JOC Article

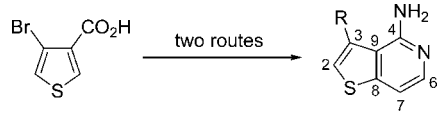
Improved Synthesis of 3-Substituted-4-amino-[3,2-*c*]-thienopyridines

Kenneth M. Engstrom,* Amanda L. Baize, Thaddeus S. Franczyk, Jeffrey M. Kallemeyn, Mathew M. Mulhern, Robert C. Rickert, and Seble Wagaw

Global Pharmaceutical R&D, Process Research & Development, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064-6290

kenneth.engstrom@abbott.com

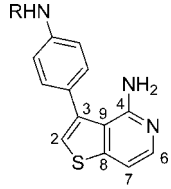
Received February 19, 2009



Two syntheses of 3-substituted-4-amino-[3,2-*c*]thienopyridines have been developed to replace the standard literature route to these compounds, which uses unattractive conditions involving azide and high temperatures. The first synthesis utilizes a Friedel−Crafts reaction as its key ring-forming step, whereas the second route relies on an unprecedented intramolecular reductive cyclization between a nitroolefin and a nitrile as its key ring-forming step. The development and optimization of each 3-substituted-4-amino-[3,2-*c*]thienopyridine synthesis is discussed and a comparison of the routes is presented.

Introduction

Thienopyridines are pharmacophores present in a variety of pharmaceutical targets for multiple indications.[1] As part of our multitarget kinase oncology program, we required the synthesis of 3-substituted-4-amino-[3,2-*c*]-thienopyridine **1**.[2] Although the synthesis of [3,2-c]-thienopyridine itself has been known for over 50 years, it remains one of the more difficult thienopyridine isomers to synthesize.[3] Of the few published routes to [3,2-*c*]-thienopyridines substituted with a heteroatom at the 4-position, most are relatively low yielding or install difficult to remove functionality at the 6-position.[4]



1

The route most applicable to the synthesis of **1**, which we have labeled the "thermal route", is shown in Scheme 1 and has been previously described.[5−7] This route relies on the thermal isomerization and cyclization of a vinyl isocyanate to form the pyridine ring as the key step. Although these reactions provide an acceptable yield of 3-bromo-4-hydroxy-[3,2-*c*]-thienopyridine **3**, several factors limit its scalability. The product **3** is unstable under the reaction conditions; a 20% decrease in product concentration is seen in 30 min in diphenyl ether at 250 °C.[6,7] In addition, the use of sodium azide in this sequence presents safety and environmental concerns because of its toxicity, shock-sensitivity, and explosiveness near 300 °C. Because of the difficulties surrounding the scalability of the thermal route and faced with the prospect of larger material demands, we sought alternative routes to 3-substituted-4-amino-[3,2-*c*]-thienopyridine **1**.

The thermal route shown in Scheme 1 relies on bond formation between C-9 and C-4 as the key ring closure step, but bond formation between other atoms of the resulting thienopyridine to effect ring closure has been precedented. In particular, intramolecular Friedel−Crafts reaction between

(1) Litvinov, V. P.; Dotsenko, V. V.; Krivokolysko, S. G. *Adv. Het. Chem.* **2007**, *93*, 117–178.

(2) Heyman, H. R.; Frey, R. R.; Bousquet, P. F.; Cunha, G. A.; Moskey, M. D.; Ahmed, A. A.; Soni, N. B.; Marcotte, P. A.; Pease, L. J.; Glaser, K. B.; Yates, M.; Bouska, J. J.; Albert, D. H.; Black-Schaefer, C. L.; Dandliker, P. J.; Stewart, K. D.; Rafferty, P.; Davidsen, S. K.; Michaelides, M. R.; Curtin, M. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1246–1249.

(3) For a review on the synthesis of thienopyridines, see ref 1. Barker, J. M. *Adv. Heterocycl. Chem.* **1977**, *21*, 65–118.

(4) (a) Ikeura, Y.; Tanaka, T.; Kiyota, Y.; Morimoto, S.; Ogina, M.; Ishimaru, T.; Kamo, I.; Doi, T.; Natsugari, H. *Chem. Pharm. Bull.* **1997**, *45*, 1642–1652. (b) Molina, P.; Fresneda, P. M.; Hurtado, F. *Synthesis* **1987**, *1*, 45–48. (c) Farnier, M.; Soth, S.; Fournari, P. *Can. J. Chem.* **1976**, *54*, 1066–1073.

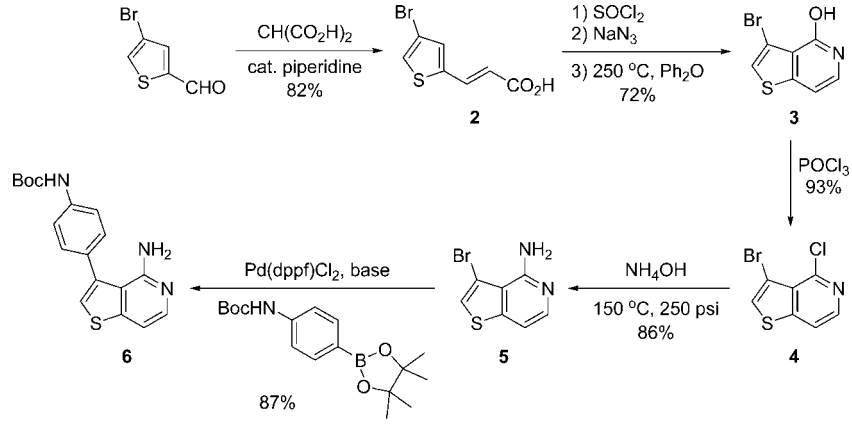
(5) (a) New, J. S.; Christopher, W. L.; Yevich, J. P.; Butler, R.; Schlemmer, R. F.; VanderMaelen, C. P.; Cipollina, J. A. *J. Med. Chem.* **1989**, *32*, 1147–1156. (b) Eloy, F.; Deryckere, A. *Bull. Soc. Chim. Belges* **1970**, *79*, 301–312.

