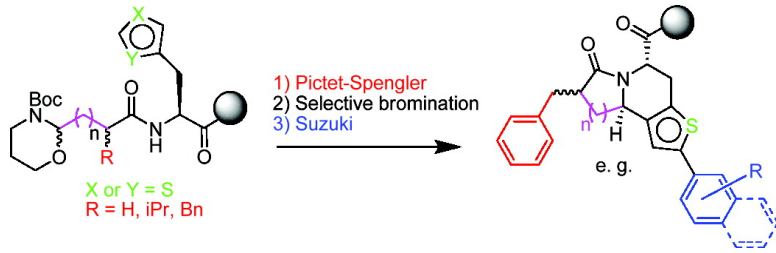
JOURNAL OF combinatorial CHEMISTRY

Article

Solid-Phase Synthesis of Aryl-Substituted Thienoindolizines: Sequential Pictet#Spengler, Bromination and Suzuki Cross-Coupling Reactions of Thiophenes

Sebastian T. Le Quement, Thomas E. Nielsen, and Morten Meldal

J. Comb. Chem., **2008**, 10 (3), 447-455• DOI: 10.1021/cc700199n • Publication Date (Web): 04 April 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Solid-Phase Synthesis of Aryl-Substituted Thienoindolizines: Sequential Pictet−Spengler, Bromination and Suzuki Cross-Coupling Reactions of Thiophenes

Sebastian T. Le Quement, Thomas E. Nielsen, and Morten Meldal*

Carlsberg Laboratory, SPOCC Centre, Gamle Carlsberg Vej 10, DK-2500 Valby, Denmark

Received December 18, 2007

The solid-phase synthesis of a range of novel heterocyclic scaffolds based on the thiophene ring system, including thienoindolizines and aryl-substituted thiophenes, is presented. Specifically, a sequential methodology for the decoration of thienoindolizine scaffolds has been developed. This method involves a highly efficient and diastereoselective intramolecular Pictet−Spengler reaction, a quantitative and regioselective bromination of the thiophene ring, and a final Suzuki cross-coupling with an arylboronic acid. Crude products were generally obtained in high purities (>90%). In addition, an investigation on the acidic and electronic effects governing the rate of the Pictet−Spengler reactions was performed. Finally, a range of substituted thiophenes was attached to solid supports and subjected to the regioselective bromination and Suzuki cross-coupling reactions, thus providing substituted thiophenes with high purities of crude products.

Introduction

The design and synthesis of novel heterocyclic and constrained scaffolds incorporating heterocycles and aromatic moieties is one of the cornerstones of modern combinatorial and medicinal chemistry. In the search for new drugs, the thiophene scaffold has been widely investigated.[1] This ring is readily available, highly stable and is easily functionalized.[2] Many functionalized building blocks constructed around the thiophene core are commercially available. The structural resemblance of the thiophene with the pyrrole and the furane rings and their chemical properties as excellent C-nucleophiles provides a useful pyrrole and furane isoster from a medicinal chemistry point of view. It is present in a number of currently marketed drugs such as the non-steroidal anti-inflammatory drug Lornoxicam and the semisynthetic penicillins Temocillin and Ticarcillin. Furthermore, a growing number of recent reports have been emphasizing the bioactivity of compounds containing a thiophene unit[3–6] and specifically annulated thiophenes are becoming more and more interesting as therapeutic agents (Figure 1).[7–11]

Compounds based on oligomeric thiophenes have been intensively studied for their physical properties, showing promising properties as conducting polymers or as new materials for electronic and photonic applications.[12–14]

Considering these findings and the need for synthesis of combinatorial and parallel libraries of small molecules with drug-like properties, it is of general interest to develop solution- and solid-phase library methods incorporating decorated thiophene motifs.

In high-throughput drug discovery, it is essential to have access to and robust solid-phase synthesis procedures. Due to the nature of solid-phase chemistry, the removal of by-products is always at the end of the synthetic sequence and it is therefore of outmost importance to develop reactions that are generally efficient, stereo- and regioselective, as well as quantitative on the solid support. The direct transfer of solution procedures to the solid phase is rarely successful, and frequently specific protocols, which are compatible with the selection of linker and resin, need to be developed.

Intramolecular reactions yielding constrained heterocyclic motifs are key reactions in drug discovery. In recent years, we have investigated a solid-phase cascade reaction comprising the formation of a cyclic *N*-acyliminium ion followed by intramolecular reaction with C-, N-, S-, or O-nucleophiles.[15–17]

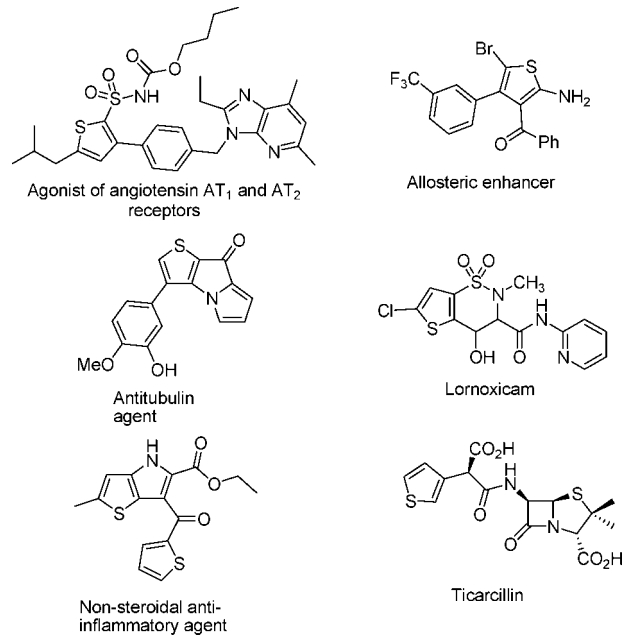
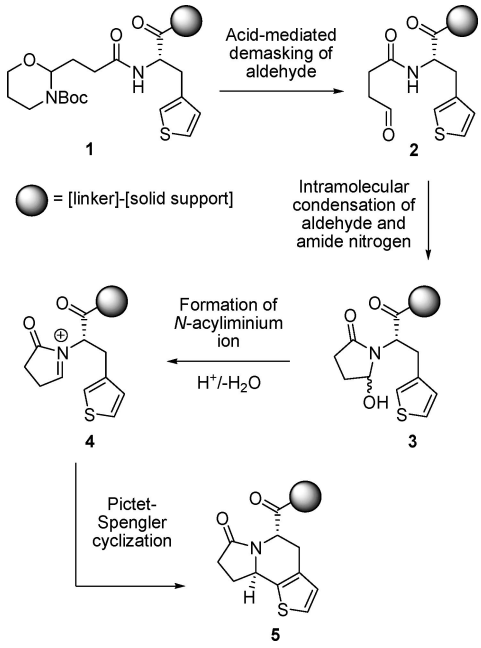


