Organic Process Research & Development **2003**, *7*, 676−683

Cross-Coupling Methods for the Large-Scale Preparation of an Imidazole−Thienopyridine: Synthesis of [2-(3-Methyl-3H-imidazol-4-yl)-thieno[3,2-*b*]pyridin-7-yl]-(2-methyl-1H-indol-5-yl)-amine

J. A. Ragan,[*,†] J. W. Raggon,[†] P. D. Hill,[†] B. P. Jones,[†] R. E. McDermott,[†] M. J. Munchhof,[‡] M. A. Marx,[‡]
J. M. Casavant,[‡] B. A. Cooper,[‡] J. L. Doty,[‡] and Y. Lu[‡]

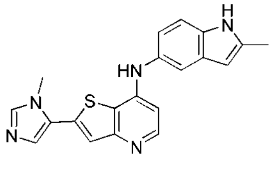
*Chemical Research and Development, Discovery Chemistry, Pfizer Gobal Research & Development,
Eastern Point Road, Groton, Connecticut 06340, U.S.A.*

Abstract:

The multihundred-gram synthesis of [2-(3-methyl-3H-imidazol-4-yl)-thieno[3,2-*b*]pyridin-7-yl]-(2-methyl-1H-indol-5-yl)-amine (1) is described utilizing a Stille cross-coupling of an iodothienopyridine (3) with 5-(tributylstannyl)-1-methylimidazole (11). Several cross-coupling methods were evaluated for the conversion of thienopyridine 3 to imidazole−thienopyridine 2, but only two were effective: the Stille coupling and a Negishi cross-coupling of the organozinc reagent derived from 2-(*tert*-butyldimethylsilyl)-1-methylimidazole and iodothienopyridine (3). The latter procedure worked well on laboratory scale (<50 g), but was capricious upon scale-up. The issues with scale-up of an organostannane reagent are discussed, including control and analysis of organotin levels.

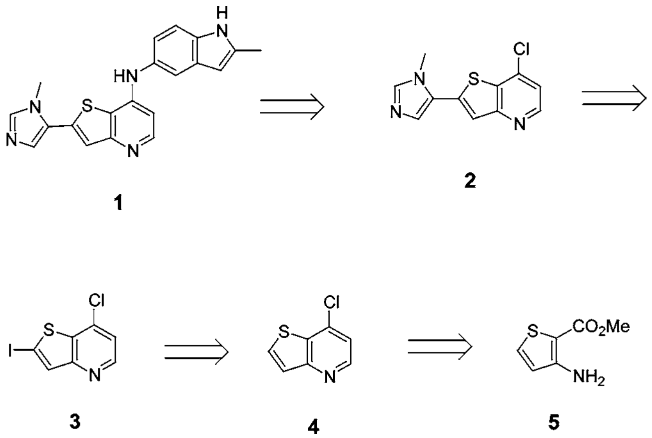
Introduction

Angiogenesis is a requirement for tumor growth and metastasis and occurs through several discrete biochemical signaling pathways. One key pathway that initiates proliferation and migration of endothelial cells is signaling through the vascular endothelial growth factor receptor-2 (VEGFR-2).[2] Therefore, small molecules that block this signaling pathway through inhibition of VEGFR kinase activity could potentially inhibit angiogenesis and tumor growth. [2-(3-Methyl-3H-imidazol-4-yl)-thieno[3,2-*b*]pyridin-7-yl]-(2-methyl-1H-indol-5-yl)-amine (**1**) recently emerged as a promising VEGFR kinase inhibitor (7 nM IC_{50} against VEGFR-2) and was thus of interest for clinical evaluation in the treatment of cancer. This motivated us to seek a practical synthesis of this imidazole−thienopyridine, which could provide the multikilogram quantities required for regulatory toxicology studies and clinical evaluation.



1

Scheme 1



Scheme 1 outlines our retrosynthesis, which identifies chloropyridine **2** and iodothienopyridine **3** as key intermediates. The preparation of thienopyridine **4** was known,[3] and multikilogram quantities of this intermediate were available from outside sources. Likewise, conversion of chloropyridine **2** to **1** was relatively straightforward. However, the cross-coupling of a suitable *N*-methylimidazole derivative with thienopyridine **3** or an appropriate derivative was extremely challenging and demonstrates that, of the many transition metal-catalyzed cross-coupling methods available, only a portion are effective in a complex heterocyclic system such as imidazole−thienopyridine **2**.

Discussion

Scheme 2 describes our synthesis of thienopyridine **4**, which closely followed the literature synthesis.[3] 3-Aminothiophene (**6**) was prepared by hydrolysis and decarboxylation of 3-amino-2-carbomethoxythiophene.[4] Condensation with the adduct of triethylorthoformate and Meldrum's acid generated vinylogous carbamate **7**, which was cyclized by heating to 245 °C in diphenyl ether or Dowtherm. The

---

[†] Chemical Research and Development.

[‡] Discovery Chemistry.

(1) To whom correspondence should be addressed: Pfizer Global Research & Development, Mailstop 8118D-4010, Groton, CT, 06340, U.S.A. Telephone: (860) 441-6334. Fax: (860) 715-9469. E-mail: john_a_ragan@groton.pfizer.com.

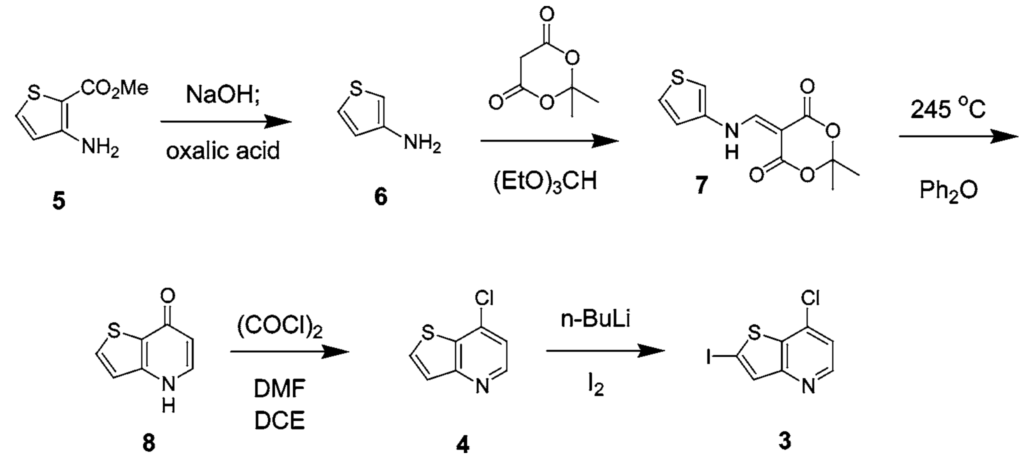
(2) (a) Fan, T. P. D.; Jaggar, R.; Bicknell, R. *Trends Pharmacol. Sci*. **1995**, *16*, 57−66. (b) Folkman, J. *Nat. Med.* **1995**, *1*, 27−31.

