry and Biology, Proceedings of the Tenth Am. Peptide Symposium*; Marshall, G. R., Ed.; ESCOM Sci. Pub. B. V.: Leiden, The Netherlands, 1988; pp. 270−272.

10.1021/jo982413c CCC: $18.00
Published on Web 03/17/1999

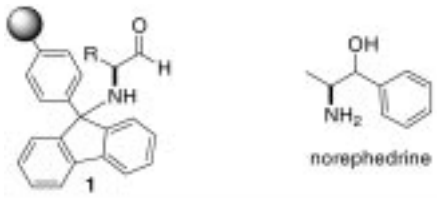


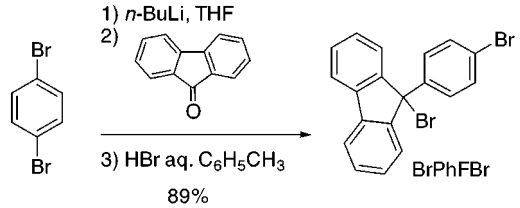
Figure 1. Resino *N*-(PhF)-α-amino aldehyde **1** and norephedrine.

antiaromatic character of the fluorenyl cation.[13] Because of these attributes, we began to study the conversion of the PhF protecting group into a new linker for the solid-phase synthesis and manipulation of α-amino carbonyl compounds.

Initially, we synthesized 9-bromo-9-phenylfluorenyl cross-linked polystyrene by lithiation of cross-linked polystyrene,[14,15] followed by addition of fluorenone and treatment of the tertiary alcohol with acetyl bromide in benzene.[15,16] L-Alanine methyl ester hydrochloride was anchored to the polymer using Et_3N in 1:1 CH_2Cl_2/CH_3CN, as indicated by a strong band for the ester carbonyl at 1736 cm^{-1} in the PA-FTIR spectrum.[16,17] During the course of our investigation, papers appeared describing the preparation of 9-chloro-9-phenylfluorenyl cross-linked polystyrene resin and a phenylfluorenyl acetic acid linker, as well as their employment in peptide chemistry and manipulations of achiral amines, which demonstrated the greater acid stability of the PhF supports relative to trityl resins.[18] Focusing our attention on the synthesis and configurational stability of resino α-amino carbonyl compounds such as α-amino aldehyde **1** (Figure 1), we realized that a limitation of the phenylfluorenyl cross-linked polystyrene resins was the requirement to employ several steps on the solid phase in order to convert the starting resino ester into the desired α-amino aldehyde. Since such reactions could be more effectively accomplished on large scale in solution,[11] we discontinued our studies on the PhF-resin; instead, we chose to develop a PhF linker for synthesizing the penultimate intermediate prior to resin attachment.

In developing a PhF linker, we pursued a protecting-linking group that was synthesized in few steps from inexpensive starting materials, compatible with solution- and solid-phase chemistry, and attachable to an assortment of different solid supports. The employment of esters for joining the PhF group to the resin was judged inadequate due to their reactivity with organometallic reagents. Similarly, the phenylfluorenyl acetic acid linker[18] was deemed unsuitable because the amide used to link the PhF group to the resin was also expected to react competitively with organometallic reagents during transformations of the resino α-amino carbonyl compounds. Furthermore, initial attempts to attach the PhF group to the support by an ether bond proved cumbersome due to difficulties in synthesizing PhF groups possessing protected ethers.

Scheme 1. Synthesis of 9-Bromo-9-*p*-bromophenylfluorene (BrPhFBr)



Transition metal catalyzed cross-coupling chemistry was examined for linking the PhF group and support, because these reactions are usually high yielding both in solution and on solid phase.[19,20] Mild conditions for converting aryl bromides into their respective aryl boronates had recently been reported and appeared compatible with a broad spectrum of functional groups.[21] We perceived that amino acids could be protected with 9-bromo-9-*p*-bromophenylfluorene in solution and that palladium-catalyzed cross-coupling reactions could then be used to link the *N*-(BrPhF)amino acid derivative to the solid support (BrPhF = 9-(9-*p*-bromophenylfluorenyl)).

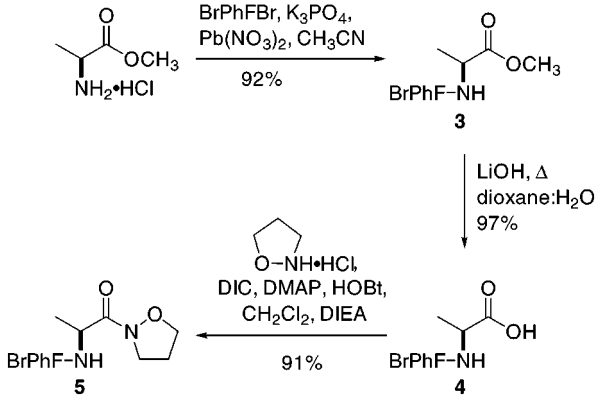
This concept has now been validated by the solution-phase synthesis of *N*-(BrPhF)alanine isoxazolidide and its conversion into polymer-bound α-amino aldehyde **1** (Figure 1, R = CH_3). Alaninal **1** was examined because α-amino aldehydes have been previously shown to be susceptible to racemization from various reactions in solution.[11,22] By employing polymer-bound α-amino aldehyde **1** in the synthesis of enantiopure norephedrines, we have demonstrated that the PhF protecting-linking group approach can provide configurational stability during the synthesis and modification of support-bound α-amino carbonyl compounds.

Results

9-Bromo-9-*p*-bromophenylfluorene (BrPhFBr) was first synthesized in two steps and 89% overall yield from fluorenone by a procedure that was patterned closely after the preparation of 9-bromo-9-phenylfluorene published originally by Christie and Rapoport (Scheme 1).[6,23] Metal−halogen exchange on 1,4-dibromobenzene with *n*-butyllithium in THF at −78 °C gave *p*-bromophenyllithium,[24] which was treated with fluorenone to furnish 9-*p*-bromophenylfluoren-9-ol. The crude alcohol was sub-