Figure 1. Bioactive compounds containing the thiophene ring system.[4,5,10,11]

* Corresponding author. E-mail: mpm@crc.dk.

10.1021/cc700199n CCC: $40.75
Published on Web 04/04/2008

Scheme 1. Solid-Phase Intramolecular Pictet−Spengler Reaction of Thienyl-Peptidoaldehydes (3-Thienyl Derivative)[15]



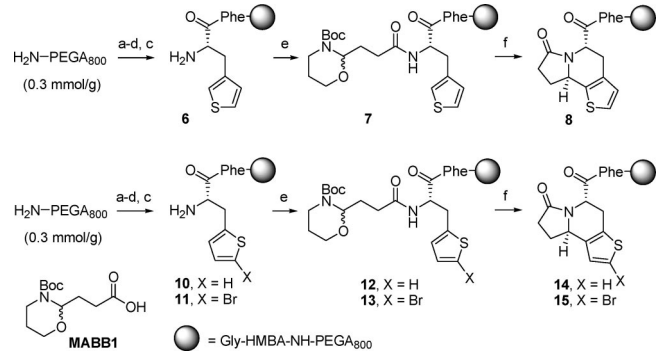
With aromatic C-nucleophiles, this Pictet−Spengler reaction (PS) provided a range of scaffolds including the pyrroloisoquinoline,[16] the indolizinoindoles[15] and the thienoindolizine[15] with excellent efficiency and diastereoselectivity. Due to the entropically favored intramolecular cascade reaction of preorganized reaction partners, the reaction is orthogonal to a large variety of functional groups, and assumes the character of an intramolecular "click" reaction. The cascade reaction leading to thienoindolizines involved the coupling of a masked aldehyde *N*(Boc),*O*-acetal building block to the N^{α} of thienylalanine-containing peptides on solid support (Scheme 1, **1**).[15] Upon addition of acid the aldehyde was rapidly released (**2**) and condensed with a backbone amide to generate a 5-membered hydroxylactam (**3**). Subsequently, an intramolecular nucleophilic attack of the aromatic thiophene on the intermediate *N*-acyliminium ion (**4**) generated the bicyclic thienoindolizine (**5**).

Results and Discussion

Thus, thienoindolizine derivatives could be produced quantitatively on solid support,[15] and this facilitated the study of further decoration of the thiophene ring by quantitative chemical transformations. The halogenation of thiophenes in solution is a well-studied reaction.[2] Halogenation of thiophene-containing scaffolds on solid support could provide a valuable route to diversification by Pd-catalyzed Suzuki cross-coupling reactions,[18] thereby providing a variety of aryl-substituted thienoindolizines through high-yielding reactions.

In principle, three different sequential schemes are feasible: (i) PS reaction/bromination/cross-coupling, (ii) bromination/PS reaction/cross-coupling, or (iii) bromination/cross-coupling/PS reaction. With the aim of parallel and library synthesis of thienoindolizines, it is evident that appendage diversification should advantageously be placed late in the synthetic sequence, thus minimizing the number of synthetic manipulations while reducing exposure of any sensitive groups, introduced through the cross-coupling, to the chemistry of subsequent synthetic steps. It also seems more elegant to conduct a selective monobromination after the cascade reaction and in this way benefit from the more electron-rich thiophene as a nucleophile for the reaction with the *N*-acyliminium ion intermediate.

Scheme 2. Solid-Phase Synthesis of Pictet−Spengler Products **8**, **14**, and **15**[a]



[a] Reagents and conditions: (a) HMBA, TBTU, NEM, DMF; (b) Fmoc-Gly OH, MSNT, 1-methylimidazole, CH_2Cl_2; (c) 20% piperidine (DMF); (d) Fmoc-Aa-OH, TBTU, NEM, DMF; (e) MABB1, TBTU, NEM, DMF; (f) 50% TFA (aq).

Upon preliminary investigation of the influence of halogenation on the kinetics of the PS reaction a strategy with sequential execution of cascade reaction, bromination and Pd-catalyzed Suzuki cross-coupling with arylboronic acids was selected.

PS Reaction and Reaction Rate Measurements. The resin bound substrates for the PS cascade reaction of the present study were prepared by Fmoc-based solid-phase peptide synthesis.[19–21] PEGA resin[22] was functionalized with the base labile and acid stable 4-hydroxymethylbenzoic acid (HMBA) linker via *N*-[1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU)-activation procedure.[23] Then followed esterification with Fmoc-Gly-OH by activation with 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT).[24] Subsequent cycles of Fmoc deprotection/TBTU-mediated couplings of building blocks provided PS substrates **7**, **12**, and **13**.