(3) (a) Barker, J. M.; Huddleston, P. R.; Holmes, D.; Keenan, G. J.; Wright, B. *J. Chem. Res. Miniprint* **1984**, 771−795. (b) Barker, J. M.; Huddleston, P. R.; Holmes, D.; Keenan, G. J. *J. Chem. Res. Miniprint* **1982**, 1726−1746.

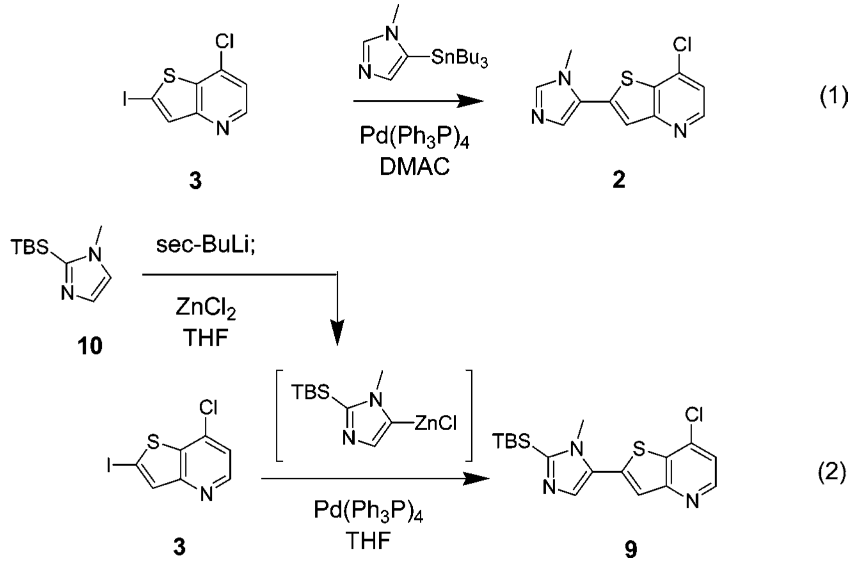
(4) Barker, J. M.; Huddleston, P. R.; Wood, M. L. *Synth. Commun.* **1995**, *25*, 3729−3734.

10.1021/op0340457 CCC: $25.00

Scheme 2



Scheme 3



initially generated 3-carboxy-4-pyridone underwent decarboxylation under these conditions, thus avoiding a separate hydrolysis/decarboxylation (this strategy is well-precedented).[5] Treatment of pyridone **8** with oxalyl chloride in dichloroethane with DMF activation then provided 4-chloropyridine **4**, which was converted to iodothienopyridine **3** via deprotonation with *n*-BuLi and trapping with I$_2$.

Our first synthesis of **1** utilized a Stille cross-coupling[6] with iodide **3** as shown in Scheme 3 (eq 1).[7] From a scale-up perspective, we were concerned with the issues associated with the use of a stoichiometric organostannane reagent (e.g., tank contamination, contamination of drug substance), and sought an alternative method. An organozinc coupling (eq 2, Scheme 3) was identified as an early alternative and provided an effective, nonstannane coupling on laboratory scale (up to 50-g batches of **3** could be coupled). Unfortunately, the reaction was capricious, and further scale-up led to reactions that would occasionally (and unpredictably) fail completely.

Due to the toxicity concerns with the organostannane method and the capriciousness of the organozinc method, we examined a variety of alternative cross-coupling approaches, as summarized in Table 1. Despite these efforts, only two methods were identified which successfully provided coupled product on laboratory scale (entries 1 and 12). Of those, only the Stille coupling (entry 12) proved reliable on >50-g scale.

The failure of these studies to identify non-stannane alternatives was frustrating, particularly since the Negishi coupling (entry 1) worked fairly reliably on 5−10-g scale. The presence of several heteroatoms in both substrates and the product renders them potential metal-chelators, and is a possible culprit (although why this would be scale-dependent is not immediately clear). Another potential issue was

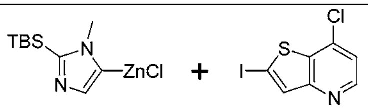
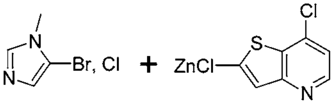
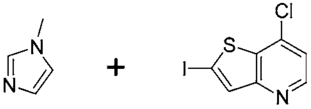
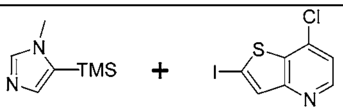
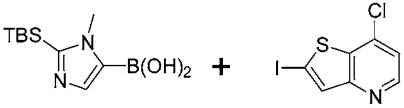
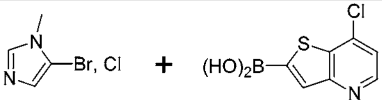
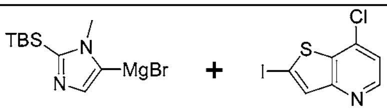
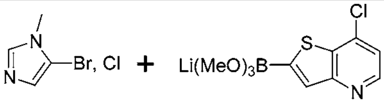
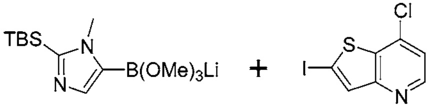
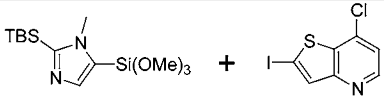
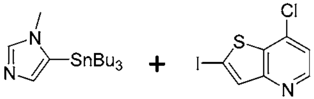
---

(5) (a) Cassis, R.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* **1985**, *15*, 125−134. (b) Andrew, R. G.; Raphael, R. A. *Tetrahedron* **1987**, *43*, 4803−4816. (c) Moron, J.; Huel, C.; Bisagni, E. *Heterocycles* **1993**, *36*, 2753−2764. (d) Marcos, A.; Pedregal, C.; Avendano, C. *Tetrahedron* **1995**, *51*, 1763−1774. (e) Toedter, C.; Lackner, H. *Synthesis* **1997**, 567−572.