(13) The solvolysis of TrCl is 6000 times faster than PhFCl: Bolton, R.; Chapman, N. B.; Shorter, J. *J. Chem. Soc.* **1964**, 1895.
(14) Farrall, M. J.; Fréchet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.
(15) Fyles, T. M.; Leznoff, C. C. *Can J. Chem.* **1976**, *54*, 935.
(16) Preliminary results were presented in part: Gosselin F.; Lubell, W. D. *2nd Canadian Conference on Combinatorial Chemistry*, Oct 6−7, 1997, Montréal, Québec, Canada.
(17) Gosselin, F.; Di Renzo, M.; Ellis, T.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 7980.
(18) (a) Bleicher, K. H.; Wareing, J. R. *Tetrahedron Lett.* **1998**, *39*, 4587. (b) Bleicher, K. H.; Wareing, J. R. *Tetrahedron Lett.* **1998**, *39*, 4591. A related 9-(4-carboxyphenyl)fluorenyl linker is presented: (c) Henkel, B.; Bayer, E. *Tetrahedron Lett.* **1998**, *39*, 9401.
(19) Reviewed in: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(20) Illustrative transition metal-catalyzed cross-coupling examples on solid-phase include: (a) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177. (b) Koh, J. S.; Ellman, J. A. *J. Org. Chem.* **1996**, *61*, 4494. (c) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076. (d) Deshpande, M. S. *Tetrahedron Lett.* **1994**, *35*, 5613. (e) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306. (f) Jones, L. I.; Schumm, J. S.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1388.
(21) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Giroux, A.; Han, Y.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841.
(22) Epimerization of α-heterosubstituted aldehydes is discussed in refs 1 and 2 in: Lubell, W.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824.
(23) Jamison, T. F.; Lubell, W. D.; Dener, J. M.; Krisché, M. J.; Rapoport, H. *Org. Synth.* **1992**, *71*, 220.
(24) (a) Ravindar, V.; Hemling, H.; Schumann, H., Blum, J. *Synth. Commun.* **1992**, *22*, 841. In our hands, the Grignard reagent from 1,4-dibromobenzene could not be prepared: (b) Pink, H. S. *J. Chem Soc.* **1923**, *123*, 3418.

Scheme 2. Synthesis of *N*-(BrPhF)alanine Isoxazolidide 5



sequently agitated vigorously with aqueous HBr in toluene to afford the desired bromide after crystallization from isooctane.

L-*N*-[*p*-(Pinacolboronato)phenylfluorenyl]alanine isoxazolidide (**2**), the polymer-bound aldehyde precursor, was synthesized in four steps and 74% overall yield using solution-phase chemistry (Schemes 2 and 3). Initially, L-*N*-(BrPhF)alanine methyl ester **3** was synthesized in 92% yield from L-alanine methyl ester hydrochloride and 9-bromo-9-*p*-bromophenylfluorene using the literature procedure for phenylfluorenation of α-amino esters.[25] Hydrolysis of the methyl ester with aqueous LiOH in dioxane furnished *N*-(BrPhF)alanine **4** in 97% yield. *N*-(BrPhF)alanine isoxazolidide **5** was isolated as a white crystalline solid in 91% yield from coupling alanine **4** and isoxazolidine hydrochloride with *N*,*N*-diisopropylcarbodiimide and Et(*i*-Pr)$_2$N in dichloromethane.[11] Conversion of *p*-bromophenylfluorenyl-protected amide **5** into its corresponding boronate **2** was accomplished in 92% yield after chromatography by treatment of isoxazolidide **5** with diboron pinacol ester, potassium acetate, and [PdCl$_2$-(dppf)][26] in DMSO at 80 °C for 20 h (Scheme 3).[21]

Different supports were examined in the palladium-catalyzed cross-coupling reaction with boronate **2**. For example, boronate **2** was reacted with two soluble polymer supports.[27] Poly(ethylene glycol) monomethyl ether (MeO-PEG-5000)[28] and non-cross-linked-polystyrene (NCPS)[29] were used to anchor *N*-(phenylfluorenyl)amino acid analogues because reaction conversions could be monitored by ^{1}H NMR spectroscopy of these supports in solution. Boronate **2** was also cross-coupled with two nonsoluble supports. Chloromethyl cross-linked polystyrene (Merrifield resin)[30] and *p*-benzyloxybenzyl alcohol resin (Wang resin)[31] were linked to *N*-(phenylfluorenyl)-amino acid analogues because of the importance of these supports in solid-phase organic synthesis.

Aryl halide terminals were attached to the four different supports (Scheme 4). For example, MeO-PEG-5000-*p*-bromobenzyl ether **6** was synthesized by alkylation of MeO-PEG-5000 using *p*-bromobenzyl bromide in THF in the presence of NaI and 18-crown-6.[28] Non-cross-linked polystyrene (NCPS) *m*-iodophenyl ether **7** was prepared by anionic polymerization of styrene using *n*-butyllithium as initiator in toluene,[32] chloromethylation using chloromethyl methyl ether in the presence of ZnCl$_2$,[33] and ether formation with *m*-iodophenol, NaI, and NaH in a solution of 1:1 DMA/THF. Proton NMR spectroscopy was used to determine the yield of the ether-forming reactions to synthesize **6** and **7**. Measurement of the methylene proton signals of the benzylic ethers showed that MeO-PEG-5000-*p*-bromobenzyl ether **6** and NCPS-*m*-iodophenyl ether **7**, were both prepared in >96% yield. Treatment of Merrifield resin under similar conditions as described for the synthesis of NCPS-*m*-iodophenyl ether **7** gave Merrifield resin *m*-iodophenyl ether **8** in 82% yield as ascertained by the increase in polymer weight. Alkylation of Wang resin using KN(SiMe$_3$)$_2$ and *p*-bromobenzyl bromide in THF at room temperature furnished Wang resin *p*-bromobenzyl ether **9** in 78% yield as determined by the increase in polymer weight.

Boronate **2** was coupled to polymer supports **6**−**9** using [PdCl$_2$(dppf)] as catalyst and Na$_2$CO$_3$ as base in DMF at 80 °C (Scheme 3).[21] In the case of soluble polymer supports **6** and **7**, conversions were estimated by comparing the integrations of the resino benzylic protons and the alanine methyl doublet in the ^{1}H NMR spectra. The cross-coupling of boronate **2** and MeO-PEG-5000-*p*-bromobenzyl ether **6** gave a 50−60% conversion to resino isoxazolidide **10a**. Cross-coupling of NCPS-iodophenyl ether **7** with boronate **2** gave NCPS-supported isoxazolidide **10b** in >98% conversion. Merrifield resin **8** reacted with **2** to provide resino isoxazolidide **10c** in 78% conversion based on proton MAS NMR spectroscopic analysis and comparison of the integrations for the alanine methyl doublet and benzyl methylene protons.[34] Finally, cross-coupling of **2** to Wang resin **9** gave a 70% conversion to resino isoxazolidide **10d** as determined by weighing the cleavage product, (*p*-hydroxymethylphenyl-PhF)alanine isoxazolidide,[35] obtained from exposing the polymer to a 1:1 TFA/CH$_2$Cl$_2$ solution.

At present, we have focused our attention on the use of the soluble polymer-supported isoxazolidides **10a** and **10b** because reactions on these materials were effectively monitored using solution-phase NMR spectroscopy. Alaninals **1a** and **1b** were respectively synthesized by reduction of polymer-bound isoxazolidides **10a** and **10b** with LiAlH$_4$ in THF and identified by ^{1}H NMR spectroscopy, which showed an aldehyde peak at 9.1−9.2 ppm (Scheme 5).[11] In the case of MeO-PEG-5000-supported alaninal **1a**,

(25) Jamison, T. F.; Rapoport, H. *Org. Synth.* **1992**, *71*, 226.