These were further treated with 50% TFA (aq) overnight, affording PS products **8**, **14**, and **15** in excellent purities (>95%), when released from the solid-support with dilute sodium hydroxide (Scheme 2).

In order to analyze the influence of bromine substitution on the rate and course of the PS cascade reaction, the conversion of the peptidic *N*(Boc),*O*-acetals **12** and **13** into the corresponding Pictet−Spengler products was studied. Substrates **12** and **13** (Scheme 2) were subjected to 10% TFA (aq) and 50% TFA (aq), and resin aliquots were analyzed at fixed time intervals (Figure 2).

For both substrates under the two acidic reaction conditions investigated, a rapid aldehyde deprotection was observed. Within a few minutes the Boc-*N*,*O*-acetals in **12** and **13** were cleaved and the resulting aldehyde had reacted with the penultimate amide nitrogen of the peptide backbone to form a hydroxylactam intermediate (observed as two adjacent

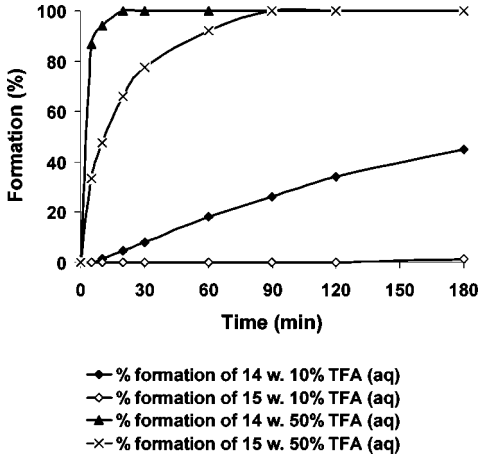


Figure 2. Curves showing the proton-activity dependent kinetics for the formation of PS products **14** and **15** from precursors **12** and **13**.

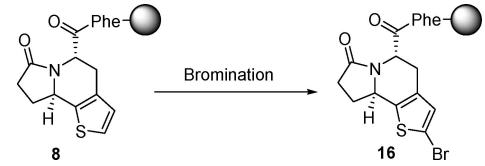
peaks of identical mass by LC-HRMS). Using 10% TFA (aq), the formation of compound **14** from **12** reached 45% conversion after 3 h, whereas the hydroxylactam from compound **13** remained unchanged during the same period of time. After exposure for 24 h, compound **12** was fully converted to **14**, whereas conversion of the hydroxylactam from compound **13** only had reached ca. 5%. However, a dramatic change was observed when changing reaction conditions to 50% TFA (aq), where compound **12** was converted to **14** in only 20 min while compound **13** was fully converted to **15** in 1.5 h. Although the synthesis of **15** from **13** was indeed feasible, results clearly demonstrated the electron-withdrawing effect of the bromine atom resulting in a decrease in nucleophilicity of the thiophene ring in the PS reaction. This difference could be essential in more sterically demanding PS reactions and confirm the argument for performing the bromination step subsequent to the PS reaction. The results furthermore indicate that the rate of the PS reaction is dependent on proton activity and the acidic conditions applied leading to a 250-fold increase in the initial rate of conversion of **13** to **15** at only a 5-fold increase in TFA concentration.

Solid-Phase Bromination of Thiophenes. Next, a reliable solid-phase procedure for the regioselective α-bromination of thienoindolizines **8** and **14** was developed.

The 2- and 5-position of thiophene residues are nucleophilic and are readily functionalized by reaction with a variety of electrophiles. Protocols for halogenation of the 2-position of thiophene rings in solution are numerous.[2] However, only few reports exist on the solid-phase version of this reaction,[25–32] mostly describing the synthesis of oligothiophenes on polystyrene resins. The reactions involved the use of an iodine donor in combination with either LDA or mercuric hexanoate or the application of *N*-bromosuccinimide (NBS) in different solvents. However, the excess of halogenation reagent used to drive the solid phase reaction to completion frequently leads to overhalogenation at the 3-position.[25]

Initial attempts to employ NBS for the bromination of PS products **8** and **14**, indicated that the bromination of 2-thienylalanine derivative **14** was more facile than bromination of 3-thienylalanine derivative **8**. Optimization of reaction parameters was therefore performed with compound **8**. Solvents, reaction times, and different brominating agents were investigated (Table 1). In general, purities above 90% of product were difficult to obtain at 100% conversion as unidentified byproducts appeared. Methods for bromination of thiophenes frequently involve the use of excess NBS, but in our hands, the use of NBS proved to be of poor reliability. On the other hand, bromine particularly when dissolved in acetic acid, afforded the product (**16**) in the purity (>95%) required for successful applications in solid-phase synthesis, according to analysis upon cleavage off the solid support with dilute sodium hydroxide. Furthermore, the processing used to isolate the product turned out to be crucial. Any addition of water prior to complete removal of all traces of bromine with acetic acid and DMF, resulted in significant decrease of purity.

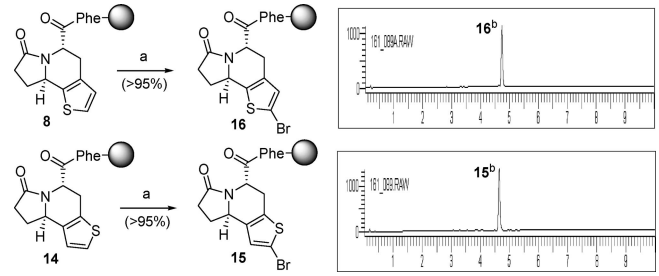
Table 1. Optimization of Bromination of Pictet−Spengler Product **8**



entry	Br	solvent	equiv	reaction time (min)	purity[a] (%)
1	NBS	DMF	4	30	39
2	NBS	DMF	12	30	28
3	NBS	AcOH	2	45	59
4	NBS	AcOH: $CHCl_3$	2	45	70
5	NBS	ACN	2	45	65
6	NBS	CH_2Cl_2	2	45	79
7	NBS	AcOH: CH_2Cl_2	2	90	71
8	NBS	AcOH: CH_2Cl_2	3	90	52
9	Br_2	AcOH	2	90	>95
10	Br_2	$CHCl_3$	2	90	45[b]
11	Br_2	DMF	2	90	26[b]

[a] The compound was cleaved off the resin for HPLC analysis with 0.1 M NaOH (aq). [b] Incomplete conversion of substrate.