(6) For reviews, see: (a) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 1998; Chapter 4. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.

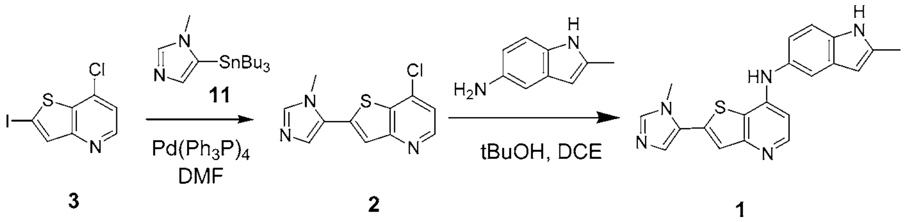
(7) Similar Stille and Negishi couplings with 4-susbstituted *N*-alkylimidazoles (vs 5-substituted in the present study) have been reported: (a) Jetter, M. C.; Reitz, A. B. *Synthesis* **1998**, 829−831. (b) Cliff, M. D.; Pyne, S. G. *Tetrahedron* **1996**, *52*, 13703−13712.

Table 1.

Entry	Reference	Reaction/Catalyst	Comments
1	Negishi[8]	 $Pd(Ph_3P)_4$ (numerous other Pd sources also examined)	Effective on lab scale (<50 g), but capricious upon scale-up. Purity of iodide (**3**) was critical, but no analytical method identified to predict coupling success (HPLC, combustion analysis, Karl-Fischer analysis).
2	Negishi[8]	 $Pd(Ph_3P)_4$	"Reverse Negishi" worked with PhI as model, but failed with bromo- and chloroimidazoles.
3	Heck[9]	 $Pd(OAc)_2/Ph_3P$ or $Pd(OAc)_2/Cy_2NMe$	No reaction under standard Heck conditions. In a phosphine-free system (Cy_2NMe, $Pd(OAc)_2$, Et_4NCl, DMAC),[10] 16% conversion was observed after 24 h at 110 °C, but a second regioisomer was formed.
4	Hiyama[11]	 Pd(0) or Pd(II), Ph_3P or BINAP	No coupling observed, reduction of iodide was seen. Added CsF led to rapid desilylation.
5	Suzuki - Miyaura[12]	 $Pd(Ph_3P)_4$ or $Pd(OAc)_2$ / dppf, dppb, etc.	Isolation of the requisite boronic acid was problematic. Competitive deborylation was observed to form 2-TBS-*N*-methylimidazole.
6	Suzuki - Miyaura[12]	 $Pd(Ph_3P)_4$ or $Pd(OAc)_2$ / dppf, dppb, etc.	The thienopyridine-boronic acid was isolated as a stable, well-behaved solid. Couplings with haloimidazoles were unsuccessful, however. Deborylation observed in some cases.
7	Kumada - Tamao[13]	 Pd(0) or Ni(0) catalysts	No coupling observed. Model study with PhMgBr and iodothienopyridine was successful.
8	Kumada - Tamao[13]	 Pd(0) or Ni(0) catalysts	No coupling observed. Also failed with model electrophile (PhI).
9	Kobayashi[14]	 $NiCl_2(Ph_3P)_2$ or $Pd(Ph_3P)_4$	No coupling observed. Model study with PhI was successful.
10	Kobayashi[14]	 $NiCl_2(Ph_3P)_2$ or $Pd(Ph_3P)_4$	Poor conversion, several byproducts.
11	DeShong[15]	 $Pd(dba)_2$ / Bu_4NF	Desilylation observed, no coupling product formed. Model study with $PhSi(OMe)_3$ also failed to couple.
12	Stille[6]		**Robust and scaleable, only method which was reliable on >50 g scale.**

isolation of byproducts which appeared to arise from competitive lithiation of one of the two methyl groups attached to the TBS protecting group, suggesting that the deprotonation of the TBS–imidazole might have been part

Table 2. **Tin and Palladium Levels in Laboratory Pilots**[a]



entry	compound	purification method	Sn level (ppm)	Pd level (ppm)
1	**2**	aqueous pH workup, then reslurry with MTBE (57% yield)	154	52
2	**2**	recrystallization of entry 1 material from ethyl acetate (73% recovery)	19	38
3	**1**	aminoindole coupling of **2** (from entry 1), followed by crystallization from MeOH (isolated HCl salt, 37% yield)	5	7
4	**1**	aminoindole coupling of **2** (from entry 1), followed by silica gel chromatography (isolated free base, 50% yield)	2	<1

[a] For clarification, note that entries 2−4 all involve further processing of the material from entry 1: recrystalliztion (entry 2), aminoindole coupling followed by recrystallization (entry 3), or aminoindole coupling followed by silica gel chromatography (entry 4).

of the problem for cases which required its intermediacy (e.g., entries 1, 5, 7, 10, and 11).

With the Stille coupling as the only robust method identified in our studies, we decided to utilize this method for preparation of the initial cGMP bulk lot. The major issues we faced with this approach were tank contamination and contamination of drug substance with residual organostannane byproducts. The former issue was addressed by limiting our runs to 22 L glassware, so that we could simply dispose of the reaction vessel when the campaign was completed. While obviously not a long-term solution to the problem, this strategy was acceptable for an initial campaign of <2 kg. For the latter issue, inductively coupled plasma emission spectroscopy (ICP) analysis was used to determine total stannane and palladium content to a lower limit of <2 ppm, which was sufficient for releasing drug substance (the upper limit for stannane content was set at 20 ppm by our toxicologists, taking into consideration the proposed clinical doses). Fortunately, both **2** and **1** are solids which crystallize to purge residual organic impurities quite efficiently.