(6) For the use of catalytic iodine to lower the isomerization reaction temperature, see: (a) Miyazaki, Y.; Nakano, M.; Sato, H.; Truesdale, A. T.; Stuart, J. D.; Nartey, E. N.; Hightower, K. E.; Kane-Carson, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 250–254.

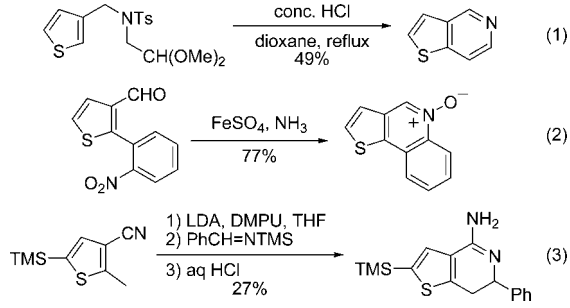
(7) For the use of tributylamine as an additive, see: (a) Abbott, L.; Betschmann, P.; Burchat, A.; Calderwood, D. J.; Davis, H.; Hrnciar, P.; Hirst, G. C.; Li, B.; Morytko, M.; Mullen, K.; Yang, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1167–1171.

10.1021/jo9003772 CCC: $40.75
Published on Web 04/16/2009

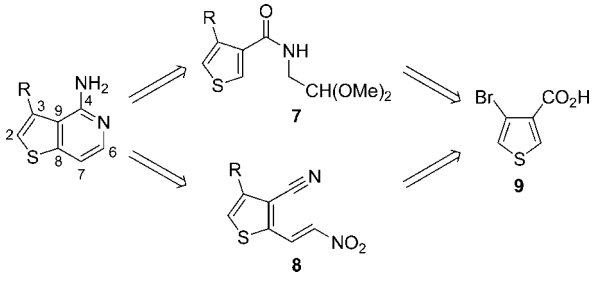
SCHEME 1



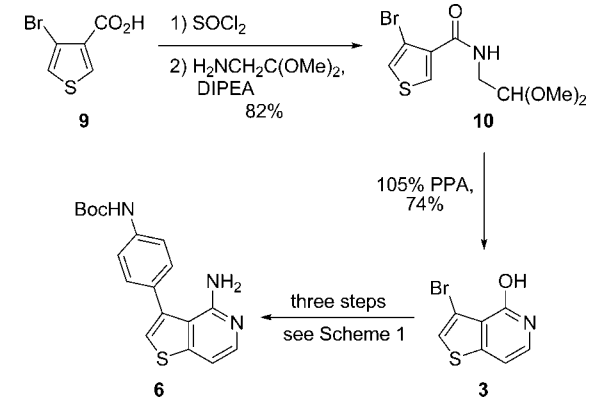
SCHEME 2



SCHEME 3



SCHEME 4



a dimethyl acetal and the thiophene ring, which constitutes bond formation between C-7 and C-8, has been demonstrated in the synthesis of unsubstituted [3,2-*c*]-thienopyridine (Scheme 2, eq 1).[8] Intramolecular reductive cyclization between a nitroarene and an aldehyde, which constitutes bond formation between N-5 and C-4, has been demonstrated in the synthesis of thieno-[3,2-*c*]-isoquinoline N-oxide (Scheme 2, eq 2).[9] Acid-catalyzed intramolecular addition of an imine/enamine to a nitrile, which also constitutes bond formation between N-5 and C-4, has been demonstrated in the synthesis of a 6-substituted-6,7-dihydro-4-amino-[3,2-*c*]-thienopyridine (Scheme 2, eq 3).[10]

Applying these disconnections to the 3-substituted-4-amino-[3,2-*c*]-thienopyridine **1** leads to the retrosyntheses shown in Scheme 3. The "Friedel-Crafts route" would go through key intermediate **7** while the "reductive cyclization route" would go through key intermediate **8**. Both of these key intermediates can be synthesized from **9**, which is accessible from commercially available 3,4-dibromothiophene by metal−halogen exchange and quenching with carbon dioxide.[11]

Results and Discussion

Friedel−Crafts Route. Synthesis of **6** via the Friedel−Crafts route (Scheme 4) began with coupling of bromoacid **9** with aminoacetaldehyde dimethylacetal via the acid chloride, which provided the Friedel−Crafts substrate **10** in 82% yield. Screening of a multitude of Bronsted and Lewis acids to effect cyclization of **10** resulted mostly in complex mixtures containing little or no desired product **3**. Aluminum trichloride (4.0 equiv) and a substoichiometric amount of acetic acid (0.67 equiv) afforded a modest yield of 41%. However, equivalents of aluminum trichloride and acetic acid had to be carefully controlled to prevent complete decomposition and workup to remove aluminum byproducts was tedious.

Better results were obtained by running the Friedel−Crafts cyclization in polyphosphoric acid (PPA). Using 115% PPA, the yield of **3** was improved to 63%, with the major impurity being 16 peak area percent of oxazole **11** as determined by HPLC analysis. The amount of oxazole was reduced to 2% by using 105% PPA. The product could be crystallized directly

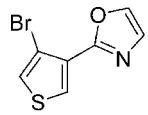
(8) (a) Wikel, J. H.; Denney, M. L.; Vasileff, R. T. *J. Heterocyclic Chem.* **1993**, *30*, 289–290. (b) Herz, W.; Tsai, L. *J. Am. Chem. Soc.* **1953**, *75*, 5122–5123.

(9) Gronowitz, S.; Timari, G. *J. Het. Chem.* **1990**, *27*, 1127–1129.

(10) Beaton, H.; Hamley, P.; Tinker, A. C. *Tetrahedron Lett.* **1998**, *39*, 1227–1230.

(11) (a) Steinkopf, W.; Jacob, H.; Penz, H. *Just. Leib. Ann. Der Chem.* **1934**, *512*, 136–156. (b) Lawesson, S. *Ark. Kemi* **1957**, *11*, 325–336. (c) Hawkins, D. W.; Iddon, B.; Longthorne, D. S.; Rosyk, P. J. *J. Chem. Soc. Perkin Trans. 1* **1994**, *19*, 2735–2744.

