JOC Article

^{14}C-Labeled and Large-Scale Synthesis of the Angiotensin-(1−7)-receptor Agonist AVE 0991 by Cross-Coupling Reactions†

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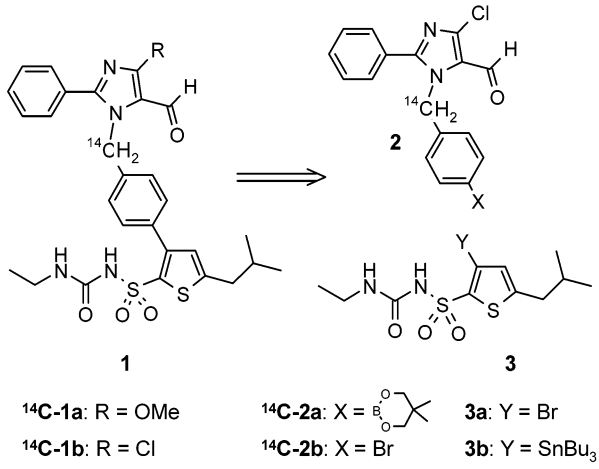
The synthesis of ^{14}C-labeled AVE 0991 (**^{14}C-1a**) and large-scale synthesis of AVE 0991 (**1a**) are described. In the key step of the synthesis, the C−C coupling reaction of the imidazole (**2**) and thiophene (**3**) building blocks was studied under Suzuki and Stille reaction conditions, respectively. Suzuki reaction gave only moderate yields, whereas the best results were obtained under Stille reaction conditions with up to 64% yield.

Introduction

Substituted imidazole derivatives have proven to be potent ligands for angiotensin receptors and a number of them are used as valuable cardiovascular drugs.[1] Recently, compounds of this class were found to be potent agonists of the angiotensin-(1−7)-receptor.[2] The stimulation of the endothelial cell connected angiotensin-(1−7)-receptor initiates the release of vasodilating and cardioprotective messengers such as cyclic 3′,5′-guanosine monophosphate (cGMP) and nitrogen monoxide (NO). As a result, imidazole-derived angiotensin-(1−7)-agonists may serve as valuable agents in the treatment or prophylaxis of hypertension, heart hypertrophy, heart failure, and coronary heart diseases such as angina pectoris, myocardial infarct, and endothelial dysfunction, (e.g. as a result of diabetes mellitus and arterial or venous thrombosis). In conjunction with pharmacokinetic and metabolism studies, the synthesis of ^{14}C-labeled AVE 0991 (**^{14}C-1a**) became necessary. We report the elaboration of suitable conditions for the radiosynthesis of **1a** with unlabeled material to gain sufficient information for the synthesis of corresponding ^{14}C-labeled AVE 0991. Furthermore, we describe the synthesis of AVE 0991 in kilogram scale. The retrosynthetic analysis (Scheme 1) pointed to the cross-coupling of imidazole **2** and thiophene **3** as a crucial step for the synthesis of **1a**. In the consideration of possible cross-coupling conditions the Suzuki reaction was favored initially due to the selectivity of the reaction.[3]

SCHEME 1



Results and Discussion

Starting from 4-bromotoluene (**4**), a halogen−metal exchange was performed with *n*-BuLi at −78 °C, followed by quenching with isopropyl borate (Scheme 2). After treatment with diol **5** the cyclic boronic ester **6** was obtained in 50% yield. Without further purification, compound **6** was brominated under radical conditions with 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione to yield benzylic bromide **7**[4] in 60% yield. Alternatively, **6** could be prepared from *p*-tolylboroxine in one step. Imidazole **8** was synthesized according to Matsumura et al.[5] and alkylated[6] with benzyl bromide **7** in DME to give 55% of the boronic ester coupling partner **2a**. Under these

† Dedicated to Dr. Gerhard Beck on the occasion of his 60th birthday.

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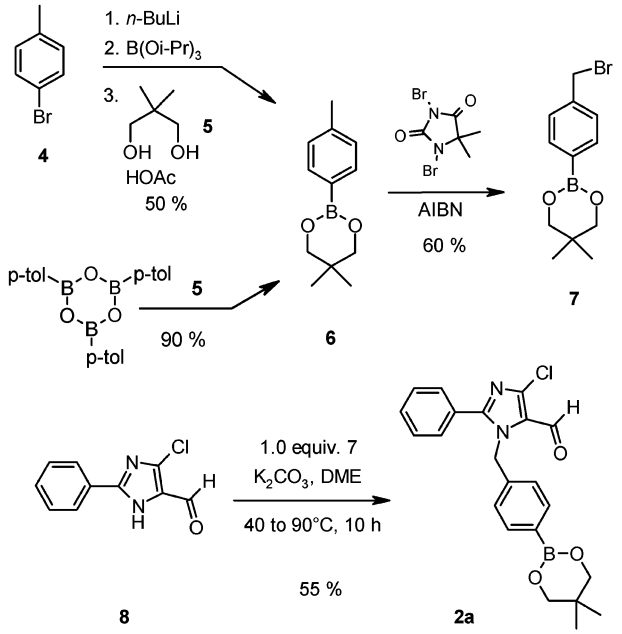
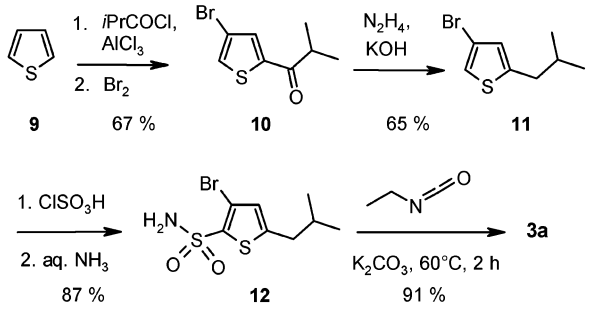
SCHEME 2



