Solid-Phase Synthesis of 4-Arylazetidin-2-ones via Suzuki and Heck Cross-Coupling Reactions

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Application of the Suzuki and the Heck cross-coupling reactions for efficient synthesis of diverse biaryl- and styryl-substituted β-lactams on solid support using an optimized catalyst system is reported. The coupling of phenylboronic acid with the resin-bound 3-phenoxy-4-iodophenyl β-lactam **1a** proceeded in 89% isolated yield by employing 20 mol % of the bidentate phosphine−palladium complex, [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride {$PdCl_2$(dppf)} as catalyst in the presence of triethylamine (TEA, 10 equiv) in DMF at 65 °C for 12 h. Efficient cross-coupling of the iodophenyl β-lactam to heterocyclic boronates and aryl boronates substituted with various electron-donating and -withdrawing groups is also demonstrated. The reverse coupling reactions of immobilized arylboronic acid **1c** with a variety of substituted aryl iodides were found to proceed in excellent yields using the same catalyst system in a 3/7 mixture (v/v) of H_2O:DMF at 40 °C. The use of this catalyst for the vinylation of aryl iodide **1a** via the Heck reaction was also examined.

Introduction

Combinatorial synthesis has emerged within the past few years as an important new approach for the discovery and optimization of pharmaceutical lead compounds.[1] Generating diversely functionalized sets of many different compound classes is currently a major preoccupation within most drug companies. The types of structural templates receiving particular attention include both familiar heterocycles (e.g. benzodiazepines, β-lactams) with proven pharmaceutical utility as well as novel or less extensively investigated scaffolds with some intuitive medicinal chemical appeal. Biaryl fragments represent one class of structural motif that has been the focus of considerable synthetic interest since the biaryl moiety is an important pharmacophore present in many biologically active molecules.[2] In particular, palladium-catalyzed carbon−carbon bond formation provides a very attractive method for the generation of libraries of diverse biphenyl compounds. Recently, several groups have described intermolecular palladium cross-coupling reactions on solid support via Stille,[3] Suzuki,[4] and Heck[5] reactions, yet applications of these synthetic strategies to produce more complex biaryl heterocyclic molecules have to date been rather limited in scope.[3b,4f] We recently reported a solid-supported combinatorial synthesis of structurally diverse β-lactams via a [2 + 2] cycloaddition reaction of ketenes with resin-bound imines derived from amino acids.[6] To complement this strategy, we were interested in producing combinatorial libraries of substituted 4-biaryl azetidin-2-ones that represent a novel and pharmaceutically attractive class of β-lactams. Herein we report an application of the Suzuki and the Heck cross-coupling reactions for efficient synthesis of biaryl and styryl β-lactams on solid support. In addition we describe the first example of a resin-bound imine derived from a boronic acid, prepared without prior protection, and its application in [2 + 2] cycloaddition and subsequent Suzuki coupling reactions. Although there have been several reports published on solid-phase palladium catalyzed C−C bond formation, these methods require different sets of conditions (catalysts, base, temperature) depending upon the substrate (aryl iodides vs aryl bromides; immobilized boronic acid vs immobilized aryl halides). Our objective was to identify mild reaction conditions requiring a single catalyst system that would be suitable for the automated construction of libraries of diverse biaryl- and styryl-substituted β-lactams and allow complete conversion to product with a wide range of substrates.

Results and Discussion

Our initial experiments began by studying the coupling of phenylboronic acid with resin-bound 3-phenoxy-4-iodophenyl β-lactam **1a**, obtained as a mixture of two cis diastereoisomers via [2 + 2] cycloaddition reaction of phenoxy ketene with an alanine aldimine ester derivative of Sasrin or Wang resin (Scheme 1). Since one recent

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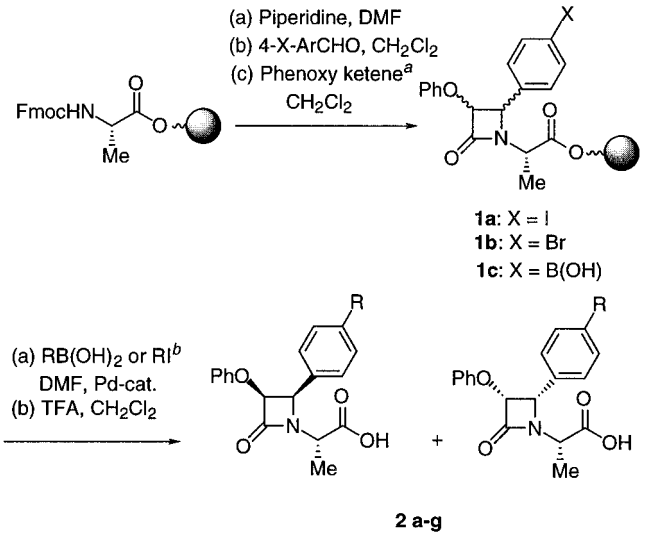
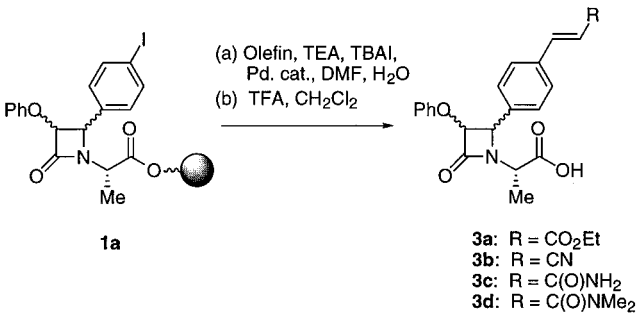
Scheme 1[a]



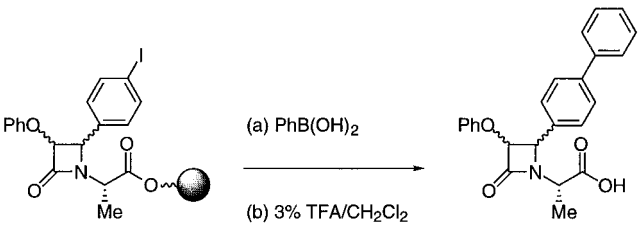
[a] Sasrin, Wang, or ArgoGel-MB-OH resins can be used for the synthesis of **1a** and **1b**, and for the coupling reactions of **1a** and **1b** with boronates. ArgoGel-MB-OH is the resin of choice for synthesis of **1c** and for the coupling reactions of **1c** with aryl iodides. [b] $RB(OH)_2$ used with **1a** and **1b,** RI used with **1c**.