(26) [PdCl$_2$(dppf)] was prepared according to: Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. The dppf ligand was prepared according to: Bishop, J. J.; Davison, A.; Katcher, M. L.; Lichtenberg, D. W.; Merrill, R. E.; Smart, J. C. *J. Organomet. Chem.* **1971**, *27*, 241.

(27) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.

(28) The use of MeO-PEG-5000 has been reviewed in ref 27. Ether formation with MeO-PEG-5000 was conducted as described in: (a) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1995**, *117*, 2116. (b) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5095.

(29) Examples of the employment of NCPS-polymer include: (a) Cramer, F. Helbig, R.; Hettler, H.; Scheit, K. H.; Seliger, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 601. (b) Green, B.; Garson, L. R. *J. Chem. Soc. C* **1969**, 401. (c) Guthrie, R. D.; Jenkins, A. D.; Stehlícek, J. *J. Chem. Soc. C* **1971**, 2690. (d) Narita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1477. (e) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724 and references cited in ref 27.

(30) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

(31) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

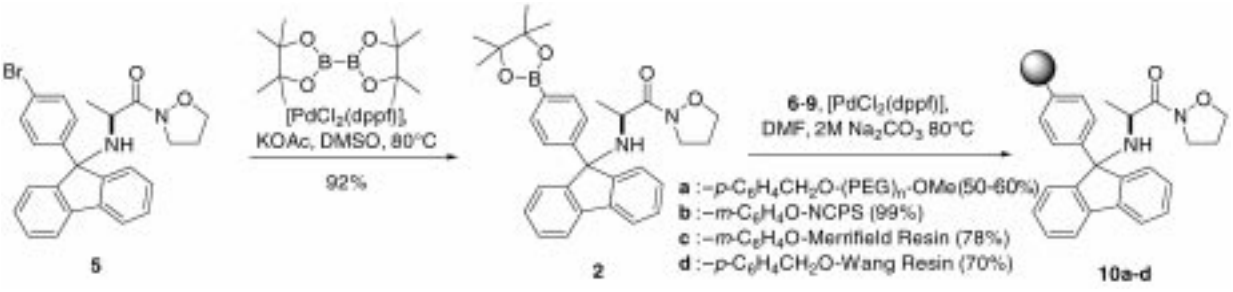
(32) Van Beylen, M.; Bywater, S.; Smets, G.; Szwarc, M.; Worsfold, D. J. *Adv. Polym. Sci.* **1988**, *86*, 87.

(33) Andreatta, R. H.; Rink, H. *Helv. Chim. Acta* **1973**, *56*, 1205.

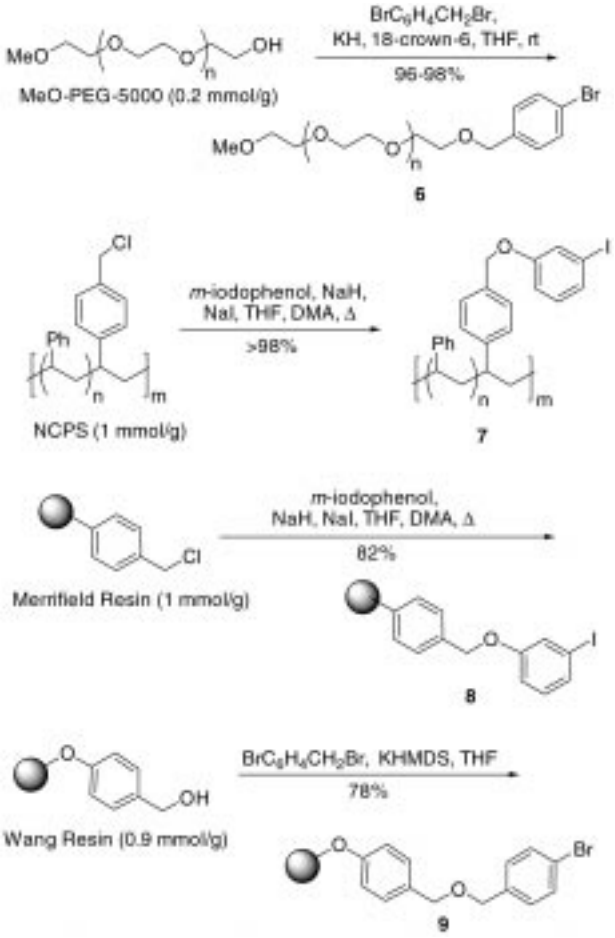
(34) The use of MAS NMR spectroscopy for monitoring solid-phase chemistry is described: (a) Pop, I. E.; Dhalluin, C. F.; Déprez, B. P.; Melnyk, P. C.; Lippens, G. M.; Tartar, A. L. *Tetrahedron* **1996**, *52*, 12209. (b) Sarkar, S. K.; Garigipati, R. S.; Adams, J. L.; Keifer, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 2305 and references therein.

(35) ^{1}H NMR (CD$_3$OD) δ 8.0−7.05 (m, 16 H), 5.4 (s, 1 H), 5.3 (s, 1 H), 4.25 (m, 1 H), 4.12 (m, 1 H), 4.02 (m, 1 H), 3.83 (m, 1 H), 3.56 (m, 1 H), 2.37 (m, 1 H) 2.10−1.98 (m, 1 H), 1.45 (d, 3 H, J = 7.0 Hz).

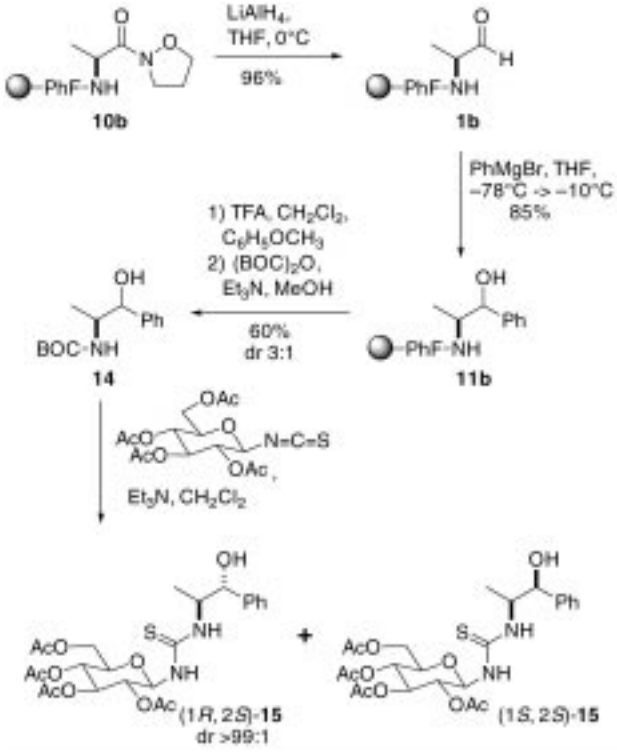
Scheme 3. Attachment of *N*-(BrPhF)alanine Isoxazolidide 5 to Polymeric Supports via Arylbroronate 2