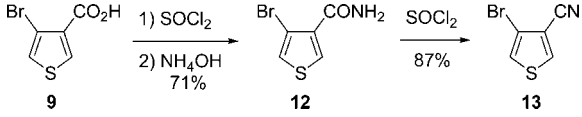
from the reaction mixture by addition of water to give a 74% isolated yield of **3**.



11

Since intermediate **3** is common to both the Friedel−Crafts route and the thermal route shown in Scheme 1, the same chemistry can be used to complete the synthesis of **6** in 65% yield over the three steps. The overall yield of **6** from **9** utilizing the Friedel−Crafts cyclization route was 42% for five steps.

SCHEME 5



Reductive Cyclization Route. Synthesis of **6** via the reductive cyclization route began with synthesis of bromonitrile **13** (Scheme 5).[12,13] Acid **9**, which was previously used in the Friedel−Crafts route, was converted to the acid chloride using thionyl chloride and catalytic DMF in THF. Quenching into concentrated aqueous ammonia, extractive workup, and crystallization from ethyl acetate and heptane gave amide **12** in 71% isolated yield.[11b] Dehydration of this amide to the nitrile with thionyl chloride proceeded smoothly in DMF and the product was isolated in 87% yield simply by addition of the crude reaction mixture to water.

Suzuki cross-coupling between **13** and *t*-butyl-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate under biphasic conditions proceeded to greater than 99% conversion. A purification sequence of carbon treatment, chromatography, and recrystallization provided pure **14** in 80% isolated yield (Scheme 6). Regioselective deprotonation of **14** using 2.5 equiv of LDA followed by DMF quench installed the aldehyde functional group alpha to the nitrile. Following aqueous workup, chromatography, and crystallization, the isolated yield of **15** was 85%. Aldehyde **15** was then homologated to the α,β-unsaturated nitroalkene by way of a DMAP-catalyzed Henry reaction using acetic anhydride as the dehydrating agent. Nitroalkene **16** was isolated in 91% yield by simply filtering the crystallized product from the crude reaction mixture.

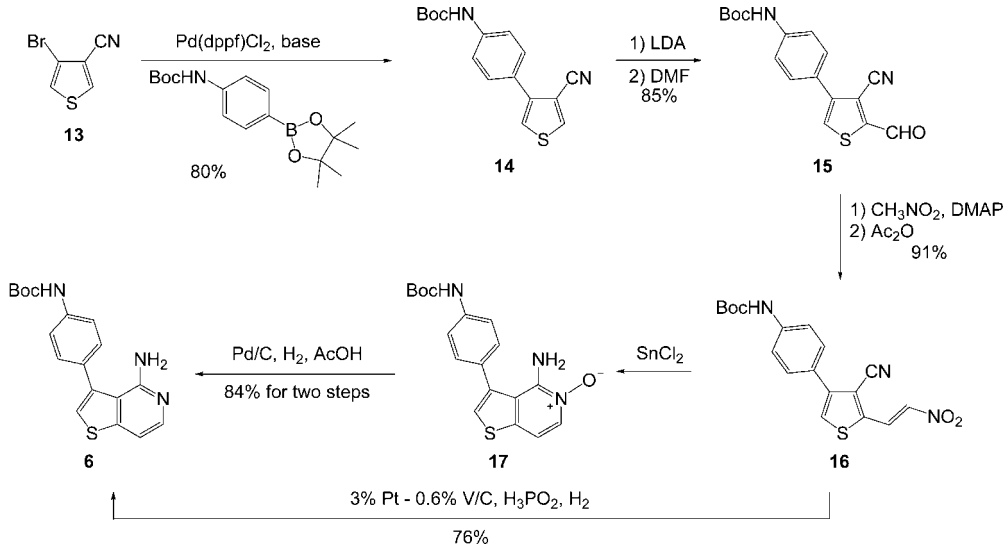
The key step in this route is reductive cyclization of **16** to **6**. While intramolecular reductive cyclization between nitroarenes and nitriles to form aminopyridines is well precedented (vide infra), there were no known examples of this type of intramolecular reductive cyclization where the nitroarene is replaced with an α,β-unsaturated nitroalkene. However, we hoped that a judicious choice of reagents and conditions might bring about the desired transformation.

Reductive cyclization of **16** using trimethylphosphite provided no desired product.[14] Zinc-catalyzed reductive cyclization using ammonium formate or formic acid also failed.[15] An excess of iron in acetic acid afforded trace amounts of product, but it was accompanied by extensive formation of numerous unidentified side products.[16] Although palladium-catalyzed reductive cyclization in acetic acid using formate salts[17] or molecular hydrogen gave full conversion of **16**, these reactions were low yielding (30−50% assay yields) due to extensive side product formation.

It was finally discovered that tin (II) dichloride dihydrate smoothly reduced and cyclized the nitroalkene to N-oxide **17**.[18,19] However, removal of the tin byproducts turned out to be more difficult than anticipated. After much experimentation, it was discovered that a solvent switch from ethyl acetate to methanol and treatment with aqueous potassium carbonate delivered a filterable precipitate that was a mixture of N-oxide **17** and tin oxide. Repeated slurrying of the precipitate in methanol followed by filtration resulted in a methanol solution of N-oxide **17** free of tin oxide. This solution was further reacted with molecular hydrogen, palladium on carbon, and substoichiometric acetic acid to give the target molecule **6** in 84% yield over the two steps.

While this two step reductive cyclization utilizing tin (II) dichloride dihydrate gave a good yield of the desired product **6**, the sequence was hampered by the tedious removal of tin oxide. This led us to further explore metal-catalyzed reductive cyclization using molecular hydrogen because of the ease with which the catalyst, excess reagent, and byproducts can be removed.

SCHEME 6



It was eventually found that a one-pot reductive cyclization of **16** to **6** using molecular hydrogen could be accomplished using a vanadium and hypophosphorous acid modified platinum on carbon catalyst.[20] Filtration to remove the catalyst followed by aqueous workup and chromatography provided **6** in 76% yield. Utilizing this operationally simpler reductive cyclization, the overall yield of **6** from **9** was 29% for six steps.