Scheme 2



report has suggested that the solid-phase Suzuki reaction can be conducted at room temperature using tetrakis(triphenylphosphine)palladium $\{Pd(PPh_3)_4\}$ as catalyst,[4c] we were interested in applying these conditions to the β-lactam scaffold. In our hands, exposure of **1a** to a variety of catalyst systems in homogeneous or heterogeneous media gave no Suzuki cross-coupling product with phenylboronic acid at ambient temperature.[7] The reaction mixture had to be heated in DMF for coupling to occur. The resulting products were cleaved from the support with TFA−CH_2Cl_2 and analyzed using reversed-phase HPLC, ^{1}H NMR spectroscopy, and electrospray mass spectrometry. These results show that the typical Suzuki reaction conditions in which $\{Pd(PPh_3)_4\}$ was used as catalyst afforded complete conversion of **1a** (see Table 1). However, the desired biaryl β-lactam **2a** was isolated in only 55% yield along with a tetraarylphosphonium β-lactam byproduct resulting from quaternization of triphenylphosphine by the iodophenyl β-lactam.[8] Treatment of **1a** with $\{Pd(PPh_3)_4\}$ in DMF at 40 °C in the presence of triethylamine (TEA) and in the absence of the boronic acid quantitatively converted the iodide to this byproduct. To circumvent this side reaction,

Table 1. Coupling of Resin-Bound Aryl Iodide 1a with Phenylboronic Acid



1a **2a**

entry	catalyst system[a]	conversion[b](yield,%)[c]
1	$\{Pd(PPh_3)_4\}$−TEA[d]	100 (55)
2	$\{Pd(OAc)_2\}$−P(*o*-tol)$_3$[e]−TEA[f]	60
3	$\{Pd(OAc)_2\}$−TEA[f]	32
4	$\{Pd_2dba_3\}$−K_2CO_3[g]	32
5	$\{Pd_2dba_3\}$−TEA[d]	32
6	$\{PdCl_2(dppf)\}$−TEA[f]	100 (89)[h]

[a] Reaction run with **1a**, boronic acid (4 equiv), and catalyst (20 mol %) in DMF at 65 °C under argon atmosphere for 12−24 h. [b] Conversion estimated from ^{1}H NMR and HPLC. [c] Isolated yields of **2a** after purification by HPLC, over the four-step sequence, based on the initial resin loading. [d] 20 equiv. [e] 40 mol %. [f] 10 equiv. [g] 2 equiv. [h] 100% (81) from **1b**.

catalyst systems containing more hindered phosphines such as tri-*o*-tolyl phosphine (P(*o*-tol)$_3$) or catalysts without phosphine ligands such as palladium(II) acetate $\{Pd(OAc)_2\}$ and tris(dibenzylideneacetone)dipalladium $\{Pd_2(dba)_3\}$ were explored but found to be only moderately reactive. We found, however, that the desired biphenyl β-lactam could be obtained in 89% isolated yield by employing modest quantities (20 mol %) of the bidentate phosphine−palladium complex, [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride $\{PdCl_2$-(dppf)$\}$ in the presence of TEA (10 equiv) in DMF at 65 °C for 12 h. Interestingly, the bromophenyl analogue, **1b**, which is expected to be significantly less reactive than the iodo derivative, also exhibited excellent conversion with this catalyst system.

The high efficiency of this catalyst has been ascribed to its large P−Pd−P angle therefore allowing facile reductive elimination during the catalytic cycle.[9] Interestingly, and in contrast to our finding that $\{PdCl_2(dppf)\}$ works best for biaryl coupling in this β-lactam system, Guiles and co-workers reported that while $\{PdCl_2(dppf)\}$ is the catalyst of choice for a coupling reaction involving an alkenyl borane, it is completely unreactive in a biphenyl coupling (at room temperature).[4c] To establish the broad applicability of our reaction conditions, we were next interested in determining the extent of the biaryl β-lactam coupling with heterocyclic boronates and aryl boronates substituted with various electron-donating and -withdrawing groups. As shown in Table 2, a wide array of functionalized boronic acids can be used. HPLC and ^{1}H NMR analysis of the crude products indicated that the reactions were typically driven to completion, and upon purification by preparative HPLC, pure biaryl products were obtained in high yields (within 65−83% based upon the initial loading of the amino acid) even when electron-deficient boronic acids (3-acetamidophenylboronic acid) or ortho-substituted boronic acids (2-methoxyphenylboronic acid) were used. In accord with

(7) In our hands, attempts to reproduce the room-temperature conditions described by Guiles et al. for coupling Sasrin (or Wang)-bound 4-iodobenzoic acid with phenylboronic acid by employing 10 mol % of $Pd_2(dba)_3$ as catalyst in the presence of 2 equiv of K_2CO_3 in DMF for 24 h under a nitrogen atmosphere proved largely unsuccessful. Analysis of the crude by HPLC (λ = 254 nm and λ = 280 nm) showed 13% of 4-phenylbenzoic acid and 87% of unreacted 4-iodobenzoic acid.

(8) Analysis of the byproduct, obtained as a mixture of two cis diastereoisomers: MS (ESI): *m*/*z* 572; ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.0−6.8 (m, 24H), 5.8 (d, 1H), 5.7 (d, 1H), 5.65 (d, 1 H), 5.55 (d, 1 H), 4.6 (q, 1 H), 4.2 (q, 1 H), 1.6 (d, 3 H), 1.2 (d, 3 H).