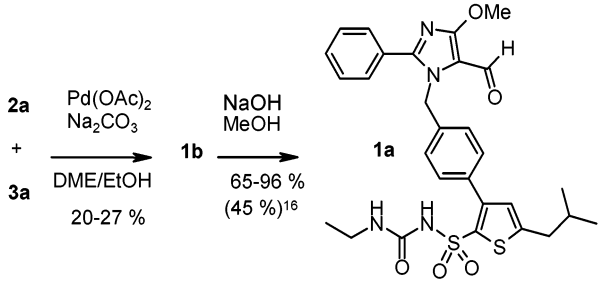
SCHEME 3



reaction conditions, 27% of the undesired *N*-substituted regioisomer was formed but could be removed by chromatography. The structures of the regioisomers were assigned on the basis of NMR measurements which showed a NOE effect between the aldehyde proton and the ortho protons of the phenylene ring only in the case of **2a**.

The synthesis of bromothiophene **3a** started with thiophene (**9**), which was acylated with isobutyryl chloride−$AlCl_3$ (Scheme 3). Subsequent bromination was performed without hydrolysis of the ketone−$AlCl_3$ complex to yield the bromoketone **10**[7] in 67% yield. Wolff−Kishner reduction[8] (65% yield) followed by chlorosulfonation[9] produced the sulfochloride, which was treated with

SCHEME 4



aqueous ammonia in THF to give the sulfonamide **12** (87% yield). In the last step the sulfonylurea **3a** was formed in 91% yield by refluxing with ethyl isocyanate in acetone.[10]

The Suzuki coupling of **2a** and **3a** proved to be the critical step in the synthesis of AVE 0991 **1a** (Scheme 4). As shown in Table 1, numerous optimization experiments to couple imidazole boronic ester **2a** and 2-bromothiophene **3a** under Suzuki reaction conditions[11,12] were performed. Under standard conditions (entry 1−4) with triphenylphosphine containing Pd catalysts, no or only very small amounts of the desired coupling product **1b** were found in different solvents and by using different bases. A major improvement of the yield was observed when the reaction was run under triphenylphosphine free conditions by using $Pd(OAc)_2$ as catalyst. The best results on small scale were achieved in a mixture of DME/ethanol (2:1) as solvent (entries 5 and 6). We identified the deboronated imidazole **13** and the dimerization product **14** as the main side products (Scheme 5). Under this condition, the reaction could be successfully upscaled to several hundred grams with acceptable yield (26%). Variation of the organic solvent systems resulted in neither significant improvements in yield nor avoidance of side product formation. To suppress the formation of the byproducts, the effect of additives was tested.

With oxidizing additives such as copper(I) chloride (Table 1, entry 7), reducing additives such as phosphines (entry 11), or silver oxide (entry 8), we were able to reduce the formation of side product **13** or **14**, mostly with no effect on the isolated yield of the desired product **1b**. Finally, during the upscaling process a combination of $PdCl_2(dppf) \times CH_2Cl_2$ as catalyst in 2-propanol/DME and KOH as base gave a further improvement. This conditions could be transferred to large scale successfully. By using this method, several kilograms of **1b** could be produced in 32% isolated yield in the pilot plant (for details see the Experimental Section). The structural correctness of the product was confirmed by X-ray-

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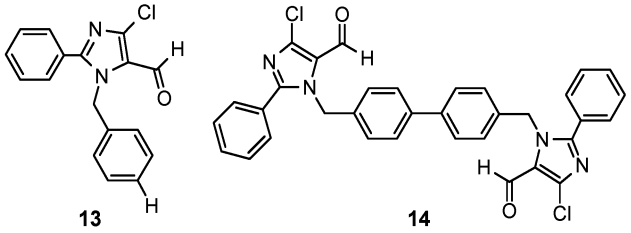
TABLE 1. Suzuki Reactions of Boronic Ester 2a and Thiophene 3a under Different Reaction Conditions[a]