TABLE 1. Comparison of Three Routes to 6

route	isolations	chromatographies	yield
thermal	5	1	41%
Friedel−Crafts	5	1	42%
reductive cyclization	6	3	29%

Conclusions

A summary of the three routes to **6** is shown in Table 1. Although the thermal route and the Friedel−Crafts route have similar step counts and overall yields, the thermal route has several flaws that make it unattractive for scale up, including the use of azide and the instability of **3** under the reaction conditions used to make it. While the reductive cyclization route is longer and lower yielding than the thermal route, it also avoids both of these pitfalls. When comparing the Friedel−Crafts and reductive cyclization routes to each other, it is clear that the Friedel−Crafts route is superior in terms of isolations and yield, as well as relative simplicity of the reagents used throughout the sequence. However, the reductive cyclization route is a novel method for accessing 3-substituted-4-amino-[3,2-*c*]-thienopyridine compounds and may prove valuable for targets for which the Friedel−Crafts chemistry fails.[21] In the end, both routes clearly overcome the major shortcomings of the thermal route and offer new alternatives for the synthesis of 3-substituted-4-amino-[3,2-*c*]-thienopyridine compounds.

Experimental Section

***trans*-3-(4-Bromothiophen-2-yl)-acrylic Acid (2).** To a 2 L round-bottom flask was charged 4-bromothiophene-2-carbaldehyde (191.04 g, 1.00 mol, 1.00 equiv) and malonic acid (124.9 g, 1.20 mol, 1.20 equiv) followed by pyridine (750 mL). The reaction was heated to 80 °C and piperidine (11.9 mL, 0.120 mol, 0.10 equiv) was added. The homogeneous solution was heated to 100 °C for 22 h, at which point 97% conversion of 4-bromothiophene-2-carbaldehyde was achieved as determined by HPLC analysis. The reaction was cooled to 50 °C and about half of the solvent was removed via rotary evaporation. Water (1900 mL) was added followed by 6 M aqueous hydrochloric acid (650 mL) to adjust the pH from 6 to 2 as determined by pH indicating strips. After one hour the solids were filtered and washed with a minimal amount of water. The wet cake was transferred to a 2 L round-bottom flask. Ethanol (475 mL) and water (375 mL) were added and the slurry was heated to 80 °C to dissolve the solids. The solution was cooled to 35 °C over 80 min. The solids were filtered and washed with a minimal amount of water. The wet cake was dried at 50 °C and 20 in. Hg to afford **2** (190.86 g, 81.9%) as a tan crystalline solid contaminated with 3% 4-bromothiophene-2-carbaldehyde as determined by ^{1}H NMR. Mp 154−156 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 7.78 (m, 1H), 7.65 (dt, J = 15.7, 0.7 Hz, 1H), 7.54 (m, 1H), 6.24 (d, J = 15.7 Hz) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 166.4, 139.7, 134.9, 132.2, 126.2, 118.6, 109.6 ppm. HRMS (ESI) for $C_7H_6BrO_2S$ ($M + H^+$) calcd 232.92664 found 232.92665.

3-Bromo-4-hydroxy-[3,2-*c*]-thienopyridine (3). To a 2 L round-bottom flask equipped with a 50% NaOH scrubber was charged **2** (166.06 g, 0.712 mol, 1.00 equiv) and chloroform (1315 mL). DMF (6.6 mL, 85.2 mmol, 0.12 equiv) and thionyl chloride (62.0 mL, 0.850 mol, 1.20 equiv) were added. The reaction was heated to reflux for one hour and cooled to 50 °C. The solvent was removed via rotary evaporation to give crude *trans*-3-(4-bromothiophen-2-yl)-acryloyl chloride.

To a 1 L Erlenmeyer flask was charged sodium azide (63.3 g, 0.974 mol, 2.0 equiv) followed by water (245 mL) and *p*-dioxane (245 mL). A solution of crude *trans*-3-(4-bromothiophen-2-yl)-acryloyl chloride (233.66 g of 47.6 wt% material, 122.55 g, 0.487 mol, 1.0 equiv) in *p*-dioxane (245 mL) was added to the 1 L Erlenmeyer flask and stirred at ambient temperature for 2.5 h. The mixture was transferred to a separatory funnel and the bottom organic layer was separated. The upper aqueous layer was washed twice with ethyl acetate (120 mL each wash). The combined organics were dried over magnesium sulfate (60 g), filtered, and concentrated. The solids were dissolved with dichloromethane (340 mL) to give a solution of approximately 1.2 M *trans*-3-(4-bromothiophen-2-yl)-acryloyl azide.

To a 500 mL round-bottom flask was charged diphenyl ether (70 mL), which was heated to 255 °C. A solution of *trans*-3-(4-bromothiophen-2-yl)-acryloyl azide (85 mL of an approximately 1.2 M solution in dichloromethane, 0.10 mol) was added over 10 min, maintaining an internal temperature above 250 °C. The dichloromethane flashed off with an accompanying large noise. The reaction was stirred at 250 °C for 5 min and then cooled to 90 °C. A 1:1 mixture of diethyl ether and heptane (350 mL) was added. The slurry was cooled to ambient temperature and stirred for 30 min. The solids were filtered, the wet cake washed with a 1:1 mixture of diethyl ether and heptane (350 mL), and the solids dried at 50 °C and 20 in. Hg to afford **3** (17.13 g, 72% from **2**) as a tan crystalline solid. Mp > 225 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 11.45 (br s, 1H), 7.64 (d, J = 0.6 Hz, 1H), 7.25 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 7.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 157.3, 148.6, 130.3, 124.5, 122.4, 106.6, 100.8 ppm. HRMS (ESI) for C_7H_5BrNOS ($M + H^+$) calcd 229.92697 found 229.92741.