Table 2 summarizes tin and palladium levels from several laboratory-scale experiments. Entry 1 shows that a simple reslurry of the crude Stille product removes the bulk of the residual stannane (154 ppm, vs an initial level of ca. 170 000 ppm based on the atomic weight of tin, the molecular weights of the reactants, and the stoichiometry of the reaction).[16] This material can be further purified by recrystallization to just below our target tin level (entry 2, 19 ppm). We hoped that we could bypass recrystallization of **2**, and proceed directly into the final aminoindole coupling, with isolation of this product providing further reduction in tin levels. This hope was born out by the following two entries, which show that utilization of the 154 ppm lot of **2** in the aminoindole coupling provides acceptable purity by either crystallization of the HCl salt (entry 3, 5 ppm), or silica gel chromatography (entry 4, 2 ppm). On the basis of these results, we were confident that we would be able to purify our bulk campaign material to <20 ppm stannane, and this prediction was confirmed in the GMP campaign (vide infra).

For the cGMP campaign (Scheme 4), we began with 3 kg of thienopyridine **4**.[3] Metalation of this material was achieved by treatment with *n*-BuLi (1.6 equiv) in THF−hexane at −70 °C for 60 min (D_2O quench of an aliquot showed >95% deuterium incorporation by ^{1}H NMR analysis), followed by addition of I_2 (1.6 equiv) in THF at such a rate that the internal temperature remained below −65 °C. Addition of water precipitated iodide **3** as a light brown solid, which was then washed with water and hexanes to provide an 84% yield of **3** with >99% HPLC (area %) purity. Running the metalation sequence at −20 °C led to increased levels (5−10%) of a bis-iodide impurity by mass spectrometry analysis. The sequential triturations were found to

---

(8) For reviews, see: (a) Negishi, E.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 1998; Chapter 1. (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648.

(9) (a) Brase, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 1998; Chapter 3. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (c) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R. Akita, Y., Ohta, A. *Heterocycles* **1992**, *33*, 257.

(10) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107−3112.

(11) For reviews, see: (a) Hiyama, T. in *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 1998; Chapter 10. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471−1478.

(12) For reviews, see (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (b) Miyaura, N. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI, London, 1998; Vol. 6, pp 187−243. (c) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, Germany, 1998; Chapter 2. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

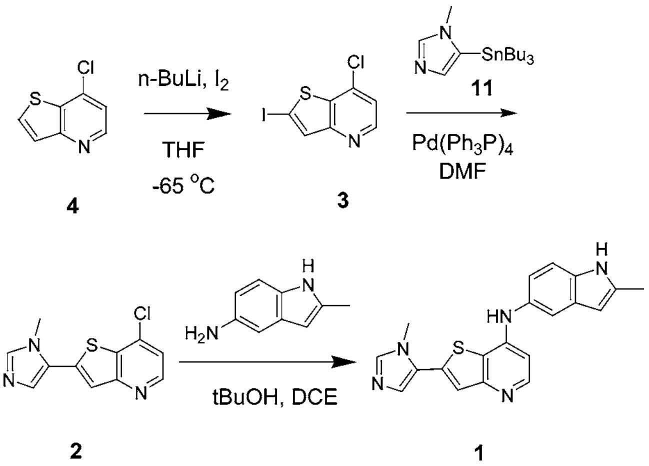
(13) (a) Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K. *Tetrahedron* **1982**, *38*, 3347−3354.

(14) Kobayashi, Y.; Ikeda, E. *J. Chem. Soc., Chem. Commun.* **1994**, 1789.

(15) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684−1688.

(16) Based on the following calculation: (at. wt Sn) × (equiv **11**)/(mol wt **3**) × (equiv **3**) + (mol wt **11**) × (equiv **11**) + (mol wt Pd(Ph$_3$P)$_4$) × (equiv cat.) $= (118 \times 1.1)/(295 \times 1.0) + (370 \times 1.1) + (1155 \times 0.05) = 0.17$ (17%) = 170 000 ppm.

Scheme 4



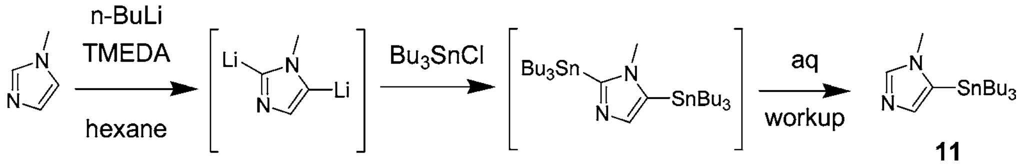
provide a more efficient isolation and purification than an aqueous workup (e.g. partitioning between EtOAc and aqueous $Na_2S_2O_3$).

The organostannane component of the Stille coupling was 5-(tributylstannyl)-1-methylimidazole (**11**). This material was prepared from *N*-methylimidazole, per the literature,[17] as shown in Scheme 5. The 2,5-dilithioimidazole was formed by metalation in TMEDA-hexane at −20 °C, and quenched with Bu_3SnCl. Aqueous workup cleaves the more labile 2-stannyl moiety to provide **11**. This material could be used in crude form in lab pilots, but on scale it was deemed prudent to remove Bu_3SnCl-derived impurities via a hexane−acetonitrile partition; the nonpolar stannane impurities were selectively partitioned into the hexane phase, while the more polar imidazole reagent **11** remained in the acetonitrile phase. This method provided 1.7 kg of **11**.

The Stille coupling was effected with 5 mol % $Pd(Ph_3P)_4$ in DMF at 90 °C. Unlike the other coupling methods investigated, this reaction was robust and nondiscriminating in the source of catalyst, and scaled from 10 to 500 g with no significant change in isolated yield (63−67% on 530 g scale).