Scheme 4. Preparation of Resino Aryl Halides 6−9



Scheme 5. Synthesis and Conversion of Polymer-bound Alaninal 1 into Enantiopure Norephedrines 14



the reaction was conducted at room temperature because the polymer had poor solubility in THF at lower temperatures. The polymer was isolated by precipitation in diethyl ether and filtration. Although ^{1}H NMR spectroscopy indicated that MeO-PEG-5000-supported alaninal **1a** was obtained in 66% yield, aldehyde **1a** was not stable and decomposed within 24 h at −20 °C. An attempt to immediately react aldehyde **1a** with excess phenylmagnesium bromide in THF at room temperature failed to provide polymer displaying amino alcohol signals in the ^{1}H NMR spectrum. These experiments indicated that MeO-PEG-5000-polymer was not suitable for α-amino aldehyde chemistry. In our hands, the breadth of chemical transformations performed with the MeO-PEG-5000-polymer was greatly limited due to low solubility in CH_2Cl_2, THF, and toluene below room temperature.

The NCPS-supported α-amino aldehyde, alaninal **1b**, was prepared by $LiAlH_4$ reduction in THF at 0 °C and stored overnight at room temperature without noticeable decomposition. Polymer-bound norephedrines **11b** were synthesized by addition of a THF solution of phenylmagnesium bromide to a −78 °C solution of NCPS-supported α-amino aldehyde **1b** in THF. Parallel experiments were conducted in solution to transform *N*-[BrPhF]alanine isoxazolidide **5** into a 1:1 mixture of diastereomeric *N*-(BrPhF)norephedrines **12** in 92% overall yield as described in the Experimental Section. Comparison of the proton NMR spectrum of NCPS-supported norephedrines **11b** with that of *N*-(BrPhF)norephedrines **12** verified the formation of the desired product from addition of phenylmagnesium bromide to polymer-bound aldehyde **1b**.

Cleavage of the amino alcohol product from the NCPS support was initially studied using solutions containing TFA in CH_2Cl_2 at room temperature; however, the polymer became insoluble under these conditions, presumably due to cross-linking of polystyrene in acid,[29b] and norephedrine could not be isolated. In examinations of the cleavage conditions using both NCPS-supported norephedrines **11b** and *N*-(BrPhF)norephedrines **12**, we found that the polymer remained soluble in solutions of TFA in CH_2Cl_2 containing anisole as cosolvent. Anisole was introduced to trap carbocations formed during the

acid-induced cleavage.[36] The reaction of the NCPS-polymer and anisole was indicated by the presence of a new peak at 3.74 ppm for the anisole methoxy group in the ^{1}H NMR spectrum of the polymer after the cleavage reaction. Treatment of polymer **11b** in a 1:2:2 TFA/CH_2Cl_2/anisole solution for 48 h at room temperature provided norephedrines that were conveniently isolated as their *N*-BOC-derivatives. After an aqueous extraction and evaporation of the aqueous phase, the purity of the crude norephedrine was estimated to be >75% by comparison of the integration of the methyl doublets for the product with that of other doublets in the same spectral region. Treatment of the crude product with di-*tert*-butyl dicarbonate and Et_3N in MeOH followed by column chromatography on silica gel provided a 3:1 mixture of diastereomeric *N*-(BOC)-norephedrines **14** in 60% yield from NCPS-supported ephedrines **11b**. For comparison, we note that a 1:1 mixture of diastereomeric *N*-(BOC)-norephedrines **14** was obtained in 66% yield from the solution-phase solvolysis of *N*-(BrPhF)norephedrines **12** and protection with di-*tert*-butyl dicarbonate. In summary, *N*-(BOC)-norephedrines **14** were produced in 46% overall yield from L-*N*-[*p*-(pinacolboronato)phenylfluorenyl]alanine isoxazolidide **2**.

The enantiomeric purity of norephedrines **14**, which were synthesized from support-bound alaninal **1b**, was determined by HPLC analysis of their 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl thioureas **15**. Diastereomeric *N*-(BOC)amino alcohols **14** were treated with trifluoroacetic acid in CH_2Cl_2 to remove the BOC group, and the crude trifluoroacetates were acylated using 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl isothiocyanate (GITC) and triethylamine in CH_2Cl_2.[37] Thioureas **15**, prepared from material cleaved from the NCPS-polymer, were then analyzed by reversed-phase HPLC using conditions that resolved all four diastereomers.[37] Comparison of the magnitudes of the major peak for the (1*R*,2*S*)-thiourea **15** and the peak that coeluted with a sample of (1*S*,2*R*)-thiourea **15** synthesized from authentic (1*S*,2*R*)-norephedrine indicated a 99:1 diastereomeric ratio of (1*R*,2*S*)- and (1*S*,2*R*)-thioureas **15**. Hence, amino alcohols **14** and polymer-bound α-amino aldehyde **1b** all are presumed to be of a 99:1 enantiomeric ratio.

Discussion

The solid-phase synthesis of enantiopure product has traditionally been addressed in peptide chemistry where a wide milieu of reagents, protecting groups, and linkers have been used to circumvent racemization.[38] The current renaissance of interest in solid-phase methods for synthesizing different organic structures in enantiopure form has created the necessity for new tools to manipulate intermediates that may be configurationally labile on polymeric supports.[1] Toward the development of a new linker for anchoring α-amino carbonyl compounds onto polymer, we selected to adapt the PhF protecting group to solid-phase chemistry because of its proven effectiveness in providing enantiomerically pure amine-bearing products in solution.[6−11] Our studies have provided the first example of a configurationally stable polymer-bound α-amino aldehyde that has been used in the synthesis of enantiopure norephedrines **14**.

Toward the development of an ideal linker, we have demonstrated that the phenyflourenyl linking/protecting group strategy is effective for loading advanced intermediates onto both soluble and insoluble supports. Alanine isoxazolidide **2** was successfully anchored to polymer-bound aryl halides by palladium-catalyzed cross-couplings in 70−99% yields. Linker stability was demonstrated both in the lithium aluminum hydride reduction of support-bound isoxazolidide **10b** and in the addition of phenylmagnesium bromide to α-amino aldehyde **1b**; both organometallic reactions proceeded without linker degradation. Final product removal was effected with TFA in CH_2Cl_2 containing anisole as cosolvent, which gave crude material of >75% purity after a simple aqueous extraction and evaporation.