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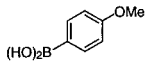
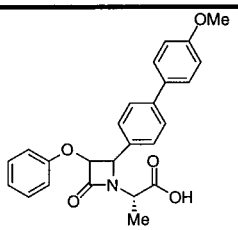
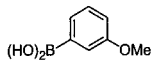
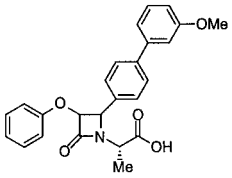
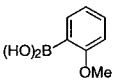
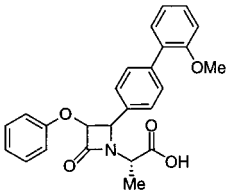
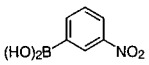
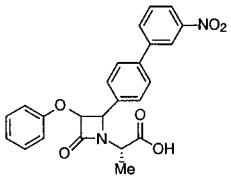
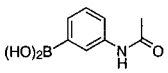
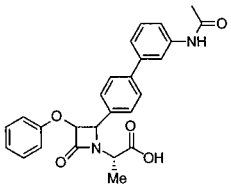
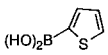
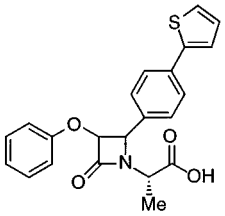
Table 2. Coupling of Resin-Bound Aryl Iodide 1a with a Variety of Boronic Acids[a]

Entry	Boronic acid	Product[b]		yield[c],%
1			**2b**	80, 75[d]
2			**2c**	72
3			**2d**	65
4			**2e**	77
5			**2f**	70
6			**2g**	83, 81[d]

[a] Reactions conditions reported in Table 1, entry 6. [b] Products were isolated as a 1:1 mixture of two cis isomers. [c] Isolated yields calculated as described in Table 1. [d] Yields obtained using aryl bromide **1b**.

our previous results, compounds **2a**−**g** were isolated as ∼1:1 mixtures of cis diastereomers, and comparable product yields were obtained from both Sasrin and Wang resins.

From the perspective of structural diversification in a library synthesis, it would be preferable to conduct Suzuki cross-coupling reactions using resin-bound boronic acids or boronic esters since the variety of commercially available substituted aryl iodides is much greater than for substituted boronates. Therefore, we were interested in modifying our Suzuki coupling substrate from the resin-bound phenyl iodide **1a** to the immobilized β-lactam phenylboronic acid **1c**. Although the Suzuki cross-coupling reaction of polymer-supported aryl iodides has been well documented, the reverse coupling reaction of resin bound arylboronic acids or boronic esters has received less attention. Guiles et al. have observed that Suzuki coupling reactions with resin-bound boronates proceed at lower rates and in poorer yields than for the alternate orientation.[4c] The phenylboronic acid **1c** was synthesized on Wang and Sasrin resins by standard [2 + 2] cycloaddition reaction of an immobilized phenylboronic acid imine.[10] Analyzing a cleaved sample of **1c** by ^{1}H NMR and MS revealed that the β-lactam boronic acid was obtained in only 80% purity due to incomplete cycloaddition reaction.[11] By switching from a polystyrene resin to a poly(ethylene glycol)-grafted resin (ArgoGel-MB-OH), the desired boronic acid **1c** was obtained with >95% purity.

The results of coupling the ArgoGel-bound boronic acid **1c** with iodobenzene using our above-mentioned Suzuki coupling conditions resulted in only 30% conversion to the desired biaryl β-lactam **2a** (see Table 3).

It was found that addition of water to the reaction medium was critical for driving the reaction to completion. When {$PdCl_2$(dppf)} plus TEA (10 equiv) was

(10) For the formation of the phenyl boronic acid imine the use of 4 Å molecular sieves as a dehydrating agent was preferred to use of trimethyl orthoformate, which resulted in incomplete imine formation.

Table 3. Suzuki Cross-Coupling Reaction of 1c with a Variety of Aryl Iodides

entry	X-C_6H_4I X	catalyst system[a]	product	conversion (%yield)[b]
1	H	$PdCl_2$(dppf)−TEA−DMF	**2a**	30
2	H	$PdCl_2$(dppf)−TEA−DMF, 10% H_2O	**2a**	60
3	H	$PdCl_2$(dppf)−TEA−DMF, 30% H_2O	**2a**	100 (86)
4	H	$Pd(PPh_3)_4$−K_2CO_3−DMF, 10% H_2O	**2a**	100 (86)
5	4-OMe	$PdCl_2$(dppf)−TEA−DMF, 30% H_2O	**2b**	100 (60)
6	3-NO_2	$PdCl_2$(dppf)−TEA−DMF, 30% H_2O	**2e**	100 (72)

[a] Reactions were carried out at 40 °C in DMF or DMF/H_2O for 12−24 h using a mixture of **1c**, phenyl iodide (10 equiv), catalyst (20 mol %), and TEA (10 equiv). [b] Isolated yields calculated as described in Table 1.

employed as catalyst in a 3/7 mixture (v/v) of H_2O:DMF at 40 °C *without exclusion of air*, the biaryl β-lactam **2a** was obtained in excellent yield. In contrast to biaryl couplings with the immobilized aryl iodide, it was found that in these reverse couplings, the nature of the solid support had a dramatic effect on the coupling yields. By using a polystyrene resin like Wang or Sasrin, the coupling of boronic acid **1c** proceeded with only 60% conversion. It is possible that the presence of water deactivates these polystyrene resins by decreasing their swelling properties. The scope of the Suzuki coupling of **1c** using the above conditions was examined by using phenyl iodides substituted with electron-donating and electron-withdrawing groups. These results (Table 3) show that biaryl couplings with an immobilized boronic acid proceed in good yields and with similar efficiency to the couplings with immobilized aryl iodides. The utility of this "boronic down" strategy should be further enhanced by the direct conversion of resin-bound aryl halides into boronate esters using Miyaura's reagent as described in two recent reports.[12a,b]

Encouraged by finding that one catalyst system, {$PdCl_2$(dppf)}-TEA, can be used for Suzuki biaryl coupling with either resin-bound halides or boronic acids, we were interested in extending the use of this catalyst to the vinylation of aryl iodide **1a**.

The Heck reaction is a very useful process for preparing disubstituted olefins,[13] and by applying it to our β-lactam system we further increase the potential for preparing diversely functionalized 4-aryl β-lactams. By coupling the resin-bound iodide **1a** with ethyl acrylate at 40 °C, in the presence of 20 mol % {$PdCl_2$(dppf)} in a 9/1 mixture (v/v) of DMF:H_2O containing TEA (10 equiv) and tetrabutylammonium iodide (TBAI, 2 equiv), the styryl β-lactam derivative **3a** was obtained in 90% yield after purification by preparative HPLC (Scheme 2). This method was found to work well with a variety of vinyl derivatives including acrylonitrile and acrylamides to afford highly functionalized 4-styryl β-lactams. Other catalyst systems commonly used in Heck reactions, including {$Pd(OAc)_2$}/PPh_3/K_2CO_3 or {$Pd(OAc)_2$}/P(*o*-tol)$_3$/TEA, were found to be ineffective here. The use of {$PdCl_2$(dppf)} in Heck reactions has previously only been reported once in the context of an intramolecular cyclization.[14]

In conclusion, this report illustrates the use of a single catalyst system, {$PdCl_2$(dppf)}−TEA, to promote C−C bond formation around a β-lactam template via Suzuki and Heck cross-coupling reactions. The remarkable versatility and stability of this catalyst obviates the requirement for an inert reaction atmosphere, and the mild coupling conditions simplify and expand the scope of Pd-catalyzed C−C bond formation and should facilitate automation of this chemistry. In addition, these reactions should be well suited for the generation of combinatorial libraries of diversely substituted 4-aryl β-lactams as well as other aryl templates.