Coupling of 5-amino-2-methylindole with chloropyridine **2** was accomplished in a Parr reactor in *tert*-butyl alcohol and dichloroethane. High concentration (2 M in 1:1 *t*-BuOH/DCE), excess indole (2 equiv), and high temperature (100 °C, 17 psi) were critical for this reaction to be driven to reasonable (>90%) conversion. A silica gel column was required to purify this reaction mixture (11 g of silica gel per g of starting material **2**). Following a reslurry from 2-propanol, a 65% yield of **1** was isolated (500-g scale). Conversion to the (−)-camphorsulfonic acid salt then provided the desired drug substance, ICP analysis of which showed 3 ppm stannane and 3 ppm palladium, consistent with the lab pilots described in Table 2.

Scheme 5



After our cGMP campaign, it was found that running the aminoindole coupling in EtOH provided much cleaner and more rapid conversion (this was not tried initially as literature precedent suggested that ethoxide would displace the 4-chloropyridine).[3,18] Thus, combining equimolar amounts of chloropyridine **2** and the aminoindole in refluxing EtOH for 48 h provided the desired product, which crystallized from the reaction upon cooling in 87% yield with >99% HPLC (area %) purity (25 g scale).

Conclusions

We have utilized a Stille coupling to prepare imidazole−thienopyridine **2**, which was then converted to clinical candidate **1**. Organostannane levels were controlled (<20 ppm) in large part due to the crystallinity of **2**, **1**, and salts of **1** (HCl, camsylate). Of several methods examined, the Stille coupling was uniquely suited to provide a robust and scaleable cross-coupling method. This suggests that the wide variety of cross-coupling methods demonstrated on simpler biaryl systems is more limited when applied to complex heterocyclic systems.

Experimental Section

Palladium tetrakis(triphenylphosphine) was ordered from Strem Chemicals (Newburyport, MA, 01950-4098). All other chemicals were ordered from commercial suppliers and used as received. For laboratory-scale experiments, *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from Aldrich in anhydrous “Sure-Seal” glass bottles; all other solvents were reagent grade. Laboratory-scale reactions were run under a positive pressure of nitrogen in glassware which was flame-dried under nitrogen. Reaction progress was monitored by TLC, GC/MS, or HPLC. HPLC purity refers to area %, and is uncorrected. TLC was performed on precoated sheets of 60 F254 (Merck Art. 5719), and visualized by UV, and/or staining with iodine, phosphomolybdic acid, ceric ammonium molybdate, or *p*-anisaldehyde solutions and heating. GC analyses were performed on a Hewlett-Packard 6890 GC/MS with a 5973 mass selective detector. Mass spectral data was collected on either a Hewlett-Packard 6890 GC/MS (electron impact ionization), or a Micromass (Fisons) Platform II mass spectrometer (atmospheric pressure chemical ionization). ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained on a Varian Unity+400 spectrometer equipped with two RF channels, indirect detection, and pulsed-field gradients (*z*-axis only). Melting points are uncorrected. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory (Woodside, NY) or Quantitative Technologies, Inc. (Whitehouse, NJ). Tin and palladium analyses were done at Quantitative Technologies, Inc. by inductively coupled plasma emission spectroscopy (ICP) analysis. Samples were digested in a mixture of aqueous $H_2SO_4-HNO_3-HClO_4$ with heating, then diluted with aqueous HCl in volumetric flasks. Multiple runs of the samples as well as positive controls demonstrated good reproducibility (±10%). The LLOQ (lower limit of quantification) was demonstrated to be <2 ppm.

7-Chloro-2-iodo-thieno[3,2-*b*]pyridine (3). A 75-L Hastelloy reactor was charged with 7-chloro-thieno[3,2-*b*]pyridine **4** (3.00 kg, 17.7 mol) and THF (30 L), and the solution was cooled to −70 °C. A solution of *n*-BuLi (2.5 M in hexane, 11.3 L, 28.3 mol) was added over 60 min. The reaction mixture was stirred for an additional 60 min and sampled for completion (quench into D_2O and analyzed by ^1H NMR), which indicated >95% deprotonation. A solution of I_2 (7.18 kg, 28.3 mol) in THF (12 L) was then added to the lithium anion solution over 80 min, maintaining the temperature between −65 and −70 °C. The reaction mixture was allowed to warm to 20 °C over 18 h, at which point HPLC analysis indicated >95% conversion to iodide **3**. Water (75 L) was added over a period of 10 min, and the resulting slurry was stirred for 3 h at 20 °C. The resulting solids were filtered, washed with water (5 L) and hexanes (3 portions of 2.5 L), and dried under vacuum at 40 °C, providing 4.39 kg of iodide **3** as an off-white solid (14.9 mol, 84% yield). HPLC analysis indicated a purity of 99.5%; mp = 187−189 °C; IR (neat): 3089, 1564, 1531, 1353, 830 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.55 (d, J = 5, 1H), 7.84 (s, 1H), 7.26 (d, J = 5, 1H); ^{13}C NMR ($CDCl_3$): δ 157.9, 148.4, 138.1, 136.8, 135.5, 119.0, 85.6; MS (EI): m/z 295 (M, 100), 260 (M − Cl, 15). Anal. Calcd for C_7H_3NSClI: C, 28.45; H, 1.02; N, 4.74; S, 10.85; Cl, 12.00; I, 42.94. Found: C, 28.48; H, 0.86; N, 4.63; S, 11.04; Cl, 11.98; I, 43.05.

2-*tert*-Butyl-dimethylsilyl-*N*-methylimidazole (10). (Although previously reported in the literature,[19] experimental details were not provided). A flame-dried, 250-mL round-bottom flask was charged with *N*-methylimidazole (4.0 mL, 50 mmol) and 40 mL of THF. The reaction mixture was cooled to −78 °C, and *n*-BuLi (2.5 M in hexane, 22.0 mL, 55 mmol) was added dropwise via syringe. The reaction mixture was stirred for an additional 45 min at −78 °C, and then *tert*-butyldimethylsilyl chloride (9.0 g, 60 mmol) was added as a solution in 10 mL of THF. The solution was stirred for 30 min at −78 °C and then allowed to warm to room temperature overnight. The reaction mixture was quenched by pouring into ice-cold, aqueous NH_4Cl (ca. 200 mL), rinsing with isopropyl ether (IPE). The layers were separated, and the aqueous was extracted with another 100-mL portion of IPE. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil (10.9 g, 110% of theory due to residual solvent). This material was suitable for use in the subsequent coupling without further purification. ^1H NMR ($CDCl_3$): δ 7.22 (s, 1H), 6.99 (s, 1H), 3.77 (s, 3H), 0.96 (s, 9H), 0.41 (s, 6H); MS (EI): m/z 196 (M, 5), 139 (M − C_4H_9, 100).