3-Bromo-4-chloro-[3,2-*c*]-thienopyridine (4). To a 1 L round-bottom flask was charged **3** (38.0 g, 165 mmol, 1.0 equiv) followed by $POCl_3$ (101 mL, 1.09 mol, 6.6 equiv). The slurry was heated to 75 °C (internal temperature) for one hour. The reaction was cooled to ambient temperature and dichloromethane (600 mL) was added. The organic solution was added dropwise to water (1400 mL) while keeping the temperature around 25 °C. The reaction flask was rinsed once with dichloromethane (400 mL). The biphasic solution was filtered through Celite and washed once with dichloromethane (200 mL). The layers were separated and the aqueous layer extracted once with dichloromethane (300 mL). The combined organics were

(12) For a one-step synthesis of **13** from 3,4-dibromothiophene using copper (I) cyanide, see: Gonzalez, I. C.; Davis, L. N.; Smith, C. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4037–4043.

(13) For a three-step synthesis of **13** from 3,4-dibromothiophene involving dehydration of 4-bromothiophene-3-carbaldehyde oxime, see: Fournari, P.; Guillard, R.; Person, M. *Bull. Chim. Soc. Fr.* **1967**, *11*, 4115–4120.

(14) Kametani, T.; Yamanaka, T.; Ogasawara, K. *J. Chem. Soc. C* **1969**, 385–387.

(15) Gowda, D. C.; Mahesh, B.; Gowda, S. *Indian J. Chem.* **2001**, *40B*, 75–77.

(16) (a) Hamid, A.; Elomri, A.; Daich, A. *Tetrahedron Lett.* **2006**, *47*, 1777–1781. (b) Wang, Y. D.; Boschelli, D. H.; Johnson, S.; Honores, E. *Tetrahedron* **2004**, *60*, 2937–2942. (c) Althius, T. H.; Kadin, S. B.; Czuba, L. J.; Moore, P. F.; Hess, H. J. *J. Med. Chem.* **1980**, *23*, 262–269.

(17) Ranu, B. C.; Sarkar, A.; Guchhait, S. K.; Ghosh, K. *J. Indian Chem. Soc.* **1998**, *75*, 690–694.

(18) For reduction of α,β-unsaturated nitroalkenes to aldoximes using tin (II) chloride, see: Kabalka, G. W.; Goudgaon, N. M. *Synth. Commun.* **1988**, *18*, 693–697.

(19) Compagnone, R. S.; Suarez, A. I.; Zambrano, J. L.; Pina, I. C.; Dominguez, J. N. *Synth. Commun.* **1997**, *27*, 1631–1641.

(20) Siegrist, U.; Baumeister, P.; Blaser, H.-U.; Studer, M.; The Selective Hydrogenation of Functionalized Nitroarenes: New Catalytic Systems. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed. Marcel Dekker, Inc.: New York, 1998; Vol 75, pp 207−219.

(21) Extension of the scope of this reductive cyclization to synthesize other [3,2-*c*]-thienopyridines and various pyridine-containing heterocycles using both the $SnCl_2$ and $Pt/V/H_3PO_2/H_2$ systems is currently under investigation and will be reported in due course.

washed once with 8% aqueous $NaHCO_3$ (500 mL) and once with 25% aqueous NaCl (500 mL). The organic layer was concentrated and chase-distilled twice with ethanol (400 mL portions). Ethanol (400 mL) was added, the slurry was heated to reflux, and water (400 mL) was added. The slurry was cooled to 0 °C and filtered. The wet cake was washed once with water (100 mL) and the solids were dried at 50 °C and 20 in. Hg to afford **4** (38.2 g, 93%) as an off-white crystalline solid. Mp 161−163 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 8.28 (d, J = 5.4 Hz, 1H), 8.20 (d, J = 5.4 Hz, 1H), 8.19 (s, 1H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 148.8, 143.3, 141.9, 129.4, 128.3, 181.1, 103.3 ppm. HRMS (ESI) for $C_7H_4BrClNS$ ($M + H^+$) calcd 247.89309 found 247.89344.

3-Bromo-4-amino-[3,2-*c*]-thienopyridine (5). To a stainless steel reactor was added **4** (403 g, 1.62 mol) followed by p-dioxane (2.8 L) and 28% aqueous ammonia (2.8 L). The mixture was heated to 150 °C and developed about 300 psi of pressure. After 19 h, the reaction was cooled to 23 °C and filtered. The wet cake was washed with water (800 mL) and dried at 23 °C and 20 in. Hg to afford **5** (235 g of 95 wt% purity, 61%) as a tan crystalline solid. A second crop of crystals was isolated from the filtrate by heating to 50 °C and adding water (6.1 L). The resulting slurry was cooled to 17 °C and filtered. The wet cake was washed with water (930 mL) and dried at 23 °C and 20 in. Hg to afford **5** (128 g of 87 wt% purity, 25%) as a tan crystalline solid. Mp 157−160 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 7.81 (d, J = 5.7 Hz, 1H), 7.74 (s, 1H), 7.25 (d, J = 5.7 Hz, 1H), 6.45 (br s, 2H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 153.6, 147.2, 142.2, 122.4, 116.7, 107.5, 103.0 ppm. HRMS (ESI) for $C_7H_6BrN_2S$ ($M + H^+$) calcd 228.94296 found 228.94338.

***t*-Butyl-4-(4-aminothieno[3,2-*c*]pyridine-3-yl)phenylcarbamate (6).** To a 25 mL round-bottom flask was charged **5** (200 mg, 0.873 mmol, 1.00 equiv), *t*-butyl-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (307 mg, 0.960 mmol, 1.10 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (35.6 mg, 0.0436 mmol, 0.05 equiv), and sodium carbonate (185 mg, 1.75 mmol, 2.0 equiv) followed by toluene (1 mL), ethanol (1 mL), and water (1 mL). The reaction was heated to 60 °C for 4 h, at which point more toluene (2 mL), ethanol (2 mL), and water (2 mL) were added. The reaction was heated at 60 °C for an additional 16 h, at which point greater than 99% conversion of **5** was achieved as determined by HPLC analysis. Water (10 mL) and ethyl acetate (10 mL) were added and the layers were separated. The organic layer was washed with brine, concentrated, and the residue purified by silica gel chromatography (1% Et_3N in hexanes grading in 15% steps to 1% Et_3N and 60% EtOAc in hexanes) to afford **6** (261 mg, 87%) as a tan crystalline solid. Mp 171−173 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 9.54 (br s, 1H), 7.80 (d, J = 5.7 Hz, 1H), 7.57 (m, 2H), 7.38 (s, 1H), 7.32 (m, 2H), 7.23 (d, J = 5.7 Hz, 1H), 5.37 (br s, 2H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 153.9, 152.1, 147.6, 141.2, 139.0, 136.0, 129.1, 122.1, 118.1, 117.5, 107.3, 79.1, 28.2 ppm. HRMS (ESI) for $C_{18}H_{20}N_3O_2S$ ($M + H^+$) calcd 342.12707 found 342.12866.