entry	catalyst	equiv of **2a**	base	solvent	additive	*t* [h]	**1b** [%][b]	**13** [%][c]	**14** [%][c]
1	$Pd(PPh_3)_4$	1.5	Cs_2CO_3	toluene		72	–	–[d]	–[d]
2	$Pd(PPh_3)_4$	1.2	Na_2CO_3	toluene/EtOH/H_2O	N(*n*-Bu)$_4$Br	44	<5	–[d]	–[d]
3	$Pd(PPh_3)_4$	1.5	K_2CO_3	DME/EtOH 2:1		96	–	22	42
4	$Pd(PPh_3)_2Br_2$	1.5	Cs_2CO_3	toluene/EtOH/H_2O		72	9	–[d]	–[d]
5	$Pd(OAc)_2$	1.3	Na_2CO_3	DME/EtOH 2:1		96	27	15	38
6	$Pd(OAc)_2$	1.3	Na_2CO_3	DME/EtOH 2:1	NaBr	96	26	12	36
7	$Pd(OAc)_2$	1.3	Na_2CO_3	DME/EtOH 2:1	CuCl	96	25	46	17
8	$Pd(OAc)_2$	1.3	Na_2CO_3	DME/EtOH 2:1	Ag_2O	96	22	5	45
9	$Pd(OAc)_2$	1.3	K_3PO_4	EtOH/H_2O 2:1		72	7	9	50
10	$Pd(OAc)_2$	1.3	K_3PO_4	DMF	N(*n*-Bu)$_4$Cl	72	5	22	53
11	$Pd(dba)_2$	1.5	Cs_2CO_3	DME/EtOH 2:1	P(*t*-Bu)$_3$	96	–	–[d]	–[d]
12	$Pd(OAc)_2$	1.3	Na_2CO_3	xylene/$(CH_2OH)_2$/H_2O	TSPP	96	11	–[d]	–[d]
13	$PdCl_2$(dppf)	1.0	KOH	DME/*i*-PrOH		2	32	–[d]	–[d]

[a] Reactions were carried out with 0.5 mmol of **3a** at 80−90 °C. [b] Isolated yield/value based on boronic ester **2a**. [c] Determined by HPLC (ν = 290 nm) after filtration of the reaction solution. [d] Not determined; TSPP = tris(3-sulfonatophenyl) phosphine.

SCHEME 5

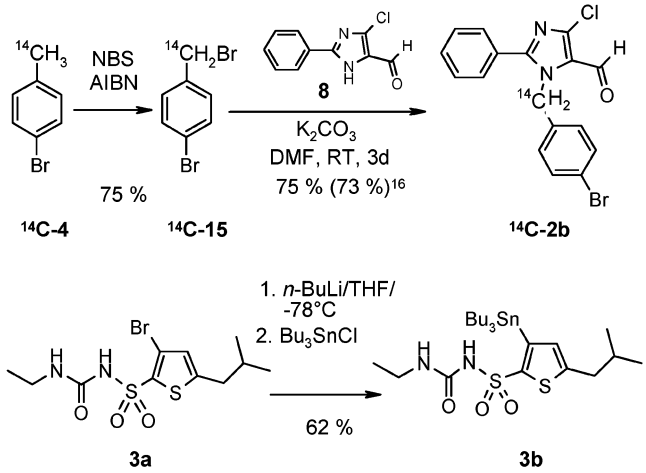


crystallography. In the last step, the coupled product **1b** was methoxylated by reaction with NaOH in methanol to give the final product **1a** in 65% yield. In the large scale, the yield could be optimized to 96% by careful control of the reaction time. Impurities of **1b** had a dramatic effect on the yield of the final product **1a**. In total, **1a** (small scale) was prepared in five reaction steps (Schemes 2 and 4) with only 3% overall yield based on 4-bromotoluene.

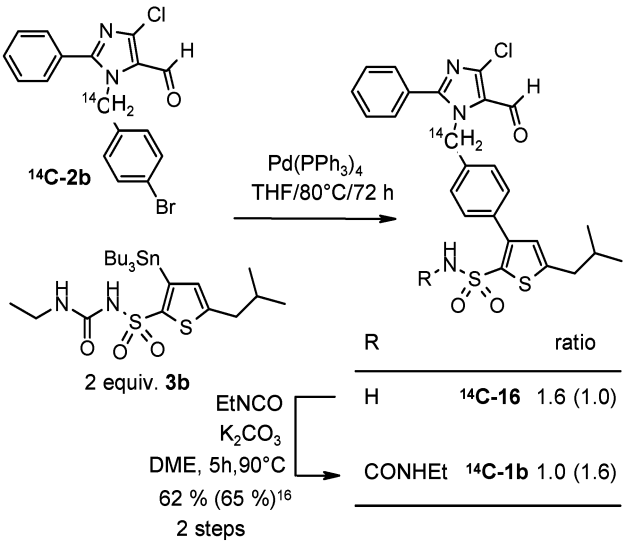
As an alternative for the synthesis of ^{14}C-AVE 0991 (**1a**) we evaluated the cross-coupling reaction under Stille conditions.[13] Imidazole derivative **2b** was prepared in two steps and 50% overall yield by bromination of 4-bromotoluene **4**, followed by alkylation of imidazole **8**. The tributyltin compound **3b** was synthesized in 62% yield by metalation of the 3-bromo-thiophene derivative **3a** with 5 equiv of *n*-BuLi and quenching with tributyltinchloride (Scheme 6).