Because this method may be extended to other amino acids and organometallic reagents, the potential exists to apply polymer-bound α-amino aldehydes in syntheses of amino alcohol libraries.[39,40] However, the present design has its limitations, and we are currently exploring modifications to make this approach more amenable to combinatorial chemistry. For example, to link the PhF group to the resin, we are now examining alternative transition metal-catalyzed cross-coupling procedures that do not involve the employment of the relatively expensive diboron pinacol ester.[21] We are also investigating similar chemistry with resino carbonyl compounds such as isoxazolidides **10c** and **10d**, because we believe that insoluble resins may be easier to manage in library syntheses relative to their soluble polymer counterparts. Considering the numerous biologically active compounds that possess amino alcohol components, this PhF protecting-linking group strategy may find significant use in combinatorial science for drug discovery.

In summary, we have developed a novel strategy for linking protected amino carbonyl compounds to solid supports that employs transition metal catalyzed cross-coupling chemistry. By employing this strategy to anchor PhF-protected amines to soluble polymers, we found that non-cross-linked polystyrene (NCPS) was better suited for the synthesis of configurationally stable polymer-bound alaninal **1** than the MeO-PEG-5000-polymer. The addition of an organometallic reagent to α-amino aldehyde **1**, polymer cleavage, and isolation via *N*-acylation provided enantiopure *N*-(BOC)norephedrines **14**. The application of this strategy to the synthesis of different configurationally stable polymer-bound α-amino carbonyl compounds is presently under investigation to furnish a variety of enantiomerically pure amine-bearing products.

Experimental Section

General Methods. Unless otherwise noted, all reactions were run under argon atmosphere and distilled solvents were transferred by syringe. THF was distilled from sodium/benzophenone immediately before use; CH_2Cl_2 and CH_3CN were distilled from CaH_2; $CHCl_3$ was distilled from P_2O_5;

(36) Svanholm, U.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 562.

(37) Noggle, F. T., Jr.; Clark, C. R.; De Ruiter, J. *J. Liquid Chromatogr.* **1991**, *14*, 29.

(38) reviewed in: Solid-Phase Peptide Synthesis. *Methods in Enzymology*; Fields, G. B., Ed.; Academic Press: New York, 1997; Vol. 289, Section I.

(39) Alternative strategies for synthesizing amino alcohols on solid supports include: (a) Kobayashi, S.; Moriwaki, M. *Tetrahedron Lett.* **1997**, *38*, 4251. (b) Kobayashi, S.; Moriwaki, M. Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 7783.

(40) For a solution-phase synthesis of amino alcohols via *N*-(PhF)-amino ketones see: Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 6862.

MeOH was distilled from Mg. DMSO and DMF were distilled and stored over 4 Å molecular sieves. Potassium acetate was recrystallized from 1:1 EtOH/H_2O and dried at >100 °C under vacuum before use. For reactions involving palladium catalysis, the solutions were degassed for 10−15 min by bubbling argon through the solution before addition of the catalyst. Final reaction mixture solutions were dried over Na_2SO_4. Chromatography was performed on 230−400 mesh silica gel, TLC on aluminum-backed silica plates. Melting points are uncorrected. Mass spectral data, HRMS, were obtained by the Université de Montréal Mass Spectrometry facility. ^{1}H NMR (400 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ units) downfield of internal TMS and coupling constants are reported in Hz. Aromatic carbons of compounds having PhF groups are not reported.

9-*p*-Bromophenylfluoren-9-yl Bromide (BrPhFBr). A solution of 1,4-dibromobenzene (5.0 g, 21 mmol) in THF (120 mL) at −78 °C was treated dropwise with *n*-butyllithium (7.98 mL, 19.95 mmol, 95 mol %, 2.5 M in hexanes), stirred for 20−25 min at −78 °C, and treated dropwise with a solution of fluorenone (3.60 g, 20 mmol, 95 mol %) in THF (30 mL). The mixture was stirred for 5 min at −78 °C, warmed to room temperature over 60 min, and quenched with H_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (20 mL), dried, and evaporated. The crude residue was immediately dissolved in toluene (70 mL), treated with HBr (60 mL, 48% aqueous solution), and stirred vigorously, protected from light, for 24 h at room temperature. The layers were separated, and the aqueous layer was extracted with toluene (2 × 20 mL). The combined organic layers were washed with brine (25 mL), dried, and evaporated to yield **BrPhFBr** as an oil. Crystallization from isooctane gave 7.14 g of colorless needles (89%): mp 112−113 °C; ^{1}H NMR δ 7.78−7.76 (m, 2 H), 7.62−7.60 (m, 2 H), 7.57−7.54 (m, 2 H), 7.50−7.43 (m, 4 H), 7.40−7.36 (m, 2 H); ^{13}C NMR δ 149.0, 140.3, 137.9, 131.3, 129.3, 129.13, 129.11, 129.0, 128.8, 128.7, 128.6, 125.8, 122.2, 120.4, 66.4. Anal. Calcd for $C_{19}H_{12}Br_2$: C, 57.04; H, 3.02. Found: C, 57.48; H, 3.00.

(2*S*)-*N*-(BrPhF)alanine Methyl Ester (3). A suspension of L-alanine methyl ester hydrochloride (3.66 g, 26.25 mmol, 150 mol %) in CH_3CN (70 mL) was treated with K_3PO_4 (11.70 g, 55.13 mmol, 210 mol %), $Pb(NO_3)_2$ (7.40 g, 22.31 mmol, 85 mol %), and BrPhFBr (7.0 g, 17.5 mmol), stirred for 36 h at room temperature, and treated with MeOH (7.10 mL, 175 mmol). After being stirred for 30 min, the mixture was filtered through a plug of Celite. The filter cake was thoroughly washed with $CHCl_3$ until the filtrate contained no UV-active material. Evaporation of the volatiles and chromatography of the residue using 5% EtOAc in hexanes as eluant gave ester **3** (7.31 g, 92%) as an oil that solidified on standing: mp 71−73 °C; R_f = 0.25 (1:9 EtOAc in hexanes); $[\alpha]^{20}_D$ −173.0 (c = 1, $CHCl_3$); ^{1}H NMR δ 7.69−7.67 (m, 2 H), 7.37−7.16 (m, 10 H), 3.29 (s, 3 H), 2.93 (bs, 1 H), 2.76 (q, 1 H, J = 7.0), 1.11 (d, 3 H, J = 7.0); HRMS calcd for $C_{23}H_{21}NO_2{}^{79}Br$ [MH^+] 422.0756, found 422.0747.

(2*S*)-*N*-(BrPhF)alanine (4). A solution of (2*S*)-*N*-(BrPhF)-alanine methyl ester (**3**, 3 g, 7.10 mmol) in dioxane (30 mL) was treated with a 2 M aqueous solution of LiOH (17.75 mL, 500 mol %), heated at a reflux for 3 h, cooled to room temperature, and acidified with concentrated H_3PO_4 to pH 5−6. The mixture was then saturated with solid NaCl and extracted with EtOAc until TLC of the organic layer contained no UV-active material. The combined organic layers were washed with brine (15 mL), dried and evaporated to give **4** (2.80 g, 97%) as a white foam: ^{1}H NMR δ 7.76−7.69 (m, 2H), 7.23 (m, 10 H), 2.70 (q, 1H, J = 7.2), 1.16 (d, 3H, J = 7.2). ^{13}C NMR ($CDCl_3$) δ 176.1, 72.9, 52.8, 19.3; HRMS calcd for $C_{22}H_{19}NO_2{}^{79}Br$ [MH^+] 408.0599, found 408.0617.