4-Bromo-thiophene-3-carboxylic Acid (2,2-Dimethoxy-ethyl)-amide (10). To a 2 L round-bottom flask was added **9** (155 g, 738.4 mmol, 1.0 equiv) and thionyl chloride (379 mL, 7.384 mol, 10 equiv). Isopropyl acetate (775 mL) was added and the mixture was heated at 50 °C until the carboxylic acid was consumed (18 h). The reaction mixture was cooled to room temperature and chase-distilled twice with isopropyl acetate (775 mL each). Isopropyl acetate (775 mL) was added and the solution cooled to 10 °C. *N*,*N*-diisopropylethylamine (319 mL, 1.846 mol, 2.5 equiv) was added followed by aminoacetaldehyde dimethyl acetal (119.7 mL, 1.108 mol, 1.5 equiv). The reaction was exothermic. The reaction was stirred at ambient temperature for 1 h and extracted with 10% aqueous phosphoric acid (860 mL). The aqueous layer was extracted with isopropyl acetate (300 mL) and the combined organic extracts washed with 10% potassium dihydrogen phosphate (300 mL) and water (150 mL). The organic layer was concentrated to a thick oil that may crystallize. The crude product was dissolved in isopropyl acetate (300 mL), heated to 55 °C, and then cooled to room temperature. Heptane (600 mL) was added dropwise and the resulting slurry stirred at ambient temperature for 16 h. The slurry was filtered and the wet cake was washed with the crystallization liquors. The product was dried at 50 °C and 20 in Hg overnight to afford **10** (189.70 g, 82%) as a light-yellow crystalline solid. Mp 94−95 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 8.36 (t, J = 5.8 Hz, 1H), 7.91 (d, J = 3.3 Hz, 1H), 7.69 (d, J = 3.3 Hz, 1H), 4.47 (t, J = 5.6 Hz, 1H), 3.29 (t, J = 5.7 Hz, 2H), 3.28 (s, 6H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 161.9, 135.7, 128.6, 125.2, 108.2, 101.5, 53.3, 40.9 ppm. HRMS (ESI) for $C_9H_{13}BrNO_3S$ ($M + H^+$) calcd 293.97940 found 293.97975.

3-Bromo-thieno[3,2-*c*]pyridin-4-ol (3) by Polyphosphoric Acid Procedure. To a 12 L round-bottom flask was charged polyphosphoric acid (3.3 kg, 105% grade) and **10** (250 g, 850 mmol). The reaction was heated to 100 °C. After 4 h the reaction was cooled to 40 °C and water (6.6 L) was added over 15 min. The slurry was cooled to 23 °C and filtered. The wet cake was washed once with water (250 mL) and once with MeCN (250 mL). The wet cake was dried at 45 °C and 20 in. Hg to afford **3** (193 g, 75.3 weight % purity as determined by HPLC assay using an analytically pure standard, 98.5 peak area % purity by HPLC, 74% purity adjusted yield) as a light-brown crystalline solid.

4-Bromothiophene-3-carboxamide (12). To a 500 mL round-bottom flask was charged **9** (19.51 g, 94.22 mmol, 1.00 equiv) followed by THF (195 mL). The solution was cooled to 10 °C and $SOCl_2$ (13.75 mL, 188.5 mmol, 2.00 equiv) was added at such a rate as to keep the internal temperature below 25 °C. DMF (0.95 mL, 12 mmol, 0.13 equiv) was added and the reaction stirred at 23 °C for 3 h. To a separate 500 mL round-bottom flask was added 28% aqueous ammonia (85 mL) and the solution cooled to −10 °C. The acid chloride solution was added to the ammonia solution at such a rate as to keep the internal temperature below 30 °C. After one hour, the reaction reached 95% conversion as determined by HPLC analysis. The reaction was diluted with EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted three times with EtOAc (100 mL each). The combined organics were washed with brine (200 mL). The organics were dried with $MgSO_4$, filtered, and concentrated. To the resulting white solid was added EtOAc (100 mL) and the slurry was heated to 75 °C to dissolve all solids. Heptane (300 mL) was added and the resulting slurry was cooled to 0 °C before filtration. The wet cake was washed with heptane (50 mL) and dried at 50 °C and 20 in. Hg to afford **12** (13.74 g, 71%) as a white crystalline solid: ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 7.97 (d, J = 3.4 Hz, 1H), 7.72 (br s, 1H), 7.68 (d, J = 3.3 Hz, 1H), 7.36 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 163.2, 135.7, 128.6, 125.1, 108.3 ppm. Anal. Calcd for C_5H_4BrNOS: C, 29.14; H, 1.96; Br, 38.78; N, 6.80; O, 7.76; S, 15.56. Found: C, 29.17; H, 1.98; Br, 39.07; N, 6.70; S, 15.21.