The Stille reaction was performed with bromide **2b** and 2 equiv of stannane **3b** in the presence of 10 mol % of $Pd(PPh_3)_4$ as catalyst in THF. The reaction mixture turned Pd(0) black after 3 days under reflux with 90−95% consumption of bromide **2b**. Incomplete consumption of bromide **2b** was observed in reactions with <2 equiv of stannane **3b**. After fast separation of Pd and Sn material by fractional filtration, the coupling products **1b** and the primary sulfonamide **16** were isolated as a mixture in a ratio of 1:1.6 (Scheme 7).[14,15] Compound **16** was then converted into the urea derivative **1b**, in an overall yield of 62−65%, by reaction with ethyl isocyanate. The methoxylation of **1b** was performed as described above to give **1a** in about 65% yield (Scheme 2). The convergent reaction sequence yielded AVE 0991 (**1a**) in six reaction steps with an overall yield of 14% (Schemes 6 and 7).

SCHEME 6



SCHEME 7



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(14) Ratios were determined by HPLC of the crude reaction mixture (see Experimental Section for further details).

(15) The primary sulfonamide **16** was formed by basic cleavage of **1b**. The ratio of the products **1b** and **16** differs slightly depending on the mol % of catalyst and the amount of solvent (solubility of the base).

Finally, we carried out the ^{14}C-labeled synthesis of **^{14}C-1a** according to the Stille variant (Schemes 6 and 7)[16] in four radioactive reaction steps with 21% overall yield starting from 4-bromo-^{14}C-benzyl bromide (purchased from Amersham Pharmacia Biotech). The final product **^{14}C-1a** was purified by HPLC to give >98% UV and radiochemical purity.

Conclusion

We described a new pathway for the large-scale synthesis of thiophene **3a**. Furthermore, we discussed different synthetic approaches for the synthesis of AVE 0991 (**1a**) using several cross-coupling reaction protocols. While Suzuki conditions proved to be the best choice in the large-scale synthesis with respect to safety issues, avoidance of chromatography, costs, and environmental risks, the Stille coupling was more convenient in the ^{14}C-labeled synthesis. This synthesis serves as a useful example for potential total synthesis endeavors under different perspectives and needs.

Experimental Section

5,5-Dimethyl-2-*p*-tolyl-[1,3,2]dioxaborinane (6).[17] *n*-BuLi (0.60 mL, 1.60 mmol, 2.7 M in heptane) was added dropwise via syringe to a solution of 4-bromotoluene (171 mg, 1.00 mmol) in dry THF (5 mL) at −78 °C under argon. After 45 min, isopropyl borate (301 mg, 1.60 mmol) in THF (5 mL) was added via syringe over 5 min. The reaction mixture was allowed to warm to −10 °C (2 h) and 2,2-dimethylpropane-1,3-diol (**5**, 167 mg, 1.60 mmol) was added in one portion followed by dropwise addition of acetic acid (1.80 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for a further 2 h. The solvent was evaporated in vacuo and the residue was dissolved in a 1:1 water/ethyl acetate mixture (10 mL). The aqueous phase was extracted three times with ethyl acetate (20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization from heptane/ethyl acetate 10:1 to give 102 mg (0.50 mmol, 50%) of **6** as a colorless solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.70 (d, J = 7 Hz, 2H), 7.15 (d, J = 7 Hz, 2H), 3.75 (s, 4H), 2.35 (s, 3H), 1.00 (s, 6H) ppm.

2-(4-Bromomethyl-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane (7).[18] Borinane **6** (10.96 kg, 53.7 mol) and 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (3.0 kg, 10.49 mol) were added to a nitrogen-flushed vessel. A suspension of AIBN (20 g) in cyclohexane (70 L) was added, and the mixture was heated to gentle reflux (79 °C). After 30 min, the condensate turned brown, indicating the onset of the reaction. After refluxing for another 30 min, the condensate was colorless again, indicating the end of the reaction. Refluxing was continued for 10 min then the reaction mixture was cooled to 60 °C and more 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (3.0 kg, 10.49 mol) was added, followed by a suspension of AIBN (20 g) in cyclohexane. The mixture was heated as described above. After complete reaction as indicated by color, a third portion of 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione (2.39 kg, 8.36 mol) and AIBN (20 g) was added and reacted as above. The mixture was cooled to 20 °C and the insoluble hydantoine was separated by pressure filtration. After being washed with cyclohexane (3 × 10 L), the filtrates were concentrated in vacuo in a separate vessel, and the residue was transferred to a rotary evaporator and evaporated to dryness in vacuo to yield **7** (14.7 kg, purity 79% by NMR, 76%) as a colorless powder, contaminated with **6** (14%) and the dibromomethyl compound (7%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.75 (d, J = 7 Hz, 2H), 7.35 (d, J = 7 Hz, 2H), 6.5 (s, impurity: methine proton of dibromomethyl derivative), 4.5 (s, 2H), 3.75 (s, 4H), 2.35 (s, impurity: phenyl-CH_3 of **6**), 1.0 (s, 6H) ppm.