Scheme 3. Bromination of Solid-Supported PS Products **8** and **14**[a]

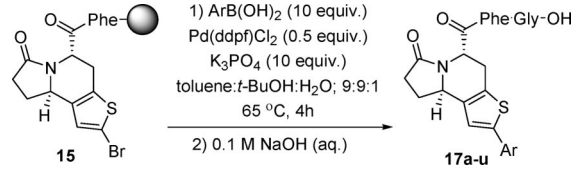


[a] Reagents and conditions: (a) Br_2, AcOH. [b] Analytical RP-HPLCs of the crude bromination products cleaved off the resin by treatment with 0.1 M NaOH (aq).

The optimal bromination conditions were investigated preparatively for 2-thienylalanine derivative **14** and indeed the reaction conditions of Br_2/AcOH provided brominated PS product **16** in excellent purity (>95%) and yield, after cleavage off the resin with sodium hydroxide (Scheme 3).

This bromination protocol was investigated for other aromatic brominations to extend the scope of the current methodology. However, the optimized conditions seemed selective for thiophenes and experiments aimed at the

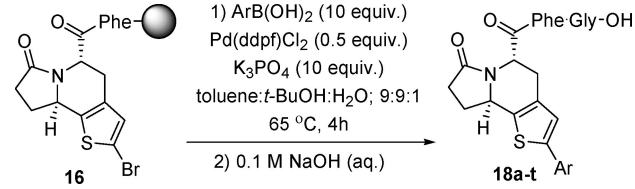
Table 2. Suzuki Cross-Coupling of Brominated PS Product **15** with Various Arylboronic Acids



entry	$ArB(OH)_2$	product, purity[a] (%)
1	4-OMe-$C_6H_4B(OH)_2$	**17a**, 85
2	4-CN-$C_6H_4B(OH)_2$	**17b**, 86
3	3-NO_2-$C_6H_4B(OH)_2$	**17c**, 87
4	3-Ph-$C_6H_4B(OH)_2$	**17d**, 86
5	4-F-$C_6H_4B(OH)_2$	**17e**, 89
6	3,5-Cl_2-$C_6H_3B(OH)_2$	**17f**, 87
7	Nap-2-$B(OH)_2$	**17g**, 84
8	3,4-(OCH_2O)-$C_6H_3B(OH)_2$	**17h**, 90
9	4-SMe-$C_6H_4B(OH)_2$	**17i**, >95
10	4-OPh-$C_6H_4B(OH)_2$	**17j**, 85
11	2,6-Me_2-$C_6H_3B(OH)_2$	**17k**, 50
12	3-CO_2H-$C_6H_4B(OH)_2$	**17l**, 69
13	3-(CHO)-4-(OMe)-$C_6H_3B(OH)_2$	**17m**, 61
14	$C_6F_5B(OH)_2$	**17n**, 0
15	4-Me-$C_6H_4B(OH)_2$	**17o**, 77
16	2-Ac-$C_6H_4B(OH)_2$	**17p**, 68
17	3,5-$(OMe)_2$-$C_6H_3B(OH)_2$	**17q**, 86
18	$PhB(OH)_2$	**17r**, 75
19	4-Cl-$C_6H_4B(OH)_2$	**17s**, 85
20	3,5-Me_2-$C_6H_3B(OH)_2$	**17t**, 86
21	4-CF_3-$C_6H_4B(OH)_2$	**17u**, 81

[a] Crude product purity as determined by RP-HPLC.

Table 3. Suzuki Cross-Coupling of Brominated PS Product **16** with Various Arylboronic Acids



entry	$ArB(OH)_2$	product, purity[a] (%)
1	3-NH_2-$C_6H_4B(OH)_2$	**18a**, 92
2	3-OH-$C_6H_4B(OH)_2$	**18b**, >95
3	2-CF_3-$C_6H_4B(OH)_2$	**18c**, 87
4	3-CF_3-$C_6H_4B(OH)_2$	**18d**, 92
5	4-(COPh)-$C_6H_4B(OH)_2$	**18e**, 90
6	3,4-(OCH_2CH_2O)-$C_6H_3B(OH)_2$	**18f**, 86
7	(2-OMe)pyrimidine-5-$B(OH)_2$	**18g**, 65
8	(2-OMe)pyridine-5-$B(OH)_2$	**18h**, 81
9	benzothiophene-2-$B(OH)_2$	**18i**, 91
10	indole-2-$B(OH)_2$	**18j**, 50
11	3-Cl-4-OMe-$C_6H_3B(OH)_2$	**18k**, 87
12	4-CHO-$C_6H_4B(OH)_2$	**18l**, 75
13	$C_6F_5B(OH)_2$	**18m**, 0
14	3-NO_2-$C_6H_4B(OH)_2$	**18n**, 88
15	4-OBu-$C_6H_4B(OH)_2$	**18o**, 82
16	3,4-$(OMe)_2$-$C_6H_4B(OH)_2$	**18p**, 85
17	3,5-$(OMe)_2$-$C_6H_4B(OH)_2$	**18q**, 92
18	4-CF_3-$C_6H_4B(OH)_2$	**18r**, 86
19	3,4-Cl_2-$C_6H_3B(OH)_2$	**18s**, 89
20	$PhB(OH)_2$	**18t**, 86

[a] Crude product purity as determined by RP-HPLC.

application of the bromination procedure to other heteroaromatics, such as furane, benzothiophene and the indole ring-systems, all proved unsuccessful. On the other hand, thiophene could be brominated in an orthogonal manner independent of the presence of other aromatic residues.