Experimental Section

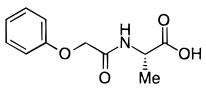
General. Reagents were purchased from Aldrich, P&B, Lancaster, Bachem Bioscience, and Argonaut and were used as received, unless otherwise noted. All reactions carried out at room temperature were conducted in standard peptide vessels placed on a shaker. Reactions performed at elevated temperature were conducted in glass vials using a heat block placed on a shaker. ^{1}H and ^{13}C NMR spectra were measured in the indicated solvent with tetramethylsilane as internal reference. Mass spectra were obtained with either ESI or FAB as the ionization method. Analytical HPLC was performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 equipped with a Econosphere C-18 reversed-phase column. Detection was performed by UV monitoring at λ = 220 nm and λ = 280 nm. Semipreparative chromatography was performed on a Beckman 110B apparatus equipped with a Waters RCM (25 × 10 cm) C-18 reversed-phase column monitoring at λ = 220 nm.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-iodophenyl)azetidin-2-one (1a).** Sasrin resin preloaded with N-Fmoc-alanine (0.24 mmol, i.e., 0.4 g of resin, loading 0.6 mmol/g) was treated with a solution of 30% piperidine in DMF for 45 min to remove the Fmoc protecting group. The resin was rinsed with DMF, CH_2Cl_2, MeOH, and Et_2O and dried under reduced pressure. The resin was suspended in 8 mL of a 1:1 mixture of CH_2Cl_2 and trimethyl orthoformate, and 4-iodobenzaldehyde (0.55 g, 10 equiv) was added. After shaking for 4 h, the resin was rinsed with DMF, CH_2Cl_2, MeOH, and Et_2O and dried under reduced pressure. The resin was transferred to a glass vial, suspended in CH_2Cl_2 (4 mL), and cooled at 0 °C. To the suspension was added triethylamine (0.68 mL, 20 equiv), followed by a slow addition of phenoxyacetyl chloride (0.5 mL, 15 equiv). The resulting slurry was left at 0 °C for 5 min and stirred overnight at room temperature. The resin was filtered, rinsed with DMF, CH_2Cl_2, MeOH, and Et_2O, and dried under reduced pressure. The product was cleaved from the support by treating 50 mg of the resin with a solution of 3% (v/v) of TFA/CH_2Cl_2 for 45 min. After filtration and removal of the solvent, the residue was purified by preparative HPLC to give the title compound (12 mg, 95%) as a gum (1.2:1 mixture of cis diastereoisomers): MS (ESI) *m/z* 438 ($M + H^+$); HRMS (FAB) *m/z* calcd for $C_{18}H_{17}INO_4$ ($M + H^+$) 438.0202, found 438.0203.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70−7.60 (m, 2H), 7.20−7.10 (m, 4H), 6.94 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 5.52 (d, J = 4.7 Hz, 1H), 5.20 (d, J = 4.7 Hz, 1H), 4.72 (q, J = 7.5 Hz, 1H), 1.22 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.4, 168.5, 158.2, 139.1, 139.0 (2C), 135.6, 132.2, 130.9 (2C), 123.9, 117.1 (2C), 96.4, 82.9, 63.5, 51.5, 17.4.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70−7.60 (m, 2H), 7.20−7.10 (m, 4H), 6.94 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 5.48 (d, J = 4.7 Hz, 1H), 5.02 (d, J = 4.7 Hz, 1H),

(11) With Sasrin and Wang resins the desired β-lactam was contaminated with a byproduct that was characterized as **4**. Running the reaction under more stringent conditions (rigorously dried reagents and vessels, plus elevated temperature for the imine formation) did not prevent its formation. Compound **4** was isolated by semipreparative HPLC and analyzed by ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.28−7.22 (m, 3H), 6.98−6.88 (m, 2H), 4.5 (q, J = 7.3 Hz, 1H), 4.4 (s, 2H), 1.4 (d, J = 7.3 Hz, 3H).



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4.05 (q, J = 7.5 Hz, 1H), 1.73 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.1, 168.5, 158.2, 139.1, 139.0 (2C), 135.6, 132.1, 130.9 (2C), 123.9, 117.1 (2C), 96.4, 83.0, 64.1, 53.3, 16.9.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-bromophenyl)azetidin-2-one (1b).** After following the above procedure using 4-bromobenzaldehyde, the title compound was obtained (10.8 mg, 92%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 390 (M + H$^+$); HRMS (FAB) calcd for $C_{18}H_{17}NBrO_4$ (M + H$^+$) 390.0341, found 390.0338.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49−7.41 (m, 2H), 7.36−7.25 (m, 2H), 7.15 (t, J = 7.7 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.7 Hz, 2H), 5.52 (d, J = 4.7 Hz, 1H), 5.22 (d, J = 4.7 Hz, 1H), 4.70 (q, J = 7.5 Hz, 1H), 1.20 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 168.6, 158.2, 134.9, 133.1 (2C), 132.04 (2C), 130.9 (2C), 124.6, 123.9, 117.1 (2C), 82.8, 63.4, 51.5, 17.4.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49−7.41 (m, 2H), 7.36−7.25 (m, 2H), 7.15 (t, J = 7.7 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.7 Hz, 2H), 5.22 (d, 1H, J = 4.7 Hz), 5.02 (d, J = 4.7 Hz, 1H), 4.02 (q, J = 7.5 Hz, 1H), 1.71 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.2, 167.8, 158.2, 133.5, 133.1 (2C), 131.9 (2C), 130.9 (2C), 124.7, 123.9, 117.1 (2C), 82.9, 63.9, 53.3, 16.9.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-boronophenyl)azetidin-2-one (1c).** ArgoGel-MB-OH resin loaded with N-Fmoc-alanine (0.11 mmol, i.e., 0.3 g of resin, loading 0.37 mmol/g) was treated with a solution of 30% piperidine in DMF for 45 min to remove the Fmoc protecting group. The resin was rinsed with DMF, CH_2Cl_2, MeOH and Et_2O and dried under reduced pressure. The resin was suspended in DMF (4 mL), and 4-formylbenzeneboronic acid (0.17 g, 10 equiv) was added. After stirring for 16 h at 40 °C in the presence of 4 Å molecular sieves, the reaction was transferred to an Alltech filter to remove the molecular sieves which remain at the bottom of the reaction vessel. The resin was rinsed with DMF and CH_2Cl_2, transferred to a glass vial, suspended in CH_2Cl_2 (5 mL), and cooled to 0 °C. To the suspension was added TEA (0.17 mL, 12 equiv) followed by a slow addition of phenoxyacetyl chloride (0.14 mL, 10 equiv). The resulting slurry was left at 0 °C for 5 min and stirred overnight at room temperature. The resin was filtered, rinsed with DMF and CH_2Cl_2, and dried under reduced pressure. The product was cleaved from the support by treating 50 mg of the resin with a solution of 5% (v/v) of TFA/CH_2Cl_2 for 45 min. After filtration and removal of the solvent, the residue was purified by preparative HPLC to give the title compound (6 mg, 92%) as a white solid (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 356 (M + H$^+$).