5-Chloro-3-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-benzyl]-2-phenyl-3*H*-imidazole-4-carbaldehyde (2a). A suspension of **7** (10.5 g, purity 98% according to HPLC, 50 mmol) and **8** (17.7 g, purity 80% by HPLC, 50 mmol) in DME (85 mL) was stirred at 40 °C until a clear solution resulted. Powdered anhyd K_2CO_3 (6.9 g, 50 mmol) was added in one portion and the mixture was refluxed for 6 h. After being cooled to room temperature, the mixture was diluted with toluene (100 mL), filtered, and evaporated to dryness. The residual brown viscous residue (24.7 g) was purified by chromatography on silica gel (0.06−0.2 mm, 250 g of SiO_2, toluene/ethyl acetate 6:1, 2% acetic acid). The early fractions afforded, after concentration in vacuo, a viscous oil that was crystallized from heptane/ethyl acetate 95:5 to give **2a** (12.4 g, 55%) as a pale yellow powder. The late fractions were also evaporated in vacuo and the residual viscous oil was crystallized from CCl_4 to give the regioisomer of **2a** (5.5 g, 27%) as a pale yellow powder. **2a**: mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.55 (m, 2H), 7.5 (m, 1H), 7.45 (m, 4H), 7.0 (d, J = 9 Hz, 2H), 5.65 (s, 2H), 3.75 (s, 4H), 1.0 (s, 6H) ppm. Anal. Calcd for $C_{22}H_{22}BClN_2O_3$: C, 64.66; H, 5.43; N, 6.85. Found: C, 64.42; H, 5.34; N, 6.84. Regioisomer of **2a**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.9 (s, 1H), 7.7 (d, J = 8 Hz, 2H), 7.25−7.45 (m, 5H), 6.9 (d, J = 8 Hz, 2H), 5.2 (s, 2H), 3.7 (s, 4H), 0.95 (s, 6H) ppm. Anal. Calcd for $C_{22}H_{22}BClN_2O_3$: C, 64.66; H, 5.43; N, 6.85. Found: C, 64.68; H, 5.48; N, 6.78.

4-Bromo-2-(2-methylpropan-1-one)thiophene (10). Anhydrous $AlCl_3$ (25 kg, 187.5 mol) was placed in a reaction vessel, the vessel was flushed with nitrogen, and CH_2Cl_2 (60 L) was added with stirring at 20−25 °C. After the solution was cooled to 5 °C, isobutyryl chloride (16.8 kg, 157.7 mol) was added slowly, maintaining the temperature below 23 °C. After the reaction mixture was stirred overnight at 20−25 °C, the temperature was reduced to 5 °C and thiophene **9** (12.6 kg, 149.8 mol) was added over 1 h at 18−23 °C. After the reaction was stirred overnight at 20−25 °C, the temperature was reduced to 3 °C and bromine (25.2 kg, 157.7 mol) was added at 3−8 °C over 1 h by using a dosing pump. The temperature was gradually raised to 20 °C within 2 h and the reaction mixture was stirred at 20−25 °C overnight. Ice (130 kg) and water (30 L) were placed in a second vessel and the reaction mixture was pumped into it during 1 h during stirring. The reaction vessel was rinsed with CH_2Cl_2 (20 L) and the organic phases were separated and stirred vigorously with water (120 L) overnight to destroy the remaining Al complexes. After phase separation and reextraction of the aqueous phase with CH_2Cl_2 (10 L), the organic extract was stirred with $Na_2S_2O_3$ solution (37.5%, 25 L), separated, and concentrated in vacuo. Heptane (58 L) was added and, after being inoculated with some crystals of the product, the mixture was cooled to 0 °C and stirred overnight. The resulting solid was pressure filtered to yield **10** (24.2 kg, purity 88.7% by GC, 61%) as a gray crystalline powder: mp 48−50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (s, 1H), 7.55 (s, 1H), 3.35 (septet, J = 7.5 Hz, 1H), 1.25 (d, J = 7.5 Hz, 6H) ppm. Anal. Calcd for C_8H_9BrOS: C, 41.22; H, 3.89; S, 13.75. Found: C, 41.13; H, 3.72; S, 13.60.

4-Bromo-2-isobutyl-thiophene (11). In a nitrogen-flushed glass vessel, KOH (8 kg, purity 85−100%, 140 mol) was dissolved in triethyleneglycol (22 L) and the temperature was allowed to rise to approximately 95 °C. A solution of **10** (8.3 kg (27.5 mol); purity 77.2% by GC) in triethyleneglycol (20 L) was prepared and added to the KOH solution in one portion, followed by an aqueous solution of hydrazine hydrate (80%,

(16) The yields of the ^{14}C synthesis are listed in parentheses in schemes 4, 6, and 7.

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3.5 L) diluted with water (5 L). The mixture was heated to 120−122 °C for 1.5 h, after which time the temperature was raised to 160 °C and the product was co-distilled with water for 4−5 h. The crude yellow oily product was separated, washed subsequently with 0.2 M HCl (2.5 L) and water (2.5 L), and filtered through Na_2SO_4 (1 kg) to give **11** as a clear yellow oil (3.4 kg, purity 81.8% by GC, 46% yield). The Na_2SO_4 layer was washed with CH_2Cl_2 and the washings were concentrated to give another 0.38 kg (purity 83.5% by GC, 5% yield) of **11**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 (s, 1H), 6.7 (s, 1H), 2.65 (d, J = 8 Hz, 2H), 1.85 (m, 1H), 0.95 (d, J = 7 Hz, 6H) ppm. GC-MS (ESI): m/z 219−221 ($M + H^+$).