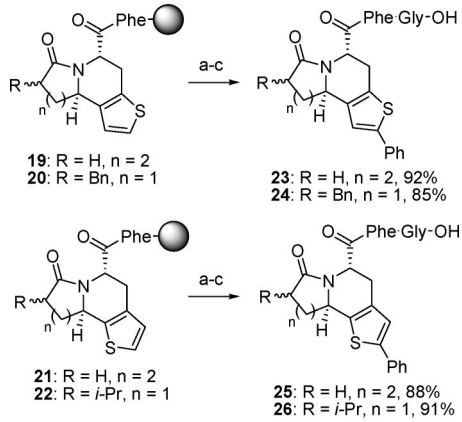
Solid-Phase Pd-Catalyzed Suzuki Cross-Coupling of Brominated PS Products with Various Boronic Acids. The palladium-catalyzed Suzuki cross-coupling reaction has become a powerful asset in medicinal chemistry for the construction of aryl−aryl bonds.[33−37] The biaryl motif is often present in natural products and constitute important structural elements for the targeting of receptors with small molecule drugs.[37] Suzuki cross-coupling offers several advantages. Reaction conditions are generally mild and compatible with most functional groups. Furthermore, boronic acids are readily available and are stable to heat, air and moisture, rendering Suzuki cross-coupling an attractive reaction for combinatorial and parallel synthesis.[38]

We have previously developed an efficient method for the solid-phase Suzuki cross-coupling of phenyl iodides with boronic acids on solid support.[39] The method involved the use of $Pd(dppf)Cl_2/K_3PO_4$ in an aqueous mixture of *t*-BuOH and toluene at room temperature, but when applied to the cross-coupling of resin bound brominated compound **16** with arylboronic acids, only incomplete conversions and poor yields were obtained. The problem was partially circumvented by raising the temperature (65 °C) and repeating the coupling procedure with 10 equivalents of boronic acid. Results from the Suzuki-coupling of compounds **15** and **16** with several boronic acids are presented in Tables 2 and 3, respectively. Products **17a**−**u** and **18a**−**t** were obtained in reasonable to excellent purities ranging from 50 to 95%. Evidently, the Suzuki reactions of brominated derivative **16** (Table 3) proceeded with better efficiency than of brominated derivative **15** (Table 2) as exemplified by the coupling of both bromo-derivatives with phenylboronic acid (entry **18**, Table 2; entry **20**, Table 3) giving 86% of **18t** and 75% of **17r**, respectively. The formation of byproducts from transition-metal-mediated cross-coupling,[40] e.g. Pd-mediated reductive debromination and homocoupling products (up to 10%), was observed. These two byproducts accounted for all impurities found in the reaction (5–15%) and formed to the same extent for bromo-derivatives **15** and **16**. Pentafluorophenyl boronic acid was not reactive.

The structure of the scaffold was modified by appending alkyl groups in the pyrrolidone ring and by expanding the ring size with a methylene group by use of the appropriate building blocks.[41,42] The products of the Pictet−Spengler reaction (**19**−**22**) were subjected to solid-phase bromination and subsequent Suzuki cross-coupling, with phenylboronic acid which provided alkylated aryl-substituted thienoindolizines **23**−**26** in good purities ranging from 85 to 92% (Scheme 4).

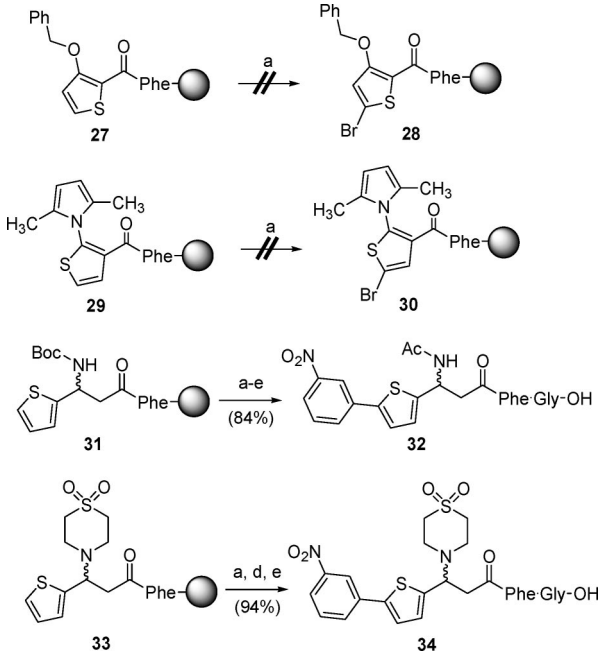
Bromination and Suzuki Cross-Coupling on Substituted Thiophenes. Considering the high efficiency of the Br_2/AcOH bromination protocol presented above, other peptidic compounds containing thiophenes were investigated for the bromination and Suzuki-coupling reactions (Scheme 5). Interestingly, electron-defficient thiophene-carboxamides **27** and **29** proved to be reluctant substrates for bromination, even under forcing reaction conditions of elevated temperatures, large excess of bromine and long reaction times. The products contained no traces of the 2-brominated product, instead affording complete recovery of the starting material. However, changing to the electron-rich thiophenes **31** and **33**, the bromination proceeded to completion using only 3

Scheme 4. Solid-Phase Sequential Bromination and Suzuki Cross-Coupling on Alkylated PS Products **19**−**22**[a]



[a] Reagents and conditions: (a) Br_2, AcOH; (b) $PhB(OH)_2$, $Pd(dppf)Cl_2$, K_3PO_4, toluene:*t*-BuOH:H_2O (9:9:1), 65 °C, 4 h; (c) 0.1 M NaOH (aq).