Major isomer: ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.78 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 8.1 Hz, 2H), 7.08−7.21 (m, 2H), 6.78−6.88 (m, 3H), 5.60 (d, J = 4.7 Hz, 1H), 5.39 (d, J = 4.7 Hz, 1H), 4.58 (q, J = 7.3 Hz, 1H), 1.18 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ: 173.6, 167.9, 159.5, 139.8, 136.1, 136.09 (2C), 131.5 (2C), 130.3 (2C), 123.9, 117.6 (2C), 83.9, 64.2, 52.2, 17.7.

Minor isomer: ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.78 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 8.1 Hz, 2H), 7.08−7.21 (m, 2H), 6.78−6.88 (m, 3H), 5.58 (d, J = 4.7 Hz, 1H), 5.27 (d, J = 4.7 Hz, 1H), 4.08 (q, J = 7.3 Hz, 1H), 1.67 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6)) δ: 173.4, 167.6, 159.5, 138.6, 136.1, 136.0 (2C), 131.5 (2C), 130.3 (2C), 124.0, 117.6 (2C), 84.0, 64.7, 53.8, 17.3.

General Method for Suzuki Cross-Coupling Reaction of Resin-Bound Halide. *cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-biphenyl)azetidin-2-one (2a). Resin-bound *cis*-1-((*S*)-1-carboxyethyl)-3-phenoxy-4-(4′-iodophenyl)azetidin-2-one (**1a**) (200 mg, loading 0.6 mmol/g) was swollen in DMF (3 mL), and the suspension was flushed with argon for 5 min. To this slurry were added phenylboronic acid (0.06 g, 4 equiv), {$PdCl_2$(dppf)} (0.02 g, 20 mol %), and triethylamine (1.7 mL, 10 equiv). The resulting mixture was heated at 65 °C overnight. After cooling to 23 °C, the resin was filtered, rinsed with DMF, CH_2Cl_2, and Et_2O, and dried under reduced pressure. The product was cleaved from the support by treating 50 mg of the resin (Sasrin or Wang) for 45 min with a solution of 5% (v/v) of TFA/CH_2Cl_2 or 50% (v/v) TFA/CH_2Cl_2, respectively. After removal of residual traces of catalyst by quick filtration through a 200 mg silica bed with ethyl acetate, the residue was purified by preparative HPLC to give the title compound (10.5 mg, 89%) as a white solid (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 410 (M + Na$^+$); HRMS (FAB) calcd for $C_{24}H_{22}NO_4$ (M + H$^+$) 388.1549, found 388.1543.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65−7.32 (m, 9H), 7.15 (t, J = 7.7 Hz, 2H), 6.91 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.4 Hz, 2H), 5.57 (d, J = 4.5 Hz, 1H), 5.30 (d, J = 4.5 Hz, 1H), 4.77 (q, J = 7.5 Hz, 1H), 1.28 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.3, 168.7, 158.4, 143.1, 141.9, 134.6, 130.8 (2C), 130.7 (2C), 130.4 (2C), 129.1, 128.6 (2C), 128.4 (2C), 123.7, 117.2 (2C), 83.2, 63.8, 51.4, 17.5.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65−7.32 (m, 9H), 7.15 (t, J = 7.7 Hz, 2H), 6.91 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.4 Hz, 2H), 5.52 (d, J = 4.5 Hz, 1H), 5.12 (d, J = 4.5 Hz, 1H), 4.05 (q, J = 7.5 Hz, 1H), 1.79 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.9, 168.0, 158.4, 143.3, 141.9, 133.3, 130.8 (2C), 130.7 (2C), 130.4 (2C), 129.1, 128.6 (2C), 128.4 (2C), 123.7, 117.2 (2C), 83.3, 64.4, 53.3, 17.0.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4″-methoxy-4′-biphenyl)azetidin-2-one (2b).** After following the above procedure using 4-methoxyphenylboronic acid, the title compound was obtained (10.0 mg, 80%) as a white powder (1.2:1 mixture of *cis* diastereoisomers): MS (ESI) m/z 418 (M + H$^+$); HRMS (FAB) calcd for $C_{25}H_{24}NO_5$ (M + H$^+$) 418.1654, found: 418.1648.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55−7.42 (m, 6H), 7.15 (t, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 7.7 Hz, 2H), 5.55 (d, J = 4.5 Hz, 1H), 5.28 (d, J = 4.5 Hz, 1H), 4.72 (q, J = 7.5 Hz, 1H), 3.82 (s, 3H), 1.27 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δSPCLN 176.2, 168.6, 160.9, 158.5, 142.7, 134.4, 132.6, 130.8 (3C), 130.7 (2C), 129.6 (2C), 127.9, 123.7, 117.2 (2C), 115.8 (2C), 83.2, 63.8, 56.9, 51.5, 17.5.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55−7.42 (m, 6H), 7.15 (t, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 7.7 Hz, 2H), 5.51 (d, J = 4.5 Hz, 1H), 5.09 (d, J = 4.5 Hz, 1H), 4.07 (q, J = 7.5 Hz, 1H), 3.82 (s, 3H), 1.78 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.8, 167.9, 160.9, 158.5, 142.9, 134.0, 132.6, 130.8 (3C), 130.7 (2C), 129.6 (2C), 128.1, 123.7, 117.2 (2C), 115.8 (2C), 83.2, 64.4, 56.9, 53.3, 17.0.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(3″-methoxy-4′-biphenyl)azetidin-2-one (2c).** After following the above procedure using 3-methoxyphenylboronic acid the title compound was obtained (9.0 mg, 72%) as a beige powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 418 (M + H$^+$); HRMS (FAB) calcd for $C_{25}H_{24}NO_5$ (M + H$^+$) 418.1654, found 418.1656.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59−7.42 (m, 4H), 7.35 (t, J = 8.0 Hz, 1H), 7.21−7.05 (m, 4H), 6.92 (d, J = 7.6 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 5.56 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 4.0 Hz, 1H), 4.75 (q, J = 7.4 Hz, 1H), 3.86 (s, 3H), 1.26 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 168.9, 161.5, 158.4, 143.4, 143.0, 134.7, 131.4, 130.9 (3C), 130.7 (2C), 128.5 (2C), 123.8, 121.1, 117.2, 114.5, 114.4, 83.0, 63.9, 56.9, 51.6, 17.4.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59−7.42 (m, 4H), 7.35 (t, J = 8.0 Hz, 1H), 7.21−7.05 (m, 4H), 6.92 (d, J = 7.6 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 5.53 (d, J = 4.0 Hz, 1H), 5.12 (d, J = 4.0 Hz, 1H), 4.05 (q, J = 7.4 Hz, 1H), 3.86 (s, 3H), 1.78 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.3, 168.2, 161.5, 158.4, 143.4, 143.2, 133.4, 131.4, 130.9 (3C), 130.7 (2C), 128.6, 128.5, 123.8, 121.1, 117.2, 114.5, 114.4, 83.1, 64.5, 56.9, 51.6, 17.0.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(2″-methoxy-4′-biphenyl)azetidin-2-one (2d).** After following the above procedure using 2-methoxyphenylboronic acid, the title compound was obtained (8.2 mg, 65%) as a beige powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 418 (M + H$^+$); HRMS (FAB) calcd for $C_{25}H_{24}NO_5$ (M + H$^+$) 418.1654, found 418.1653.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52−7.38 (m, 4H), 7.38−7.22 (m, 2H), 7.13 (t, J = 7.4 Hz, 2H), 7.08−6.92 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 4.0 Hz, 2H),