3-Bromo-5-isobutyl-thiophene-2-sulfonyl Chloride. To a solution of **11** (7.58 kg, purity 81% by GC, 28.0 mol) in CH_2Cl_2 (50 L) in a nitrogen-flushed vessel was pumped chlorosulfonic acid (16.2 kg, 139 mol) at −5 °C over 1.5 h with use of a dosing pump, and the resulting mixture was stirred at 2−4 °C for 4 h. A second vessel was charged with NaCl (5 kg), ice (115 kg), and heptane (110 L) under nitrogen and the reaction mixture was quickly pumped into it (5 min) under vigorous stirring. The reaction vessel was rinsed with CH_2Cl_2 (5 L) and the washing was transferred to the second vessel. After being stirred for another 10 min at room temperature, the mixture was transferred to a separatory funnel and the vessel was rinsed with heptane (30 L). The turbid organic phase was separated and dried by filtration through a Na_2SO_4 layer (15 kg). Reextraction of the aqueous phase with heptane (30 L), phase separation, and filtration through the used Na_2SO_4 layer was followed by evaporation of the organic solution in vacuo, using a thin layer evaporator at 45 °C. Traces of residual solvent were removed with use of a rotary evaporator to yield the sulfonyl chloride (8.3 kg, 84% yield; purity 90.2% by GC) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.9 (s, 1H), 2.7 (d, J = 7 Hz, 2H), 1.95 (m, 1H), 1.0 (d, J = 7 Hz, 6H) ppm. Anal. Calcd for $C_8H_{10}BrClO_2S_2$: C, 30.25; H, 3.17; S, 20.19. Found: C, 30.44; H, 2.98; S, 20.20.

3-Bromo-5-isobutyl-thiophene-2-sulfonic Acid Amide (12). Aqueous ammonia (22.4%, 8.6 L) and THF (16.0 L) were placed in a nitrogen-flushed vessel at 10 °C. A solution of 3-bromo-5-isobutyl-thiophene-2-sulfonyl chloride (8.3 kg, 23.6 mol, purity 90.2% according to GC) in THF (24 L) was added with stirring and cooling in such a way that the temperature was maintained between 10 and 15 °C (about 1 h) and the resulting solution was stirred at this temperature for an additional hour. The solvent was evaporated to dryness in vacuo at 20 °C, heptane (24 L) and water (20 L) were added, and the mixture was stirred for 15 min. The mixture was cooled and stirred at 0−1 °C to initiate crystallization. The product was pressure filtered, washed with water, and dried at 35 °C in vacuo to afford **12** (6.88 kg, 98%) as pale yellow crystals: mp 87−88 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.8 (s, 2H), 7.0 (s, 1H), 2.7 (d, J = 7 Hz, 2H), 1.85 (m, 1H), 0.9 (d, J = 7 Hz, 6H) ppm. Anal. Calcd for $C_8H_{12}BrNO_2S_2$: C, 32.22; H, 4.06; N, 4.70; S, 21.50. Found: C, 32.28; H, 4.01; N, 4.77; S, 21.39.

3-Bromo-5-isobutyl-thiophene-2-(3-ethyl) Sulfonylurea (3a). A nitrogen-flushed vessel was charged with **12** (8.0 kg, 26.8 mol), anhyd K_2CO_3 (8.6 kg, 62.2 mol), and acetone (60 L). The vessel was set under slight vacuum and ethylisocyanate (3.2 kg, 45 mol) was siphoned in through a PTFE tube. The tube was rinsed with acetone (2 L) and the mixture was heated to 54 °C (0.5 h) with stirring. After being refluxed for 2 h, the mixture was pressure filtered and the K-salts were washed with acetone (2 × 10 L). Water (58 L) and HCl (37%, 12 L) were placed in a separate vessel at 10 °C and the K-salts were added in several portions to prevent foaming. The product was allowed to crystallize overnight at room temperature, pressure filtered, washed with a little water, and dried in vacuo at 60 °C to furnish **3a** (10.2 kg, 91%) as a colorless crystalline powder: mp 191−191.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.0 (br s, 1H), 7.05 (s, 1H), 6.35 (br t), 3.0 (pentet, J = 7 Hz, 2H), 2.7 (d, J = 7 Hz, 2H), 1.9 (m, 1H), 0.9 (m, 9H) ppm. Anal. Calcd for $C_{11}H_{17}BrN_2O_3S_2$: C, 35.78; H, 4.64; N, 7.59. Found: C, 35.40; H, 4.51; N, 7.55.