2-[2-(*tert*-Butyl-dimethylsilyl)-3-methyl-3H-imidazol-4-yl]-7-chloro-thieno[3,2-*b*]pyridine (9). A 5 L, four-neck, round-bottom flask equipped with two 500-mL addition funnels was flame-dried under a positive pressure of nitrogen. The flask was charged with 2-(*tert*-butyldimethylsilyl)-*N*-methylimidazole **10** (66.5 g, 338 mmol). Anhydrous THF (1.1 L) was added, and the flask was immersed in a room-temperature water bath. A solution of *sec*-BuLi (1.3 M in cyclohexane, 274 mL, 355 mmol) was then added dropwise via addition funnel at a rate such that the temperature remained at or below 25 °C. The reaction was stirred for an additional 2.5 h at room temperature, then cooled to −78 °C in a dry ice−acetone bath. A solution of $ZnCl_2$ (0.5 M in THF, 744 mL, 372 mmol) was then added via addition funnel at a rate such that the temperature remained at or below −65 °C. Upon complete addition, the cold bath was removed, and the reaction was allowed to warm to room temperature and was stirred for 60 min. Iodothienopyridine **3** (50.0 g, 169 mmol) and $Pd(PPh_3)_4$ (19.6 g, 17 mmol, 10 mol %) were then added, and the reaction was warmed to reflux for 45 min. [Note: as discussed in the text, this coupling was capricious; the best success was obtained with batches of iodothienopyridine **3** that had been triturated with hot isopropyl ether, filtered, and vacuum-dried within 24 h of use]. HPLC analysis indicated complete conversion to product, at which point the reaction mixture was allowed to cool to room temperature. The reaction mixture was carefully poured into 2 N NH_4OH (4 L), and extracted with three 1.4-L portions of $CHCl_3$. The combined organic extracts were washed with brine (1.2 L), dried over Na_2SO_4, filtered, and concentrated to provide a solid. This material was triturated with 400 mL of hexanes, cooling in a 0 °C ice bath. The solids were collected and rinsed with 75 mL of cold hexanes, and dried in a vacuum oven to provide 25−30 g (69−82 mmol, 41−49%) of the product **9** as a tan solid: ^1H NMR ($CDCl_3$): δ 8.61 (d, J = 5, 1H), 7.57 (s, 1H), 7.55 (s, 1H), 7.31 (d, J = 5, 1H), 3.93 (s, 3H), 1.04 (s, 9H), 0.49 (s, 6H); MS (EI): m/z 363 (M, 10), 306 (M − C_4H_9, 100).

***N*-Methyl-5-(tributylstannyl)-imidazole (11).** A 22 L, three-neck, round-bottom flask equipped with a mechanical stirrer and addition funnel was charged with tetramethylethylenediamine (1.99 L, 13.2 mol). After cooling to −20 °C, *n*-BuLi (2.5 M in hexane, 5.26 L, 13.2 mol) was added over 90 min, maintaining the temperature between −10 and −20 °C. After stirring 20 min, a solution of *N*-methylimidazole (450 g, 5.48 mol) in THF (2.6 L) was added over 60 min, maintaining the temperature below −10 °C. Cooling was removed, and the resulting yellow suspension was allowed to warm to 20 °C over 3 h. The reaction mixture was then cooled to −20 °C, and Bu_3SnCl (3.72 L, 13.7 mol) was added over a period of 2 h. The resulting solution was allowed to warm to 20 °C over 16 h. Water (5.7 L) was added, vigorous stirring was maintained for 30 min, and then the layers were allowed to settle. The top organic layer was separated and washed with water (3 L). The combined aqueous phases were extracted with 4 L of ethyl acetate. The organic extracts were

---

(17) Gaare, K.; Repstad, T.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1993**, *47*, 57−62.

(18) (a) Barker, J. M.; Huddleston, P. R.; Holmes, D.; Keenan, G. J.; Wright, B. *J. Chem. Res. Miniprint* **1984**, 771−795. (b) Cutler, R. A.; Surrey, A. R. *J. Am. Chem. Soc.* **1955**, *77*, 2441−2444.

(19) Walters, M. A.; Lee, M. D. *Tetrahedron Lett.* **1994**, *35*, 8307−8310.

combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to provide 4.44 kg (218% of theoretical) of crude **11** as a yellow oil. This material was divided into two roughly equivalent portions for the hexane−acetonitrile extractive purification. Each portion was partitioned into hexanes (9 L) and CH_3CN (7 L). The top hexane layer was separated and extracted with four portions of CH_3CN (6, 4, 3, and 3 L). The CH_3CN extracts were combined and washed with hexanes (4 L). Concentration of the combined CH_3CN extracts under vacuum provided 1.70 kg (4.58 mol, 84% yield) of **11** as a colorless oil. This material was used in the Stille coupling with no further purification. ^1H NMR ($CDCl_3$): δ 7.64 (s, 1H), 7.05 (s, 1H), 3.70 (s, 3H), 1.60−1.50 (m, 6H), 1.42−1.30 (m, 6H), 1.15−1.09 (m, 6H), 0.92 (t, $J = 7$, 9H).