(2*S*)-*N*-(BrPhF)alanine Isoxazolidide (5). A stirred mixture of *N*-(BrPhF)alanine (**4**, 1.50 g, 3.68 mmol), hydroxybenzotriazole (596 mg, 4.41 mmol, 120 mol %), and isoxazolidine hydrochloride (806 mg, 7.36 mmol, 200 mol %) in CH_2Cl_2 (36 mL) was treated with Et(*i*-Pr)$_2$N (1.92 mL, 300 mol %) and DMAP (45 mg, 10 mol %), cooled to 0 °C for 15 min, and treated with *N*,*N*-diisopropylcarbodiimide (1.15 mL, 200 mol %). The mixture was stirred for 3 h at 0 °C, warmed to room temperature, and evaporated to dryness. The residue was purified by chromatography using 20−30% EtOAc in hexanes as eluant to yield isoxazolidide **5** as a white solid. Recrystallization from Et_2O in hexanes gave white needles (1.54 g, 91%): mp 143−144 °C; $[\alpha]^{20}_D$ −140.5 (c = 1, MeOH); R_f = 0.41 (1:1 EtOAc/hexanes); ^{1}H NMR δ 7.66−7.17 (m, 12 H), 3.56 (bm, 3 H), 3.13−3.01 (bm, 2 H), 2.64 (bs, 1 H), 1.97 (bm, 1 H), 1.80 (bm, 1 H), 1.12 (d, 3 H, J = 7.0); ^{13}C NMR δ 176.7, 73.1, 68.4, 48.6, 42.9, 27.0, 22.5; HRMS calcd for $C_{25}H_{24}N_2O_2{}^{79}Br$ [MH^+] 463.1021, found 463.1010. Anal. Calcd for $C_{25}H_{23}N_2O_2{}^{79}Br$: C, 64.80; H, 5.00; N, 6.05. Found: C, 64.92; H, 5.12; N, 6.12.

(2*S*)-*N*-[*p*-(Pinacolboronato)phenylfluorenyl]alanine Isoxazolidide (2). A solution of isoxazolidide **5** (247 mg, 0.53 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (diboron pinacol ester, 137 mg, 0.53 mmol, 100 mol %), and KOAc (157 mg, 1.59 mmol, 300 mol %) in DMSO (5 mL) was degassed for 10−15 min and treated with [$PdCl_2$(dppf)] (10 mg, 3 mol %). The mixture was heated at 80 °C overnight. Isoxazolidides **2** and **5** had the same R_f values in a variety of eluants; however, staining with a ceric ammonium molybdate solution showed a pink color for bromide **5** and a deep-blue color for boronate **2**. After complete disappearance of the pink staining bromide was observed by TLC, the reaction was cooled to room temperature and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O until TLC of the organic layer showed no UV-active material. The combined organic layers were washed with brine (10 mL), dried, and evaporated to a residue that was chromatographed using 20−30% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave boronate **2** (251 mg, 92%) as a colorless solid: mp >230 °C; $[\alpha]^{20}_D$ −164.4 (c = 0.23, $CHCl_3$); R_f = 0.41 (1:1 EtOAc/hexanes); ^{1}H NMR δ 7.65−7.64 (m, 4 H), 7.41−7.15 (m, 8 H), 3.64−3.5*6 (bm, 3 H), 3.03−2.98 (bm, 2 H), 2.63 (bs, 1 H), 1.95−1.94 (bm, 1 H), 1.84−1.79 (bm, 1 H), 1.28 (s, 12 H), 1.80 (d, 3 H, J = 7.0); ^{13}C NMR δ 176.9, 83.7, 73.5, 68.3, 48.5, 42.9, 27.0, 24.9, 22.6; HRMS calcd for $C_{31}H_{36}N_2O_4B$ [MH^+] 511.2768, found 511.2753. Anal. Calcd for $C_{31}H_{35}N_2O_4B$: C, 72.95; H, 6.91; N, 5.49. Found: C, 72.88; H, 7.06; N, 5.47.

MeO-PEG-5000 *p*-Bromobenzyl Ether 6. To a suspension of KH (574 mg, 5 mmol, 500 mol %, 35wt % in mineral oil) prewashed with hexanes and 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane, 10 mg) in THF (50 mL) at room temperature was added MeO-PEG-5000 (5 g, 1 mmol, 0.2 mmol/g, dried at room temperature overnight under vacuum in the presence of P_2O_5). After the mixture was stirred for 10 min, *p*-bromobenzyl bromide (1.25 g, 5 mmol, 500 mol %) was added to the mixture, which was stirred for 24 h at room temperature and filtered on Celite. The filter cake was washed with CH_2Cl_2 (15 mL) and evaporated to a volume of 15−20 mL of solvent. Diethyl ether was added to precipitate the polymer, which was then filtered and washed with ether. The polymer was recrystallized from EtOH in Et_2O in the freezer, filtered, and dried under vacuum to give **6** (4.4 g, 85%) as a white powder: ^{1}H NMR δ 7.45 (d, 2 H, J = 8.4), 7.22 (d, 2 H, J = 8.6), 4.51 (s, 2 H).

Non-Cross-Linked Polystyrene *m*-Iodophenyl Ether (NCPS-*m*-iodophenyl Ether) 7. A solution of *m*-iodophenol (1.32 g, 6 mmol) in THF (50 mL) was treated with NaH (720 mg, 18 mmol, 60% in mineral oil), stirred for 30 min, and treated with a solution of chloromethylated polystyrene (2 g, 2 mmol, 1 mmol/g, molecular weight = 38634, molecular weight distribution = 1.56) and NaI (300 mg, 2 mmol) in *N*,*N*-dimethylacetamide (25 mL). The mixture was heated at 60 °C for 24 h and poured slowly into MeOH (200 mL) with vigorous agitation. The precipitated polymer was collected, dissolved in a minimal amount of THF, and reprecipitated on addition of MeOH. The polymer was dried under vacuum to give NCPS-*m*-iodophenyl ether **7** (2.1 g, 97%) as a powder: ^{1}H NMR δ 7.35−6.25 (m, 40 H), 4.89 (bs, 2 H), 2.25−1.15 (m, 22 H).