Scheme 5. Solid-Phase Sequential Bromination and Aryl-Substitution on Substituted Thiophenes[a]



[a] Reagents and conditions: (a) Br_2, AcOH; (b) 50% TFA (CH_2Cl_2); (c) 20% Ac_2O (DMF)); (d) $ArB(OH)_2$, $Pd(ddpf)Cl_2$, K_3PO_4, toluene:*t*-BuOH:H_2O (9:9:1), 65 °C, 4 h; (e) 0.1 M NaOH (aq).

equiv bromine. It was noted that the acidic reaction conditions led to partial deprotection of the nitrogen protecting group in the case of Boc-protected derivative **31**. The compound was therefore fully deprotected using 50% TFA (CH_2Cl_2) and acetylated. Suzuki cross-coupling of the bromothiophenes with *m*-(NO_2)-phenylboronic acid afforded **32** and **34** in high purity after cleavage off the resin (84% and 94%, respectively).

Conclusions

In summary, efficient solid-phase protocols for the functionalization of thiophenes have been developed from readily accessible building blocks. This involved an efficient and regioselective bromination of the thiophene ring followed by a Suzuki cross-coupling with arylboronic acids, thereby providing aryl-functionalized thiophenes of interest for combinatorial synthesis and screening on solid support. In addition, this protocol has been combined with a highly diastereoselective and quantitative intramolecular Pictet−Spengler reaction, providing a range of pharmacologically relevant aryl-substituted thienoindolizines. Finally, two alkyl substituted thiophenes were readily 2-brominated on solid support using the Br_2/AcOH conditions, while electron-deficient thiophenes were unreactive. Currently, libraries of Suzuki products derived from complex supported ligands for the MC4R and other GPCRs are under development and the present bromination is a valuable tool for the diversification of these libraries.

Experimental Details

General Methods. General methods are reported in the Supporting Information.

Solid-Phase Procedures. Attachment of the HMBA linker to the amino-functionalized resin was carried out by premixing HMBA (3.0 equiv), *N*-ethylmorpholine (NEM, 4.0 equiv), and TBTU (2.88 equiv) for 5 min in DMF. The resulting solution was added to DMF preswollen resin and allowed to react for 2 h, followed by washing with DMF (6×) and CH_2Cl_2 (6×). Coupling of the first amino acid (Gly) to the HMBA-derivatized resin was accomplished by treating the freshly lyophilized resin with a mixture of the Fmoc-Gly-OH (3.0 equiv), 1-methylimidazole (MeIm, 2.25 equiv), and MSNT (3.0 equiv) in CH_2Cl_2:THF (20:1). The coupling was repeated once. Peptide synthesis and attachment of the different building blocks to the amino-functionalized resin were subsequently accomplished following standard amino acid coupling procedures (Fmoc-Aa-OH, TBTU, NEM, DMF) as described above for the attachment of the HMBA linker. The usual washing protocol followed each coupling and deprotection step. Completion of the reaction was monitored using the Kaiser test. Fmoc-deprotection was accomplished with 20% piperidine in DMF, first for 2 min, and then for 18 min, followed by washing with DMF (6×).

The solid-phase bromination procedure was carried out by addition of a solution of bromine (2 equiv) in AcOH to the resin. The reaction was left for 1 h at RT, by which time the resin was washed with AcOH (3×), DMF (4×), water (3×), DMF (3×), and CH_2Cl_2 (5×).

The solid-phase Suzuki cross-coupling reaction was performed by addition of K_3PO_4 (10 equiv) and arylboronic acid (10 equiv) to the resin preswollen in degassed toluene:*t*-BuOH:H_2O (9:9:2). $Pd(dppf)Cl_2$ (0.5 equiv) was then added to the reaction mixture under Ar, and the reaction vessel was sealed before shaking for 4 h at 65 °C. Subsequently, the resin was washed with CH_2Cl_2 (6×), DMF (6×), water (6×), DMF (3×), and CH_2Cl_2 (6×). The procedure was repeated once to ensure quantitative conversion.

Characterization of Pictet−Spengler Products 8 and 14. Compound 8 (Cleaved off the Resin). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.36 (t, J = 5.7 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 5.0 Hz, 1H), 7.27–7.12 (m, 5H), 6.74 (d, J = 5.0 Hz, 1H), 4.88 (d, J = 6.8 Hz, 1H), 4.58–4.42 (m, 1H), 4.14 (t, J = 7.3 Hz, 1H), 3.75 (dd, J = 5.7 Hz, J = 1.7 Hz, 2H), 3.19 (d, J = 16.2 Hz, 1H), 3.06 (dd, J =

13.8 Hz, J = 4.0 Hz, 1H), 2.88 (dd, J = 13.6 Hz, J = 11.3 Hz, 1H), 2.67–2.53 (m, 1H), 2.53–2.14 (m, 3H), 1.74–1.46 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.1, 171.3, 170.9, 168.8, 137.9, 135.2, 131.3, 128.9, 127.8, 126.9, 126.0, 123.4, 54.1, 52.3, 48.6, 40.8, 36.5, 30.5, 27.4, 25.6; MS (ESI) calcd for $C_{22}H_{22}N_3O_5S$ [M − H]$^-$ 440.1, found 440.1; HRMS (ESI) calcd for $C_{22}H_{24}N_3O_5S$ [M + H]$^+$ 442.1437, found 442.1434.