7-Chloro-2-(3-methyl-3H-imidazol-4-yl)-thieno[3,2-*b*]-pyridine (2). *Method A (Laboratory Pilot).* A 250-mL round-bottom flask was charged with stannane **10** (15.7 g, 42.2 mmol), iodothienopyridine **3** (11.2 g, 37.9 mmol), $Pd(Ph_3P)_4$ (2.19 g, 1.89 mmol, 5 mol %), and DMF (120 mL). After purging with nitrogen, the solution was placed in a 90 °C oil bath for 22 h. The solution was then cooled to room temperature, diluted with 240 mL of 1 N HCl, and extracted with three 50-mL portions of EtOAc (the product remains in the acidic aqueous phase). The aqueous phase was adjusted to pH 10 with 2 N NaOH and then extracted with three 50-mL portions of CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$. Filtration and concentration provided an oily, tan solid. Addition of 100 mL of methyl-*tert*-butyl ether (MTBE) and stirring overnight provided a tan solid, which was filtered to provide 5.39 g of product **2**, ICP analysis of which indicated 154 ppm tin (entry 1 in Table 2). One gram of this material was recrystallized from hot EtOAc to provide a light tan solid: 0.73 g, ICP analysis showed 19 ppm tin (entry 2 in Table 2).

Method B (GMP Bulk Campaign). A 22-L, three-neck, round-bottom flask equipped with a mechanical stirrer was charged with stannane **10** (672 g, 1.81 mol), iodothienopyridine **3** (535 g, 1.81 mol), $Pd(Ph_3P)_4$ (105 g, 0.091 mol, 5 mol %), and DMF (2.7 L), and heated to 95 °C under N_2. After 40 h, HPLC analysis indicated complete conversion. The reaction mixture was cooled to 10 °C and quenched by the addition of 1 N HCl (5.3 L). Ethyl acetate (4.2 L) was added, and the mixture was filtered. The layers were separated, and the aqueous phase was extracted with two 4-L portions of ethyl acetate. The combined organic layers were washed with water (3 L). The aqueous extracts were combined, the pH was adjusted to 10−10.5 by addition of 5 N NaOH, and extracted with three 4.5-L portions of 1:1 THF−EtOAc (v/v). The aqueous pH was monitored after each extraction and readjusted to pH 10−10.5 as needed. HPLC analysis indicated essentially complete extraction of product from the aqueous phase at this point. The organic extracts were combined, washed with water (three portions of 4 L each) and brine (2 L), and concentrated under vacuum to provide a tacky solid. MTBE (4 L) was added, and the mixture was concentrated under vacuum. An additional 3 L of MTBE was then added, and the resulting slurry was stirred for 2 h. The solids were collected by filtration, rinsing with MTBE. After drying at 40 °C under vacuum, the product was obtained as an off-white solid (302 g, 1.21 mol, 67% yield); mp = 178−180 °C; IR (neat): 3084, 1533, 1265, 1123, 838 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.61 (d, $J = 5$, 1H), 7.63 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.31 (d, $J = 5$, 1H), 3.91 (s, 3H); ^{13}C NMR (CD_3OD): δ 157.2, 148.4, 141.6, 137.9, 136.8, 132.6, 129.7, 126.3, 121.4, 119.1, 32.7; HRMS $[MH]^+$ (m/z) for $C_{11}H_8ClN_3S$ calcd 250.0205; obsd 250.0199; Anal. Calcd for $C_{11}H_8ClN_3S$: C, 52.91; H, 3.23; N, 16.83; S, 12.84; Cl, 14.20. Found: C, 52.56; H, 2.92; N, 16.55; S, 12.75; Cl, 14.44.

[2-(3-Methyl-3H-imidazol-4-yl)-thieno[3,2-*b*]pyridin-7-yl]-(2-methyl-1H-indol-5-yl)-amine (1). *Method A (Laboratory Pilot, Isolation by Crystallization of HCl Salt: Table 2, Entry 3).* A resealable tube reactor was charged with chloropyridine **2** (1.00 g, 4.00 mmol), 5-amino-2-methylindole (1.17 g, 8.00 mmol), *tert*-butyl alcohol (1.0 mL), and dichloroethane (1.0 mL). The reactor was then placed in a 100 °C oil bath for 60 min, at which point HPLC analysis indicated <5% starting material. The reaction was cooled to room temperature, and the dark material was dissolved in 5 mL of MeOH. After stirring overnight, a green solid was isolated by filtration to provide 1.21 g of crude product. This material was redissolved in a minimum volume of hot MeOH and cooled to room temperature. The resulting yellow solids were collected to provide 0.59 g of product **1**−HCl (37% yield); ICP analysis indicated 5 ppm tin (Table 2, entry 3). ^1H NMR (DMSO-d_6): δ 11.3 (s, 1H), 10.7 (s, 1H), 8.26 (d, $J = 7$, 1H), 7.94 (s, 1H), 7.61 (s, 1H), 7.38−7.32 (m, 3H), 6.95 (dd, $J = 8, 2$, 1H), 6.77 (d, $J = 8$, 1H), 6.10 (s, 1H), 3.76 (s, 3H), 2.37 (s, 3H).

Method B (Laboratory Pilot, Isolated by Silica Gel Chromatography of Free Base: Table 2, Entry 4). A resealable tube reactor was charged with chloropyridine **2** (1.00 g, 4.00 mmol), 5-amino-2-methylindole (1.17 g, 8.00 mmol), *tert*-butyl alcohol (1.0 mL), and dichloroethane (1.0 mL). The reactor was then placed in a 100 °C oil bath for 60 min, at which point HPLC analsysis indicated <5% starting material. The reaction was cooled to room temperature, and the dark material was dissolved in 5 mL of MeOH. After stirring overnight, a green solid was isolated by filtration to provide 0.98 g of crude product. This material was redissolved in MeOH and coated onto 2.5 g silica gel; the product/silica gel mixture was placed on top of a 5-g silica gel column and eluted with 94:5:1 CH_2Cl_2−MeOH−Et_3N. The product-containing fractions were combined, concentrated, and triturated with a minimal volume of CH_2Cl_2 to provide product **1** (free base) as a light yellow solid: 0.72 g (50% yield); ICP analysis indicated 2 ppm tin (Table 2, entry 4). IR (neat): 3327−2959 (br), 1574, 1552, 1516, 1489, 1460, 1365, 1303, 1185, 1125, 1113 cm^{-1}; ^1H NMR (CD_3OD): δ 8.12 (d, $J = 6$, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 7.39 (s, 1H), 7.34 (d, $J = 8$, 1H), 7.28 (s, 1H), 6.99 (d, $J = 8$, 1H), 6.70 (d, $J = 6$, 1H), 6.16 (s, 1H), 3.85 (s, 3H), 2.44 (s, 3H).