Merrifield Resin *m*-Iodophenyl Ether 8. A suspension of *m*-iodophenol (6.05 g, 27.5 mmol, 250 mol %) in THF (50

mL) and *N*,*N*-dimethylacetamide (50 mL) was treated with NaH (1.32 g, 33 mmol, 300 mol %, 60% in mineral oil), stirred for 15 min, and treated with chloromethylated cross-linked polystyrene (Merrifield resin, 2% cross-linked, 10 g, 11 mmol, 1.1 mmol/g) and NaI (300 mg, 2 mmol). The mixture was heated at 70 °C for 48 h, cooled to room temperature, filtered, and washed sequentially with 15 mL/g resin of the following solvents: dioxane, THF, water, acetone, MeOH, and Et_2O. The polymer was then dried under vacuum to give 11.7 g of ether **8** (82% yield by weight increase).

Wang Resin *p*-Bromobenzyl Ether 9. A suspension of Wang resin (1.0 g, 0.92 mmol, 0.92 mmol/g) in THF (15 mL) at room temperature was treated with $KN(SiMe_3)_2$ (3.68 mL, 1.84 mmol, 200 mol %, 0.5 M in toluene), stirred for 30 min, and treated with *p*-bromobenzyl bromide (460 mg, 1.84 mmol, 200 mol %). After being stirred overnight, the reaction mixture was quenched with excess water, filtered, and washed sequentially with 15 mL/g resin of the following solvents: dioxane, THF, water, acetone, MeOH, and Et_2O. The resin was dried under vacuum to give 1.12 g of ether **9** (78%).

MeO-PEG-5000-supported isoxazolidide 10a was prepared using the reaction conditions described below for **10b** in the general protocol, precipitated from cold diethyl ether, filtered, and washed with cold diethyl ether. The polymer was then dried under vacuum. Proton NMR spectroscopic analysis of the polymer **10a** showed a conversion of 50−60% by integration of the methyl doublet of alanine isoxazolidide relative to the benzylic methylene protons of the polymer: ^{1}H NMR δ 7.50−7.21 (m, 16 H), 4.58 (bs, 2 H), 3.15 (bs, 1 H), 3.05 (bs, 1 H), 2.60 (bs, 1 H), 1.95 (bm, 1 H), 1.80 (bm, 1 H), 1.15 (bd, 3 H).

General Procedure for Cross-Coupling to Polymeric Aryl Halides: Synthesis of NCPS-Supported Isoxazolidide 10b. A solution of polymer **7** (350 mg, 0.35 mmol) and boronate **2** (241 mg, 0.47 mmol, 134 mol %) in DMF (10 mL) containing aqueous 2 M Na_2CO_3 (588 μL, 1.18 mmol, 250 mol %) was degassed for 10−15 min, treated with [$PdCl_2$(dppf)] (14 mg, 5 mol %), heated at 80 °C overnight, and then cooled to room temperature. The polymer was precipitated by addition of excess MeOH and collected by decanting the solvent away from the solid after placing the mixture in a centrifuge for 3−5 min. The collected polymer was dissolved in a minimal amount of $CHCl_3$, precipitated with MeOH, and recollected using a centrifuge as described. This process was repeated three times, and the recovered polymer was dried under vacuum, which provided 411 mg, (93%) of isoxazolidide **10b**: ^{1}H NMR δ 4.94 (bs, 2 H), 3.64 (bs, 1 H), 3.59 (bs, 2 H), 3.15 (bs, 1 H), 3.07 (bs, 1 H), 2.62 (bs, 1 H), 1.16 (bd, 3 H, J = 6.2).

Merrifield resino isoxazolidide 10c was prepared using the reaction conditions described for **10b**, filtered, and washed sequentially with 15 mL/g resin of the following solvents: DMF, water, acetone, THF, MeOH, and Et_2O. The resin was dried under vacuum to give **10c**, which was shown by ^{1}H MAS NMR spectroscopic analysis to be of 78% conversion by integration of the methyl doublet of alanine isoxazolidide relative to the benzylic methylene protons of the polymer: ^{1}H MAS NMR (300 MHz with nanoprobe) δ 4.90 (bs, 2 H), 3.60 (bm, 3 H), 3.15−3.00 (bm, 2 H), 2.60 (bs, 1 H), 1.15 (bs, 3 H).

Wang resino isoxazolidide 10d was prepared using the reaction conditions described for **10b**, isolated by filtration, and washed sequentially with 15 mL/g resin of the following solvents: DMF, water, acetone, THF, MeOH, and Et_2O. The resin was dried under vacuum to give **10d**, which was estimated to be of 70% conversion by cleavage of a 60 mg sample (0.04 mmol, 0.72 mmol/g) using TFA (2 mL) in CH_2Cl_2 (2 mL), which gave 15 mg of *N*-(*p*-hydroxymethylphenyl-PhF)-alanine isoxazolidide.[35]

NCPS-Supported (2*S*)-*N*-(PhF)alaninal 1b. A solution of polymer-supported isoxazolidide **10b** (60 mg, 0.05 mmol) in THF (6 mL) was cooled to 0 °C and treated with a 1.5 M solution of $LiAlH_4$ (50 μL, 0.075 mmol, 150 mol %) in THF. The clear solution was stirred for 25 min at 0 °C, quenched by the addition of EtOAc (2 mL) followed by water (1 mL), and filtered through a plug of sodium bicarbonate on Celite. The filter cake was washed thoroughly with EtOAc, and the filtrate was washed with brine, dried, and evaporated to furnish polymer-bound aldehyde **1b** (50 mg, 96%): ^{1}H NMR δ 9.25 (bs, 1 H), 4.93 (bs, 2 H), 2.65 (bs, 1 H), 0.98 (bs, 3 H).

NCPS-Supported (1*RS*,2*S*)-1-Phenyl-2-*N*-(PhF)amino-1-propanol 11b. A solution of alaninal **1b** (106 mg, 0.11 mmol) in THF (6 mL) was cooled to −78 °C and treated with a 1 M solution of PhMgBr (450 μL, 400 mol %) in THF. The stirred clear solution was allowed to warm to −10 °C over 3 h and quenched with MeOH (5 mL). The polymer was precipitated by addition of excess MeOH and collected by decanting the solvent away from the solid after placing the mixture in a centrifuge for 3−5 min. The collected polymer was dissolved in a minimal amount of $CHCl_3$, precipitated with MeOH, and recollected using a centrifuge as described. This process was repeated three times, and the recovered polymer was dried under vacuum, which provided amino alcohol **11b** (111 mg, 85% yield): ^{1}H NMR δ 4.93 (bs, 2 H), 4.11 (bs, 1 H), 2.41 (bs, 0.5 H), 2.28 (bs, 0.5 H), 0.57 (1.5 H), 0.44 (bs, 1.5 H).