Suzuki Reaction Conditions: 3-[4-(4-Chloro-5-formyl-2-phenyl-imidazol-1-ylmethyl)phenyl]-5-isobutyl-thiophene-2-(3-ethyl) Sulfonylurea (1b). Large-scale conditions with $Pd(OAc)_2$ as catalyst: A nitrogen-flushed 50-L glass vessel was filled with **3a** (560 g, 1.52 mol), $Pd(OAc)_2$ (25 g, 0.11 mol), Na_2CO_3 (400 g), and NaBr (200 g) and flushed again with nitrogen. Dry dimethoxyethane (8 L) and ethanol (3 L) were added and the mixture was stirred and heated to slight reflux. A solution of **2a** (800 g, 1.96 mol) in 4 L of dry dimethoxyethane and 3 L of ethanol was added slowly (0.25 L/h) and the mixture was refluxed for about 4 days. The mixture was cooled to 20 °C and 12 L of ice water was added in one portion with stirring followed by 0.9 L of concentrated aqueous HCl, which was added dropwise until pH 1−2. Ethyl acetate (9 L) was added and the mixture was filtered through a Büchner funnel charged with 500 g of Celite. The residue was washed with 2 L of ethyl acetate, the aqueous layer of the combined filtrates containing the product was separated and extracted with 6 L of ethyl acetate, and the combined organic layers were concentrated in vacuo. The residue was dried by repeated mixing with toluene and evaporation. The crude product was purified by medium-pressure chromatography (30 kg SiO_2, 35−70 μm, toluene/ethyl acetate, 1% acetic acid) to yield **1b** (231 g, 26%): mp 190 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.50−7.42 (m, 5H), 7.03 (d, J = 7.6 Hz, 2H), 6.74 (s, 1H), 6.09 (br s), 5.64 (s, 2H), 3.09−3.02 (m, 2H), 2.68 (d, J = 6.9 Hz, 2H,), 1.94−1.87 (m, 1H), 0.99−0.96 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 152.7, 150.7, 150.7, 145.5, 144.0, 136.8, 133.6, 131.8, 130.9, 129.9, 129.8, 129.3, 129.1, 127.7, 126.1, 125.2, 49.6, 39.3, 35.2, 30.6, 22.2, 14.8 ppm. X-ray analysis: crystal size 0.52 × 0.3 × 0.15 mm^3, monoclinic, space group $P2_1/c$, a = 16.180(1) Å, b = 9.701(1) Å, c = 20.007(1) Å, β = 108.45(1)°, V = 2785.25 Å^3, ρ_{calcd} = 1.395 Mg/m^3, T = 293 K, Z = 4, 7113 independent reflexes, 4830 refined parameters, R1 = 0.0357, wR2 = 0.0838. Anal. Calcd for $C_{28}H_{29}ClN_4O_4S_2$: C, 57.47; H, 5.00; N, 9.57; S, 10.96. Found: C, 56,95; H, 4.99; N, 9.46; S, 10.91. Byproducts **13**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.4−7.65 (m, 5H), 7.3 (m, 3H), 7.0 (m, 2H), 5.65 (s, 2H) ppm. Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.53; H, 4.34; N, 9.26. **14**: mp 239−240 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 2H), 7.55 (d, J = 7 Hz, 4H), 7.5 (m, 10H), 7.05 (d, J = 7 Hz, 4H), 5.65 (s, 4H) ppm. Calcd for $C_{34}H_{25}Cl_2N_4O_4$ ($M + H^+$) 591.13565, found 591.13546 (HRMS).

3-[4-(5-Formyl-4-methoxy-2-phenyl-imidazol-1-ylmethyl)phenyl]-5-isobutyl-thiophene-2-(3-ethyl) Sulfonylurea (1a). Compound **1b** (280 mg, 0.48 mmol) was suspended in methanol and a freshly prepared methanolic NaOH solution (48 mg in 5 mL of methanol) was added dropwise over 5 min. The reaction mixture was heated at 70 °C for 9 h and the conversion was followed by TLC. The reaction was cooled to room temperature and acidified with 2 N HCl to pH 2. The solvent was nearly evaporated in vacuo, then ethyl acetate (20 mL) was added and the organic and aqueous phases were separated. The aqueous phase was extracted twice with ethyl acetate (20 mL), the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$, and the solvent was evaporated in vacuo to give the crude product as a yellow oil. Purification by HPLC [Zorbax Sil, 250 × 9.4 mm; 5 μm, Fa. Bischoff with toluene/(ethyl acetate/2% acetic acid) 2:1, flow 5 mL/min] yielded **1a** (181 mg, 0.31 mmol, 65%) as a colorless solid; purity 99.6% (HPLC); R_f (heptane/ethyl acetate/acetic acid 100:50:1) 0.40, mp 191−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.61−7.45 (m, 7H), 7.12 (d, J = 7.9 Hz, 2H), 6.78 (s, 1H, th), 6.13 (br s, 1H), 5.61 (s, 2H), 4.19 (s, 3H), 3.12−3.08 (m, 2H), 2.72 (d, J = 7.0 Hz, 2H), 1.99−1.92 (m, 1H), 1.03−1.00 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 150.7, 150.5, 145.6, 137.5, 133.3, 131.9, 130.6, 129.7, 129.6, 129.2, 129.0, 128.4, 126.0, 113.0, 56.3, 49.6, 39.3, 35.0, 30.5,

22.2, 14.7 ppm. MS (ESI) *m*/*z* 581 (100) [M^+ + H]. Anal. Calcd for $C_{29}H_{32}N_4O_5S_2$: C, 59.88; H, 5.72; N, 9.63; S, 11.02. Found: C, 59.82; H, 5.44; N, 9.77; S, 11.02.