Method C (Bulk Campaign, Isolated as Free Base). A 2-L Parr pressure reactor was charged with chloropyridine

2 (260 g, 1.04 mol), 5-amino-2-methylindole (304 g, 2.08 mol), *tert*-butyl alcohol (260 mL), and dichloroethane (260 mL). The reactor was sealed, purged with nitrogen, and heated to 90−100 °C for 2 h (the pressure rose to 17 psi during heating). The reactor was cooled to 60 °C and opened, and the very thick (nearly solid) reaction slurry was transferred out of the reactor, rinsing with methanol. This process was repeated on the same scale, such that a total of 520 g (2.08 mol) of chloropyridine **2** was processed.

The crude product from each run was purified by silica gel chromatography: the crude product in ca. 8 L of MeOH was treated with 3 kg of silica gel and concentrated on a rotary evaporator to a dark brown solid. An additional 2-L portion of dichloroethane was added and concentrated to solids to facilitate removal of most of the MeOH. The solids were then charged to the top of a 20-gal glass chromatography column previously charged with 10 gal of CH_2Cl_2 and 9 kg of silica gel. The column was eluted with a 98:2 (v/v) CH_2Cl_2−MeOH solution to remove less polar impurities (assayed by TLC), collecting 7-L fractions. The eluant was then changed to a 93.5:5:1.5 CH_2Cl_2−MeOH−Et_3N mixture to elute the desired product. The product-containing fractions (26−36 in the case of one column) were combined and concentrated. This chromatography was repeated for the second reaction, and the product-containing fractions from both columns were combined and concentrated (distillation under partial vacuum) to a volume of ca. 5 L. Four liters of 2-propanol was added, and distillation resumed to a volume of ca. 3 L. Another 4-L portion of 2-propanol was added, and distillation continued to a volume of ca. 4 L. The resulting slurry was stirred overnight at room temperature, then filtered and dried under vacuum to provide 483 g (1.34 mol, 65% yield) of tan solids. This material was further purified by slurrying in 4.8 L of a 98:2 (v/v) H_2O−2-propanol mixture: the slurry was warmed to 55 °C for 60 min, then cooled to room temperature and stirred for 2 h. Solids were collected and then recrystallized by dissolving in 9.4 L of a 50:50 CH_2Cl_2−MeOH mixture with warming to 35 °C, then concentrating under partial vacuum to ca. 4 L. 2-Propanol (8 L) was added, and distillation was resumed to a volume of ca. 4 L. The resulting slurry was stirred at room temperature for 2 h, and the solids were collected by filtration. Vacuum drying provided 390 g (1.08 mol, 52% yield for the overall reaction and purification) of off-white solids, with an HPLC purity of 98.7%.

Method D (Lab Scale in EtOH, Isolated as HCl Salt). A 2-L round-bottom flask was charged with chloropyridine **2** (25 g, 0.10 mol), 5-amino-2-methylindole (14.6 g, 0.10 mol), and 400 mL of absolute EtOH. The resulting mixture was stirred vigorously and heated to reflux for 48 h. During the course of the reaction, a solid precipitated from the reaction mixture. After cooling the reaction mixture to 25 °C, the solids were collected by filtration, washed with EtOH, and dried in a vacuum oven. This provided the HCl salt of **1** as a crystalline solid with 99% HPLC purity (34.5 g, mol, 87% yield).

***(1R)*-(−)-10-Camphorsulfonic Acid Salt of 1.** [2-(3-Methyl-3H-imidazol-4-yl)-thieno[3,2-*b*]pyridin-7-yl]-(2-methyl-1H-indol-5-yl)-amine (**1**) (386 g, 1.07 mol) was dissolved in 3.9 L of CH_2Cl_2 and 3.9 L of MeOH with warming to 35 °C. The solution was filtered through paper, and speck-free conditions (free of particulates) were maintained for the duration of the operations. (*1R*)-(−)-10-Camphorsulfonic acid (246 g, 1.06 mol) was dissolved in 2 L of THF, filtered into a spec-free flask, and added to the solution of free base over 10−15 min. The resulting solution was concentrated under partial vacuum to a volume of ca. 3 L. An additional 8 L of THF was added, and a seed crystal was introduced. Distillation was resumed to a volume of ca. 3 L. Additional THF was added to a final volume of ca. 10 L. The resulting slurry was stirred overnight at room temperature. The solids were collected by filtration, rinsing with THF. Vacuum drying provided off-white solids (589 g, 0.996 mol, 93% yield); mp = 269−270 °C dec. ICP analysis indicated 3 ppm for both Sn and Pd. ^{1}H NMR (CD_3OD): δ 8.20 (d, J = 7, 1H), 7.89 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 7.43 (d, J = 8, 1H), 7.37 (s, 1H), 7.05 (dd, J = 8, 2), 6.85 (d, J = 7), 6.24 (s), 3.88 (s, 3H), 3.35 (d, J = 16, 1H), 2.80 (d, J = 16, 1H), 2.72−2.63 (m, 1H), 2.49 (s, 3H), 2.35 (dt, J = 18, 4, 1H), 2.07−2.00 (m, 2H), 1.90 (d, J = 18, 1H), 1.68−1.60 (m, 1H), 1.45−1.37 (m, 1H), 1.13 (s, 3H), 0.86 (s, 3H); Anal. Calcd for $C_{20}H_{17}N_5S{\cdot}C_{10}H_{16}SO_4$: C, 60.89; H, 5.62; N, 11.84; S, 10.84. Found: C, 60.72; H, 5.62; N, 11.66; S, 10.90.

Acknowledgment

Dr. Ricardo Borjas and Mr. Eric Weiss are acknowledged for coordinating the tin and palladium analyses. Dr. Greg Cohee of QTI is acknowledged for timely assistance in executing the tin and palladium analyses. Numerous helpful discussions with Drs. Joel Hawkins, Bob Dugger, Keith DeVries, Jennifer Rutherford, and Professor Dan Kemp (MIT) are gratefully acknowledged.

Received for review April 2, 2003.

OP0340457