Compound 14 (Cleaved off the Resin). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.37 (t, J = 5.7 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 5.2 Hz, 1H), 7.25–7.13 (m, 5H), 6.64 (d, J = 5.2 Hz, 1H), 4.94 (d, J = 6.5 Hz, 1H), 4.58–4.39 (m, 1H), 4.04 (t, J = 7.7 Hz, 1H), 3.76 (dd, J = 5.7 Hz, J = 1.8 Hz, 2H), 3.31 (d, J = 16.2 Hz, 1H), 3.06 (dd, J = 13.8 Hz, J = 4.0 Hz, 1H), 2.87 (dd, J = 13.7 Hz, J = 11.0 Hz, 1H), 2.81–2.66 (m, 1H), 2.60–2.13 (m, 3H), 1.63–1.36 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.2, 171.3, 170.8, 168.5, 137.8, 135.5, 130.5, 128.9, 127.8, 126.0, 123.6, 123.6, 54.0, 52.8, 48.9, 40.7, 36.5, 30.7, 26.2, 24.9; MS (ESI) calcd for $C_{22}H_{22}N_3O_5S$ [M − H]$^-$ 440.1, found 440.0; HRMS (ESI) calcd for $C_{22}H_{24}N_3O_5S$ [M + H]$^+$ 442.1437, found 442.1436.

Characterization of Brominated PS Products 15 and 16. Compound 15 (Cleaved off the Resin). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.29 (t, J = 5.6 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.30–7.08 (m, 5H), 6.77 (s, 1H), 4.92 (d, J = 6.4 Hz, 1H), 4.60–4.46 (m, 1H), 3.97 (t, J = 7.7 Hz, 1H), 3.73 (d, J = 5.7 Hz, 2H), 3.22 (d, J = 16.4 Hz, 1H), 3.06 (dd, J = 13.9 Hz, J = 3.9 Hz, 1H), 2.86 (dd, J = 13.8 Hz, J = 11.3 Hz, 1H), 2.66 (ddd, J = 16.2 Hz, J = 6.9 Hz, J = 2.0 Hz, 1H), 2.55–2.13 (m, 3H), 1.62–1.37 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.2, 171.1, 170.9, 168.3, 137.8, 136.3, 132.6, 128.8, 127.8, 126.9, 126.0, 108.9, 53.9, 52.4, 48.8, 40.9, 36.5, 30.6, 26.1, 24.9; MS (ESI) calcd for $C_{22}H_{21}BrN_3O_5S$ [M − H]$^-$ 518.0, found 517.9; HRMS (ESI) calcd for $C_{22}H_{23}BrN_3O_5S$ [M + H]$^+$ 520.0542, found 520.0537.

Compound 16 (Cleaved off the Resin). ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.53 (bs, 1H), 8.38 (t, J = 5.7 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.33–7.11 (m, 5H), 6.88 (s, 1H), 4.85 (d, J = 6.7 Hz, 1H), 4.61–4.46 (m, 1H), 3.95 (t, J = 7.3 Hz, 1H), 3.78 (dd, J = 5.8 Hz, J = 1.4 Hz, 2H), 3.12 (d, J = 16.0 Hz, 1H), 3.07 (dd, J = 12.8 Hz, J = 4.9 Hz, 1H), 2.86 (dd, J = 13.7 Hz, J = 11.4 Hz, 1H), 2.63–2.13 (m, 4H), 1.67–1.51 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.0, 171.3, 170.9, 168.6, 137.9, 137.1, 132.4, 130.1, 128.9, 127.9, 126.0, 109.3, 53.9, 51.9, 48.5, 40.6, 36.5, 30.4, 27.1, 25.4; MS (ESI) calcd for $C_{22}H_{21}BrN_3O_5S$ [M − H]$^-$ 518.0, found 518.1; HRMS (ESI) calcd for $C_{22}H_{23}BrN_3O_5S$ [M + H]$^+$ 520.0542, found 520.0558.

Characterization of Suzuki Cross-Coupling Products 17a−u. Compound 17a. MS (ESI) calcd for $C_{29}H_{28}N_3O_6S$ [M − H]$^-$ 546.2, found 546.1; HRMS (ESI) calcd for $C_{29}H_{30}N_3O_6S$ [M + H]$^+$ 548.1855, found 548.1888.

Compound 17b. MS (ESI) calcd for $C_{29}H_{25}N_4O_5S$ [M − H]$^-$ 541.2, found 541.1; HRMS (ESI) calcd for $C_{29}H_{27}N_4O_5S$ [M + H]$^+$ 543.1702, found 543.1701.

Compound 17c. MS (ESI) calcd for $C_{28}H_{25}N_4O_7S$ [M − H]$^-$ 561.1, found 561.1; HRMS (ESI) calcd for $C_{28}H_{27}N_4O_7S$ [M + H]$^+$ 563.1600, found 563.1620.

Compound 17d. MS (ESI) calcd for $C_{34}H_{30}N_3O_5S$ [M − H]$^-$ 592.2, found 592.1; HRMS (ESI) calcd for $C_{34}H_{32}N_3O_5S$ [M + H]$^+$ 594.2062, found 594.2065.

Compound 17e. MS (ESI) calcd for $C_{28}H_{25}FN_3O_5S$ [M − H]$^-$ 534.1, found 534.1; HRMS (ESI) calcd for $C_{28}H_{27}FN_3O_5S$ [M + H]$^+$ 536.1655, found 536.1651.

Compound 17f. MS (ESI) calcd for $C_{28}H_{24}Cl_2N_3O_5S$ [M − H]$^-$ 584.1, found 584.1; HRMS (ESI) calcd for $C_{28}H_{26}Cl_2N_3O_5S$ [M + H]$^+$ 586.0970, found 586.0969.

Compound 17g. MS (ESI) calcd for $C_{32}H_{28}N_3O_5S$ [M − H]$^-$ 566.2, found 566.1; HRMS (ESI) calcd for $C_{32}H_{30}N_3O_5S$ [M + H]$^+$ 568.1906, found 568.1931.