4-Bromothiophene-3-carbonitrile (13). To a 250 mL round-bottom flask was charged DMF (36 mL). The solution was cooled to −10 °C and $SOCl_2$ (13.9 mL, 117 mmol, 2.01 equiv) was added at such a rate as to keep the internal temperature below 5 °C. The reaction was cooled to −10 °C. After stirring for 20 min, **12** (12.00 g, 58.23 mmol, 1.00 equiv) was added at such a rate as to keep the internal temperature below 10 °C. The reaction was cooled to −10 °C. After 90 min the reaction was warmed to 23 °C. After an additional 3 h the reaction mixture was added to water (192 mL) cooled to 5 °C. The reaction flask was rinsed once with DMF (12 mL). The slurry was cooled to 0 °C and filtered. The wet cake was washed with water (36 mL) and dried at 50 °C and 20 in. Hg to afford **13** (9.64 g, 87%) as a white crystalline solid: ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 8.70 (d, J = 3.1 Hz, 1H), 7.98 (d, J = 3.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 139.4, 126.5, 113.5, 112.0, 110.1 ppm. Anal. Calcd for C_5H_2BrNS: C, 31.94; H, 1.07; Br, 42.49; N, 7.45; S, 17.05. Found: C, 32.00; H, 1.06; N, 7.14; Br, 42.77; S, 16.89.

***t*-Butyl-4-(4-cyanothiophen-3-yl)phenylcarbamate (14).** To a 500 mL round-bottom flask was charged **13** (13.49 g, 71.7 mmol, 1.00 equiv), *t*-butyl-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (25.18 g, 78.9 mmol, 1.10 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (1.76 g, 2.15 mmol, 0.03 equiv), and sodium carbonate (15.20 g, 143 mmol, 2.0 equiv) followed by PhMe, EtOH, and H_2O (67.5 mL each). The mixture was heated to 60 °C for 20 h, at which point greater than 99% conversion of **13** was achieved as determined by HPLC analysis. EtOAc (100 mL) and H_2O (70 mL) were added. The mixture was filtered and the wet cake washed once with 1/1 EtOAc/brine (150 mL). The filtrate and wash were transferred to a separatory funnel and the layers separated. The organic layer was washed once with brine (150 mL). To the organic layer was added Na_2SO_4 (26 g) and charcoal (6.5 g). The suspension was stirred for 30 min and filtered through Celite (26 g). The filtrate was concentrated and the residue purified by silica gel chromatography (hexanes grading in 10% steps to 40% EtOAc in hexanes). The product fractions were pooled and concentrated. The solids were slurried in CH_2Cl_2 (40 mL) at 45 °C for 30 min and hexanes (160 mL) were added. The slurry was cooled to −4 °C, filtered, and the wet cake washed once with hexanes (40 mL). The wet cake was dried at 50 °C and 20 in. Hg to afford **14** (17.36 g, 80%) as a tan crystalline solid. Mp 132−134 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 9.51 (br s, 1H), 8.65 (d, J = 3.2 Hz, 1H), 7.81 (d, J = 3.1 Hz, 1H), 7.52 (m, 4H), 1.48 (s, 9H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 152.1, 141.4, 139.2, 138.9, 127.4, 126.2, 123.7, 117.7, 115.2, 108.5, 79.1, 28.2 ppm. HRMS (ESI) for $C_{16}H_{17}N_2O_2S$ ($M + H^+$) calcd 301.10052 found 301.10129.

***t*-Butyl-4-(4-cyano-5-formylthiophen-3-yl)phenylcarbamate (15).** To a 250 mL round-bottom flask was charged **14** (3.20 g, 10.7 mmol, 1.0 equiv) followed by THF (64 mL). The solution was cooled to − 5 °C and LDA (13.3 mL of 2.0 M in heptane/THF, 26.6 mmol, 2.5 equiv) was added at such a rate to keep the internal temperature below 5 °C. After one hour, DMF (16 mL) was added and the reaction was warmed to room temperature. After 30 min, the reaction was greater than 99% conversion as determined by HPLC analysis. Aqueous hydrochloric acid (96 mL of 1.0 M) was added followed by EtOAc (64 mL). The layers were separated and the organic layer was washed with aqueous hydrochloric acid (64 mL of 1.0 M), saturated aqueous $NaHCO_3$ (64 mL), and brine (64 mL). The organic layer was concentrated and the residue purified by silica gel chromatography (hexanes grading in 5% steps to 50% EtOAc in hexanes). The product fractions were pooled and concentrated. The solids were dissolved in CH_2Cl_2 (15 mL) at 45 °C. Hexanes (45 mL) were added and the resulting slurry was cooled to 0 °C before filtration. The wet cake was washed twice with hexanes (15 mL) and dried at 50 °C and 20 in. Hg to afford **15** (2.99 g, 85%) as a yellow crystalline solid. Mp 166−168 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 10.01 (d, J = 1.1 Hz, 1H), 9.57 (br s, 1H), 8.31 (d, J = 1.1 Hz, 1H), 7.57 (m, 4H), 1.49 (s, 9H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ: 181.2, 152.0, 149.1, 143.8, 139.8, 131.4, 127.8, 125.0, 117.8, 113.2, 112.9, 79.2, 28.1 ppm. HRMS (ESI) for $C_{17}H_{16}N_2O_3SNa$ ($M + Na^+$) calcd 351.07738 found 351.07717.

(*E*)-*t*-Butyl-4-(4-cyano-5-(2-nitrovinyl)thiophen-3-yl)phenylcarbamate (16). To a 250 mL round-bottom flask was charged **15** (8.00 g, 24.4 mmol, 1.0 equiv) followed by MeCN (20 mL) and CH_3NO_2 (20 mL). DMAP (298 mg, 2.44 mmol, 0.1 equiv) was added and the reaction reached 98% conversion after 2 h as determined by HPLC analysis. After another hour, MeCN (120 mL) was added followed by Ac_2O (3.73 g, 36.5 mmol, 1.5 equiv). After 15 min, the reaction reached greater than 99% conversion of the intermediate alcohol as determined by HPLC analysis. The reaction was cooled to −5 °C and filtered. The wet cake was washed once with MeCN (40 mL) and dried at 50 °C and 20 in. Hg to afford **16** (8.27 g, 91%) as an orange crystalline solid. Mp 219−220 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 9.56 (br s, 1H), 8.22 (ABq, 2H), 8.13 (s, 1H), 7.56 (m, 4H), 1.48 (s, 9H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$) δ:152.0, 143.0, 142.2, 139.8, 138.7, 128.8, 127.6, 127.5, 125.2, 117.8, 113.9, 112.8, 79.2, 28.1 ppm. HRMS (ESI) for $C_{18}H_{17}N_3O_4SNa$ ($M + Na^+$) calcd 394.08320 found 394.08269.