5.55 (d, J = 4.6 Hz, 1H), 5.27 (d, J = 4.6 Hz, 1H), 4.73 (q, J = 7.5 Hz, 1H), 3.76 (s, 3H), 1.28 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 169.0, 158.5, 158.0, 140.6, 134.0, 132.4 (2C), 131.5, 131.0, 130.8 (3C), 130.4, 129.9 (2C), 123.7, 122.5, 117.4, 113.1, 83.1, 64.0, 57.2, 51.7, 17.4.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52−7.38 (m, 4H), 7.38−7.22 (m, 2H), 7.13 (t, J = 7.4 Hz, 2H), 7.08−6.92 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 4.0 Hz, 2H), 5.51 (d, J = 4.6 Hz, 1H), 5.08 (d, J = 4.6 Hz, 1H), 4.03 (q, J = 7.5 Hz, 1H), 3.77 (s, 3H), 1.80 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.4, 168.3, 158.45, 158.0, 140.7, 132.7, 132.4 (2C), 131.5, 131.0, 130.80 (3C), 130.5, 129.8 (2C), 123.7, 122.5, 117.4, 113.1, 83.3, 64.6, 57.2, 53.6, 17.4.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(3″-nitro-4′-biphenyl)azetidin-2-one (2e).** After following the above procedure using 3-nitrophenylboronic acid, the title compound was obtained (10.0 mg, 77%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 433 (M + H$^+$); HRMS (FAB) calcd for $C_{24}H_{21}N_2O_6$ (M + H$^+$) 433.1400, found 433.1397.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.63−7.52 (m, 5H), 7.15 (t, J = 8.0 Hz, 2H), 6.90 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.6 Hz, 2H), 5.58 (d, J = 4.8 Hz, 1H), 5.33 (d, J = 4.8 Hz, 1H), 4.75 (q, J = 7.3 Hz, 1H), 1.27 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.2, 168.7, 158.3, 150.3, 143.6, 140.6, 136.2, 134.5, 131.4, 131.2, 131.1, 130.9 (2C), 128.5, 123.8 (2C), 123.5 (2C), 171.1 (2C), 83.1, 63.7, 51.6, 17.5.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (s, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.63−7.52 (m, 5H), 7.15 (t, J = 8.0 Hz, 2H), 6.90 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.6 Hz, 2H), 5.54 (d, J = 4.8 Hz, 1H), 5.14 (d, J = 4.8 Hz, 1H), 4.11 (q, J = 7.3 Hz, 1H), 1.78 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 Mhz, $CDCl_3$) δ: 175.9, 167.9, 158.3, 150.3, 143.6, 140.8, 136.2, 134.9, 131.4, 131.2, 131.1, 130.9 (2C), 128.7, 123.8 (2C), 123.5 (2C), 171.1 (2C), 83.1, 64.3, 53.4, 16.9.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(3″-acetamido-4′-biphenyl)azetidin-2-one (2f).** After following the above procedure using 3-acetamidophenylboronic acid, the title compound was obtained (9.4 mg, 70%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 445 (M + H$^+$); HRMS (FAB) calcd for $C_{26}H_{25}N_2O_5$ (M + H$^+$) 445.1763, found 445.1756.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (s, 1H), 7.58−7.28 (m, 8H), 7.13 (t, J = 8 Hz, 2H), 6.89 (t, J = 7 Hz, 1H), 6.75 (d, J = 7.5 Hz, 2H), 5.55 (d, J = 4.5 Hz, 1H), 5.28 (d, J = 4.5 Hz, 1H), 4.69 (q, J = 7.4 Hz, 1H), 2.23 (s, 3H), 1.25 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.2, 169.8, 166.7, 166.4, 157.8, 141.3, 141.2, 135.7, 134.7,130.6 (7C), 127.3, 122.6, 118.5, 116.5 (2C), 82.3, 62.3, 51.3, 25.5, 17.0.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (s, 1H), 7.58−7.28 (m, 8H), 7.13 (t, J = 8 Hz, 2H), 6.89 (t, J = 7 Hz, 1H), 6.75 (d, J = 7.5 Hz, 2H), 5.51 (d, J = 4.5 Hz, 1H), 5.11 (d, J = 4.5 Hz, 1H), 4.23 (q, J = 7.4 Hz, 1H), 2.22 (s, 3H), 1.68 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.05, 169.8, 166.7, 166.4, 157.8, 141.4, 141.2, 141.1, 135.7, 134.6, 130.6 (7C), 127.3, 123.0, 119.5, 118.5, 116.5 (2C), 82.3, 62.7, 52.5, 25.4, 16.6.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(2″-thiopheneyl-4′-biphenyl)azetidin-2-one (2g).** After following the above procedure using 2-thienylboronic acid the title compound was obtained (9.8 mg, 83%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 394 (M + H$^+$); HRMS calcd for $C_{22}H_{20}NO_4S$ (M + H$^+$) 394.1113, found: 394.1117.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62−7.51 (m, 2H), 7.38−7.50 (m, 2H), 7.37−7.22 (m, 2H), 7.15 (t, J = 7.7 Hz, 2H), 7.08−7.02 (m, 1H), 6.91 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 8.2 Hz, 2H), 5.55 (d, J = 4.0 Hz, 1H), 5.26 (d, J = 4.0 Hz, 1H), 4.74 (q, J = 7.5 Hz, 1H), 1.25 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 168.7, 158.4, 145.1, 136.4, 134.9, 133.4, 130.9, 131.0 (2C), 129.7, 127.3 (2C), 126.8, 125.0, 123.8, 117.1 (2C), 83.1, 63.8, 51.5, 17.4.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62−7.51 (m, 2H), 7.38−7.50 (m, 2H), 7.37−7.22 (m, 2H), 7.15 (t, J = 7.7 Hz, 2H), 7.08−7.02 (m, 1H), 6.91 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 8.2 Hz, 2H), 5.50 (d, J = 4.0 Hz, 1H), 5.05 (d, J = 4.0 Hz, 1H), 4.05 (q, J = 7.5 Hz, 1H), 1.75 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.4, 167.9, 158.4, 145.1, 136.5, 134.9, 133.4, 131.0, 130.9 (2C), 129.7, 127.1 (2C), 126.7, 125.1, 123.8, 117.1 (2C), 83.3, 64.4, 53.3, 17.0.