4-Bromobenzyl Bromide (15). 4-Bromotoluene (**4**, 1.00 g, 5.80 mmol) was dissolved in cyclohexane (10 mL) and *N*-bromosuccinimide (1.04 g, 5.80 mmol) and AIBN (10 mg, 0.8 mmol) were added in one portion. The reaction mixture was refluxed (100 °C) for 4 h, cooled to room temperature, and filtered and the solid was washed twice with cyclohexane (5 mL). The filtrate was evaporated to dryness and the residue was purified by chromatography (heptane/ethyl acetate 3:1) to give **15** (1.10 g, 4.40 mmol, 75%).

3-(4-Bromobenzyl)-5-chloro-2-phenyl-3*H*-imidazole-4-carbaldehyde (2b). Imidazole **8** (207 mg, 1.00 mmol) and 4-bromobenzyl bromide (**15,** 250 mg, 1.00 mmol) were added to a 50-mL round-bottom flask and dissolved in dry DMF (5 mL). Then K_2CO_3 (97 mg, 0.70 mmol) was added and the reaction mixture was stirred for 48 h at room temperature. The solvent was completely evaporated in vacuo and the residue was suspended in ethyl acetate and purified by chromatography (heptane/ethyl acetate 2:1) to give **2b** (281 mg, 0.75 mmol, 75%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.52 (d, J = 7.1 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.42 (dd, J = 7.1/7.3 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 5.51 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 152.8, 144.0, 135.7, 132.4, 131.3, 129.6, 129.4, 128.3, 128.0, 125.5, 122.3, 49.7 ppm. No regioisomer of **2b** was detected.

5-Isobutyl-3-tributylstannane-thiophene-2-(3-ethyl) Sulfonylurea (3b). Into a 250-mL flask was added **3a** (1.85 g, 5.00 mmol) and the flask was filled with argon over 15 min. The solid was dissolved in dry THF (45 mL) and the solution was cooled to −78 °C and treated with *n*-BuLi (10 mL, 25 mmol, 2.5 M in toluene), added dropwise via syringe. The solution was stirred for 45 min at −78 °C and tributyltinchloride (6 mL, 25 mmol) was added dropwise. The solution was allowed to warm to room temperature (2 h) and stirred for another hour at room temperature. After addition of water (10 mL) the THF was removed in vacuo. The aqueous phase was extracted with ethyl acetate (3 × 50 mL), the combined organic fractions were dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was purified by chromatography with 500 mL of heptane to remove the excess tributyltinchloride and heptane/ethyl acetate 2:1 to elute **3b** (1.80 g, 3.10 mmol, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.59 (br s, 1H), 3.34−3.30 (m, 2H), 2.74 (d, J = 7.0 Hz, 2H), 1.95−1.87 (m, 1H), 1.70−1.52 (m, 7H), 1.39−1.29 (m, 8H), 1.21−1.16 (m, 8H), 0.98−089 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 133.2, 130.6, 129.2, 113.0, 39.5, 31.1, 29.4, 27.7, 22.6, 15.3, 14.1, 11.9 ppm.

Stille Reaction Conditions: 3-[4-(4-Chloro-5-formyl-2-phenyl-imidazol-1-ylmethyl)phenyl]-5-isobutyl-thiophene-2-(3-ethyl) Sulfonylurea (1b). Into a oven or flame-dried and argon-filled 50-mL two-necked flask with reflux condenser were added imidazole **2b** (375 mg, 1.00 mmol), stannane **3b** (1.16 g, 2.00 mmol), $Pd(PPh_3)_4$ (100 mg), and dry THF (20 mL). The reaction mixture was refluxed for 72 h, the solvent was removed under vacuum, and the crude material was purified by a fast chromatography-filtration process (SiO_2): 300 mL of heptane eluted the excess and degration products of tin derivatives, and coupling products were obtained by elution with heptane/ethyl acetate/acetic acid (100:50:1) to give a mixture of **1b** and **16** (413 mg, ratio 1.6:1 determined by HPLC). This mixture was added to a 100-mL two-necked flask with condenser, which was filled with argon over 20 min. After addition of potassium carbonate (295 mg, 2.10 mmol), DME (25 mL), and ethyl isocyanate (178 mg, 2.50 mmol) the reaction mixture was refluxed for 2 h (TLC monitoring). After the solution was cooled to room temperature, the pH was adjusted to 5.2 by addition of a 5% aqueous citric acid solution. Dichloromethane was added until a clear solution with two phases was obtained. The phases were separated, the aqueous phase was extracted with dichloromethane (3 × 20 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo. Flash chromatography with heptane/ethyl acetate/acetic acid (100:50:1) as eluent gave **1b** as a colorless solid (360 mg, 0.62 mmol, 62%). **16**: R_f (heptane/ethyl acetate/acetic acid 100:50:1) 0.53; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.60−7.48 (m, 7H), 7.09 (d, J = 6.8 Hz, 2H), 6.78 (s, 1H), 5.70 (s, 2H), 4.60 (s, 2H), 2.72 (d, J = 5.7 Hz, 2H), 1.97−1.92 (m, 1H), 1.01−0.99 (m, 6H) ppm.

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Supporting Information Available: General experimental details and procedures which were optimized for the large-scale process (large-scale synthesis of compounds **6**, **2a**, **1b**, and **1a**; ^{1}H NMR spectra for **1a**, **1b**, **2b**, **3b**, and **16** and ^{13}C NMR spectra for **1a** and **1b**; X-ray data for **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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