***t*-Butyl-4-(4-aminothieno[3,2-c]pyridine-3-yl)phenylcarbamate (6) using $SnCl_2$ Reduction.** To a 50 mL round-bottom flask was added **16** (2.00 g, 5.38 mmol, 1.0 equiv) followed by EtOAc (10 mL) and $SnCl_2 \cdot 2H_2O$ (2.79 g, 12.4 mmol, 2.3 equiv). After 16 h, the reaction showed greater than 98% conversion as determined by HPLC analysis. MeOH (10 mL) was added, the reaction concentrated and chase distilled once from MeOH (20 mL). The resulting oil was dissolved in MeOH (10 mL) and aqueous K_2CO_3 (30 mL of a 10 wt% solution) was added. The resulting slurry was stirred for 2 h. The slurry was filtered and the wet cake washed once with H_2O (10 mL). The combined filtrate and wash contained 1.1% **17** as determined by HPLC analysis (for isolation and characterization of **17**, see the end of this experiment). The wet cake was slurried in MeOH (20 mL) for 30 min, filtered, and washed once with MeOH (10 mL). This wet cake reslurry procedure was repeated two more times. The combined filtrate and washes were filtered and the resulting MeOH solution contained 84.9% **17** as determined by HPLC analysis. (A pure standard of **17** was obtained by concentration of the MeOH solution and purification of the residue by silica gel chromatography (CH_2Cl_2 followed by 10% MeOH in CH_2Cl_2) to afford **17** as a tan crystalline solid. Mp 217−218 °C; ^{1}H NMR (400 MHz, $(CD_3)SO$) δ: 9.58 (br s, 1H), 8.02 (d, J = 7.0 Hz, 1H), 7.59 (m, 3H), 7.35 (m, 3H), 6.05 (br s, 2H), 1.49 (s, 9H) ppm. (400 MHz, (CD_3OD) δ: 7.94 (dd, J = 7.2, 0.5 Hz, 1H), 7.58 (m, 2H), 7.52 (d, J = 0.4 Hz, 1H), 7.38 (m, 2H), 7.34 (d, J = 7.1 Hz, 1H), 1.53 (s, 9H) ppm. ^{13}C NMR (100 MHz, $(CD_3)SO$), δ:152.1, 145.4, 139.3, 137.5, 135.5, 132.5, 129.1, 127.7, 126.4, 119.3, 117.6, 106.7, 79.1, 28.2 ppm. HRMS (ESI) for $C_{18}H_{20}N_3O_3S$ ($M + H^+$) calcd 358.12199 found 358.12316.) The solution was concentrated and the resulting solids chase distilled twice from EtOH (50 mL portions). The hazy solution was filtered and the wet cake washed twice with EtOH (20 mL). The combined filtrate and wash was concentrated and the resulting solids were dissolved in EtOH (28 mL). To a pressure bottle was added 10% Pd on carbon (150 mg) followed by EtOH (2 mL), AcOH (162 mg, 2.69 mmol, 0.5 equiv), and the EtOH solution of **17**. The mixture was put under a hydrogen atmosphere and heated to 70 °C. After 24 h, the reaction was greater than 99% conversion as determined by HPLC analysis. The reaction was filtered through a 0.2 μm Teflon filter and the wet cake washed three times with EtOH (10 mL). The combined filtrate and wash contained 84.6% **6** as determined by HPLC analysis. The solution was concentrated and chase distilled twice from EtOAc (30 mL portions). The resulting solids were dissolved in EtOAc (40 mL). The organic solution was washed once with saturated $NaHCO_3$ (30 mL) and once with H_2O (30 mL). The organic layer was concentrated and chase distilled twice from iPAc (30 mL portions). The resulting solids were slurried in iPAc (10 mL) and heated to 80 °C. The solution was cooled to ambient temperature and heptane (30 mL) was added. The slurry was filtered and the wet cake washed once with heptane (10 mL). The combined filtrate and wash contained 28.4% **6** as determined by HPLC assay. The wet cake was dried at 50 °C and 20 in. Hg to afford **6** (1.02 g, 55.6%) as a tan crystalline solid. The crystallization was not optimized further. Spectral data matched that of material synthesized by Suzuki cross-coupling of **5** and *t*-butyl-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (vide supra).

***t*-Butyl-4-(4-aminothieno[3,2-c]pyridine-3-yl)phenylcarbamate (6) using Pt−V/C Reduction.** To a 4 mL glass vial was added 3% Pt 0.6% V on carbon (9.5 mg dry basis) followed by water (0.22 mL) and 50% aqueous hypophosphorous acid (0.14 mmol, 15 μL). After 15 min, the catalyst slurry was transferred to a 50 mL Hasteloy-C microreactor containing **16** (1.06 g, 2.86 mmol) in THF (21 mL). The 4 mL vial was rinsed twice with water (0.10 mL portions). The reactor was pressurized to about 90 psig with hydrogen gas and stirred at 95 °C for 10 h, during which time the reaction reached greater than 99.9% conversion of **16** and 95%

conversion of **17** as determined by HPLC analysis. The reaction was cooled to ambient temperature, filtered through a 0.2 μm Teflon filter, and rinsed with THF. The solvent was evaporated and EtOAc (15 mL) was added. The organics were washed once with 50% saturated aqueous $NaHCO_3$ (10 mL) and twice with water (10 mL portions). The solvent was evaporated and the residue purified by silica gel chromatography (25% EtOAc in heptane grading to 100% EtOAc). The product fractions were pooled and concentrated to afford **6** (0.747 g, 77%) as a tan foam. Spectral data matched that of material synthesized by Suzuki cross-coupling of **5** and *t*-butyl-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (vide supra).

Acknowledgment. We would like to thank Bryan Macri and Brian Kotecki of the Abbott Laboratories Catalysis Laboratory for running high pressure reactions and initial screening of reductive cyclization of **16** using hydrogen. We would like to thank Dr. Ian Marsden for structural analysis of compound **16**.

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds described in the experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9003772