General Method for Suzuki Cross-Coupling Reaction of Resin-Bound Boronic Acid 1c. *cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(3″-nitro-4′-biphenyl)azetidin-2-one (2e). ArgoGel-MB-OH-bound *cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-bororophenyl)azetidin-2-one (**1c**) (0.16 g, loading 0.37 mmol/g) was swollen in a mixture of DMF (2 mL) and water (0.6 mL). To this slurry was added 3-nitrophenyl iodide (0.06 g, 4 equiv), {$PdCl_2$(dppf)} (0.01 g, 20 mol %), and TEA (84 μL, 10 equiv). The resulting mixture was heated at 40 °C overnight. After cooling to room temperature, the solvent was drained off, and the beads were washed with DMF, CH_2Cl_2, MeOH, and Et_2O and dried under reduced pressure. The product was cleaved by treating the resin with 5% (v/v) TFA/CH_2Cl_2 for 45 min. After removal of residual traces of catalyst by quick filtration through a 200 mg silica bed with ethyl acetate, the residue was concentrated under reduced pressure and purified by preparative HPLC to give the title compound (22.7 mg, 89%) as a white powder (1.2:1 mixture of cis diastereoisomers).

General Method for Heck Coupling Reaction of Resin-bound Iodide 1a. *cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-(*trans*-2″-(ethoxycarbonyl)vinyl)phenyl)azetidin-2-one (3a). Sasrin-bound *cis*-1-((*S*)-2-propionic acid)-3-phenoxy-4-(4′-iodophenyl)azetidin-2-one (**1a**) (45 mg, initial loading 0.6 mmol/g) was swollen in a mixture of DMF/H_2O/TEA (360/40/40 μL). To this slurry were added ethyl acrylate (30 μL, 10 equiv), {$PdCl_2$(dppf)} (0.02 g, 20 mol %), and tetrabutylammonium iodide (0.02 g, 2 equiv). The resulting mixture was heated at 40 °C overnight. After cooling to room temperature, the solvent was drained off, and the beads were washed with DMF, CH_2Cl_2, MeOH, and Et_2O and dried under reduced pressure. The product was cleaved from resin by treatment with 3% (v/v) (for Sasrin) or 10% (v/v) (for ArgoGel-MB-OH) TFA/CH_2Cl_2 for 45 min. After removal of residual traces of catalyst by quick filtration through a 200 mg silica bed with ethyl acetate, the filtrate was concentrated under reduced pressure, and the residue purified by preparative HPLC to give the title compound (10.0 mg, 90%) as an orange gum (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 410 (M + H$^+$); HRMS calcd for $C_{23}H_{24}NO_6$: 410.1600 (M + H$^+$), found: 410.1609.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.6 (d, J = 16.0 Hz, 1H), 7.4 (s, 4H), 7.1 (t, 2H, J = 7.6 Hz), 6.9 (t, 1H, J = 7.4 Hz), 6.7 (d, 2H, J = 7.7 Hz), 6.4 (d, 1H, J = 16.0 Hz), 5.54 (br s, 1H), 5.3 (br s, 1H), 4.7 (q, 1H, J = 7.4 Hz), 4.25 (q, 2H, J = 7.1 Hz), 1.75 (d, 3H, J = 7.4 Hz), 1.2 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.6, 168.5, 168.4, 158.2, 145.4, 138.2, 136.5, 130.9 (4C), 129.4 (2C), 123.8, 120.5, 117.1, 83.1, 63.6, 62.2, 41.8, 17.5, 15.9.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.6 (d, 1H, J = 16.0 Hz), 7.4 (s, 4H), 7.1 (t, 2H, J = 7.6 Hz), 6.9 (t, 1H, J = 7.4 Hz), 6.7 (d, 2H, J = 7.7 Hz), 6.4 (d, 1H, J = 16.0 Hz), 5.5 (br s, 1H), 5.01 (br s, 1H), 4.25 (q, 2H, J = 7.1 Hz), 4.05 (q, 1H, J = 7.4 Hz), 1.75 (d, 3H, J = 7.4 Hz), 1.3 (t, 2H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 168.5, 167.7, 158.2, 145.4, 136.7, 136.6, 130.8 (4C), 129.5 (2C), 123.8, 120.4, 117.1, 83.2, 64.2, 62.2, 41.8, 17.1, 15.9.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-(*trans*-2″-cyanovinyl)phenyl)azetidin-2-one (3b).** After following the above procedure using ArgoGel-MB-OH-bound **1a** (0.68 mmol/g) and acrylonitrile, the title compound was obtained (17 mg, 71%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 363 (M + H$^+$); HRMS calcd for $C_{21}H_{18}N_2O_4$: 363.1345 (M + H$^+$), found: 363.1339.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77−7.31 (m, 4H), 7.43 (d, J = 16.6 Hz, 1H), 7.16−7.10 (m, 2H), 6.89 (t, J = 7.4 Hz, 1H), 6.74−6.70 (m, 2H), 5.86 (d, J = 16.5 Hz, 1H), 5.55 (d, J = 4.7 Hz, 1H), 5.27 (d, J = 4.7 Hz, 1H), 4.72 (q, J = 7.4 Hz, 1H), 1.72 (d, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.3, 167.0, 166.3, 156.7, 150.2, 138.2, 136.8, 129.5 (2C), 129.4 (2C), 127.3, 122.3, 118.2, 115.4 (2C), 96.8, 81.6, 61.9, 50.2, 16.0.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77−7.31 (m, 4H), 7.41 (d, J = 15.6 Hz, 1H), 7.16−7.10 (m, 2H), 6.89 (t, J = 7.41 Hz, 1H), 6.74−6.70 (m, 2H), 5.85 (d, J = 16.8 Hz, 1H),