(1*RS*, 2*S*)-*N*-(BOC)norephedrines 14. A solution of polymer **11b** (100 mg, 0.08 mmol) in dichloromethane (2 mL) and anisole (2 mL) was treated dropwise with TFA (950 μL), stirred for 48 h at room temperature, and treated with H_2O (5 mL). The layers were separated, and the aqueous layer was evaporated to a crude amino alcohol that was treated with $(BOC)_2O$ (120 mol %) and Et_3N (200 mol %) in dichloromethane (1 mL). After being stirred for 20 h at room temperature, the solution was evaporated to a residue that was chromatographed using a gradient of 0−50% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave 12 mg of N-protected norephedrine **14** (60%) as a 3:1 mixture of diastereomers: ^{1}H NMR δ 7.35−7.26 (m, 5 H), 4.86 (d, 0.3 H, J = 2.9), 4.64 (bm, 0.5 H), 4.56 (d, 0.7 H, J = 6.1), 4.03 (bm, 0.4 H), 3.88 (bm, 0.1 H), 1.47 (s, 6 H), 1.41 (s, 3 H), 1.08 (d, 0.8 H, J = 6.9), 1.00 (d, 2.2 H, J = 6.9); HRMS calcd for $C_{14}H_{22}NO_3$ [MH^+] 252.1600, found 252.1607.

Enantiomeric Purity of Amino Alcohols 14. A solution of **14** (2 mg) in dichloromethane (500 μL) was treated with TFA (500 μL) for 1 h at room temperature. The volatiles were removed under vacuum, and the residue was treated with GITC (3.7 mg, 120 mol %) and Et_3N (1.3 μL, 120 mol %) in dichloromethane (500 μL) at room temperature for 20 min. The volatiles were removed under vacuum, and the ureas **15** were dissolved in HPLC-grade methanol (1 mg/mL) and examined by reversed-phase HPLC using H_2O/MeOH/AcOH (51:48:1) as eluant on a C_{18} column with a flow rate of 1.0 mL/min.[37] The limits of detection were determined by measuring the relative integrations of the peaks for diastereomeric thioureas **15** from the (1*R*,2*S*)- and (1*S*,2*R*)-norephedrines. Less than 1% of the 1*S*,2*R* isomer was detected in the HPLC trace of (1*R*,2*S*)-thiourea **15**.

9-Bromo-9-phenylfluorenyl Polystyrene Resin. A suspension of polystyrene (2.8 g, 27 mequiv, washed according to the procedure described in ref 14) in cyclohexane (20 mL) was treated with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (4 mL) and stirred for 20 min at room temperature. A 2.5 M solution of *n*-butyllithium (13.5 mL, 33.8 mmol) in hexanes was added, and the mixture was heated at 65 °C for 4.5 h. After cooling to room temperature, removal of the solvents by cannula, and washing of the resin with cyclohexane (2 × 10 mL), the resin was swollen in THF (15 mL) at 0 °C and treated with a solution of fluorenone (2.02 g, 11.2 mmol, 200 mol %) in THF (10 mL). After 10 min, the cooling bath was removed, and the suspension was left to stir at room temperature overnight, quenched with water (10 mL), and stirred for 5 min. The resin was filtered and washed with 15 mL/g of the following solutions: MeOH, THF, acetone, 2:1 THF/H_2O, Et_2O, H_2O, THF, MeOH, and Et_2O. The resin was dried overnight under vacuum at 55 °C to provide 3.54 g of a yellow resin (PA-FTIR: 3548 cm^{-1}) containing 1.15 mmol of alcohol per gram of resin as determined by mass increase. A suspension of resin (1.0 g, 1.15 mmol) in benzene (15 mL) was treated with acetyl bromide (444 μL, 6 mmol, 522 mol %) and heated at a reflux overnight. The solution was cooled, and the resin was filtered, washed thoroughly with Et_2O, and dried overnight under vacuum at 55 °C to furnish 1.08 g of a yellow resin with a loading of 1

mmol/g resin as ascertained by mass increase. Spectroscopic analysis by PA-FTIR indicated complete disappearance of the alcohol band at 3548 cm^{-1}.

Solution-Phase Synthesis of *N*-(BOC)-norephedrines. A solution of (2*S*)-*N*-(BrPhF)alanine isoxazolidide (**5**, 463 mg, 1 mmol) in THF (10 mL) at 0 °C was treated with a solution of $LiAlH_4$ (730 μL, 1.1 mmol, 110 mol %, 1.5 M in THF), stirred for 20 min at 0 °C, quenched with EtOAc (2 mL) and water (2 mL), and filtered through a plug of sodium bicarbonate on Celite. The filtrate was diluted with EtOAc (10 mL), washed with brine (5 mL), dried, and evaporated to a solid that was dissolved in THF (10 mL), cooled to −78 °C, and treated with a 1 M solution of phenylmagnesium bromide (5 mL, 500 mol %) in THF, stirred for 1.5 h at −78 °C, warmed to room temperature over 30 min, quenched with water (2 mL), and diluted with EtOAc (15 mL). The organic layer was washed with brine (5 mL), dried, and evaporated to a residue that was chromatographed using a gradient of 0−30% EtOAc in hexanes as eluant. Evaporation of the collected fractions gave a 1:1 diastereomeric mixture of *N*-(BrPhF)norephedrines **12** (448 mg, 95% from isoxazolidide **5**) as an oil: ^{1}H NMR δ 7.75−6.86 (m, 17 H), 4.21 (d, 0.5 H, J = 3.3), 4.13 (d, 0.5 H, J = 8.4), 3.37 (bs, 1 H), 2.40 (m, 0.5 H, J = 3.3, 6.7), 2.30 (dq, 0.5 H, J = 1.9, 6.4), 0.56 (d, 1.5 H, J = 6.7), 0.44 (d, 1.5 H, J = 6.4); HRMS calcd for $C_{28}H_{25}NO^{79}Br$ 470.1119, found 470.1132.

A solution of *N*-(BrPhF)norephedrines **12** (42.3 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) and anisole (1 mL) was treated with TFA (900 μL), stirred at room temperature overnight, and diluted with water (5 mL). The layers were separated, and the aqueous layer was evaporated to a residue. A solution of the residue in MeOH (1.2 mL) was treated with Et_3N (13 μL) and $(BOC)_2O$ (12 mg, 120 mol %), stirred overnight at room temperature, and evaporated to a residue that was chromatographed using a 0−50% gradient of EtOAc in hexanes. Evaporation of the collected fractions gave **14** (15 mg, 66%) as a 1:1 diastereomeric mixture that exhibited the same characteristics as material prepared on the NCPS-polymer.

Acknowledgment. This research was supported in part by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Ministère de l'Éducation du Québec. F.G. thanks NSERC for a PGSB Scholarship (1997−99) and FCAR for a M.Sc. Scholarship (1996−97). The authors thank Professor Todd Marder at the University of Durham, as well as Merck Frosst Canada and Sigma-Aldrich Chemicals, for generous gifts of diboron pinacol ester.

Supporting Information Available: ^{1}H NMR spectra of **3**, **4**, **6**, **7**, **10a**−**c**, **1b**, **11b**, and **14** and HPLC trace of thioureas **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982413C