5.52 (d, J = 4.6 Hz, 1H), 5.09 (d, J = 4.7 Hz, 1H), 4.06 (q, J = 7.4 Hz, 1H), 1.21 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.6, 167.1, 167.0, 156.7, 150.2, 137.9, 136.4, 129.5 (2C), 129.4 (2C), 127.4, 122.3, 118.2, 115.2(2C), 96.8, 81.5, 62.6, 52.3, 15.7.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-(*trans*-2″-carbamoylvinyl)phenyl)azetidin-2-one (3c).** After following the above procedure using ArgoGel-MB-OH-bound **1a** (0.103 mmol) and acrylamide, the title compound was obtained (25 mg, 64%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 381 (M + H$^+$); HRMS calcd for $C_{21}H_{20}N_2O_5$: 381.1450 (M + H$^+$), found: 381.1455.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77−7.31 (m, 4H), 7.43 (d, J = 16.6 Hz, 1H), 7.16−7.10 (m, 2H), 6.89 (t, J = 7.4 Hz, 1H), 6.74−6.70 (m, 2H), 5.86 (d, J = 16.5 Hz, 1H), 5.55 (d, J = 4.7 Hz, 1H), 5.27 (d, J = 4.7 Hz, 1H), 4.72 (q, J = 7.4 Hz, 1H), 1.72 (d, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.3, 167.0, 166.3, 156.7, 150.2, 138.2, 136.8, 129.5 (2C), 129.4 (2C), 127.3, 122.3, 118.2, 115.4 (2C), 96.8, 81.6, 61.9, 50.2, 16.0.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77−7.31 (m, 4H), 7.41 (d, J = 15.6 Hz, 1H), 7.16−7.10 (m, 2H), 6.89 (t, J = 7.4 Hz, 1H), 6.74−6.70 (m, 2H), 5.85 (d, J = 16.8 Hz, 1H), 5.52 (d, J = 4.64 Hz, 1H), 5.09 (d, J = 4.7 Hz, 1H), 4.06 (q, J = 7.4 Hz, 1H), 1.21 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.6, 167.1, 167.0, 156.7, 150.2, 137.9, 136.4, 129.5 (2C), 129.4 (2C), 127.4, 122.3, 118.2, 115.2 (2C), 96.8, 81.5, 62.6, 52.3, 15.7.

***cis*-1-((*S*)-1-Carboxyethyl)-3-phenoxy-4-(4′-(*trans*-2″-(dimethylcarbamoyl)vinyl)phenyl)azetidin-2-one (3d).** After following the above procedure using ArgoGel-MB-OH-bound **1a** (0.103 mmol) and *N*,*N*-dimethylacrylamide, the title compound was obtained (25 mg, 60%) as a white powder (1.2:1 mixture of cis diastereoisomers): MS (ESI) m/z 409 (M + H$^+$); HRMS calcd for $C_{23}H_{24}N_2O_5$: 409.1763 (M + H$^+$), found: 409.1756.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, J = 15.5 Hz, 1H), 7.45−7.37 (m, 4H), 7.12 (t, J = 7.9 Hz, 2H), 6.87 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 15.5 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.51 (d, J = 4.7 Hz, 1H), 5.28 (d, J = 4.7 Hz, 1H), 4.02 (q, J = 7.4 Hz, 1H), 3.17 (s, 3H), 3.07 (s, 3H), 1.69 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.0, 170.5, 169.7, 159.7, 144.6, 139.5, 138.4, 132.1 (2C), 131.8 (2C), 130.2 (2C), 124.5, 120.6, 117.8 (2C), (2C), 83.9, 65.0, 53.3, 39.5, 37.8, 17.8.

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (d, J = 15.5 Hz, 1H), 7.45−7.37 (m, 4H), 7.12 (t, J = 7.9, 2H), 6.87 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 15.5 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 5.47 (d, J = 4.6 Hz, 1H), 5.08 (d, J = 4.6 Hz, 1H), 4.68 (q, J = 7.4 Hz, 1H), 3.17 (s, 3H), 3.07 (s, 3H), 1.11 (d, J = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.8, 170.5, 170.2, 159.6, 144.6, 139.4, 132.2, 132.09 (2C), 131.8 (2C), 130.2 (2C), 124.5, 120.6, 117.8 (2C), 83.8, 65.4, 54.6, 37.8, 39.4, 17.3.

Supporting Information Available: ^{1}H NMR data of **1a**−**c**, **2a**−**g**, **3a**−**d** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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