Compound 17h. MS (ESI) calcd for $C_{29}H_{26}N_3O_7S$ [M − H]$^-$ 560.1, found 560.0; HRMS (ESI) calcd for $C_{29}H_{28}N_3O_7S$ [M + H]$^+$ 562.1648, found 562.1648.

Compound 17i. MS (ESI) calcd for $C_{29}H_{28}N_3O_5S_2$ [M − H]$^-$ 562.1, found 562.0; HRMS (ESI) calcd for $C_{29}H_{30}N_3O_5S_2$ [M + H]$^+$ 564.1627, found 564.1658.

Compound 17j. MS (ESI) calcd for $C_{34}H_{30}N_3O_6S$ [M − H]$^-$ 608.2, found 608.1; HRMS (ESI) calcd for $C_{34}H_{32}N_3O_6S$ [M + H]$^+$ 610.2012, found 610.2018.

Compound 17k. MS (ESI) calcd for $C_{30}H_{30}N_3O_5S$ [M − H]$^-$ 544.2, found 544.0; HRMS (ESI) calcd for $C_{30}H_{32}N_3O_5S$ [M + H]$^+$ 546.2062, found 546.2062.

Compound 17l. MS (ESI) calcd for $C_{29}H_{26}N_3O_7S$ [M − H]$^-$ 560.0, found 560.0; HRMS (ESI) calcd for $C_{29}H_{28}N_3O_7S$ [M + H]$^+$ 562.1648, found 562.1650.

Compound 17m. MS (ESI) calcd for $C_{30}H_{28}N_3O_7S$ [M − H]$^-$ 574.2, found 574.1; HRMS (ESI) calcd for $C_{30}H_{30}N_3O_7S$ [M + H]$^+$ 576.1804, found 576.1799.

Compound 17o. MS (ESI) calcd for $C_{29}H_{28}N_3O_5S$ [M − H]$^-$ 530.2, found 530.0; HRMS (ESI) calcd for $C_{29}H_{30}N_3O_5S$ [M + H]$^+$ 532.1906, found 532.1904.

Compound 17p. MS (ESI) calcd for $C_{30}H_{28}N_3O_6S$ [M − H]$^-$ 558.2, found 558.0; HRMS (ESI) calcd for $C_{30}H_{30}N_3O_6S$ [M + H]$^+$ 560.1855, found 560.1849.

Compound 17q. MS (ESI) calcd for $C_{30}H_{30}N_3NaO_7S$ [M + Na]$^+$ 600.2, found 600.1; HRMS (ESI) calcd for $C_{30}H_{32}N_3O_7S$ [M + H]$^+$ 578.1961, found 578.1945.

Compound 17r. MS (ESI) calcd for $C_{28}H_{26}N_3O_5S$ [M − H]$^-$ 516.2, found 516.0; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_5S$ [M + H]$^+$ 518.1750, found 518.1778.

Compound 17s. MS (ESI) calcd for $C_{28}H_{25}ClN_3O_5S$ [M − H]$^-$ 550.1 found 550.0; HRMS (ESI) calcd for $C_{28}H_{27}ClN_3O_5S$ [M + H]$^+$ 552.1360, found 552.1378.

Compound 17t. MS (ESI) calcd for $C_{30}H_{31}N_3NaO_5S$ [M + Na]$^+$ 568.2, found 568.1; HRMS (ESI) calcd for $C_{30}H_{32}N_3O_5S$ [M + H]$^+$ 546.2062, found 546.2078.

Compound 17u. MS (ESI) calcd for $C_{29}H_{25}F_3N_3NaO_5S$ [M + Na]$^+$ 608.1 found 608.1; HRMS (ESI) calcd for $C_{29}H_{27}F_3N_3O_5S$ [M + H]$^+$ 586.1624, found 586.1624.

Characterization of Suzuki Cross-Coupling Products 18a−t. Compound 18a. MS (ESI) calcd for $C_{28}H_{27}N_4O_5S$ [M − H]$^-$ 531.2, found 530.9; HRMS (ESI) calcd for $C_{28}H_{29}N_4O_5S$ [M + H]$^+$ 533.1859, found 533.1869.

Compound 18b. MS (ESI) calcd for $C_{28}H_{26}N_3O_6S$ [M − H]$^-$ 532.2, found 532.0; HRMS (ESI) calcd for $C_{28}H_{28}N_3O_6S$ [M + H]$^+$ 534.1699, found 534.1710.

Compound 18c. MS (ESI) calcd for $C_{29}H_{25}F_3N_3O_5S$ [M − H]$^-$ 584.1, found 584.0; HRMS (ESI) calcd for $C_{29}H_{27}F_3N_3O_5S$ [M + H]$^+$ 586.1624, found 586.1617.

Compound 18d. MS (ESI) calcd for $C_{29}H_{25}F_3N_3O_5S$ [M − H]$^-$ 584.1, found 584.1; HRMS (ESI) calcd for $C_{29}H_{27}F_3N_3O_5S$ [M + H]$^+$ 586.1624, found 586.1628.

Compound 18e. MS (ESI) calcd for $C_{35}H_{30}N_3O_6S$ [M − H]$^-$ 620.2, found 620.2; HRMS (ESI) calcd for $C_{35}H_{32}N_3O_6S$ [M + H]$^+$ 622.2012, found 622.2006.

Compound 18f. MS (ESI) calcd for $C_{30}H_{28}N_3O_7S$ [M − H]$^-$ 574.2, found 574.1; HRMS (ESI) calcd for $C_{30}H_{30}N_3O_7S$ [M + H]$^+$ 576.1804, found 576.1793.

Compound 18g. MS (ESI) calcd for $C_{27}H_{26}N_5O_6S$ [M − H]$^-$ 548.2, found 548.0; HRMS (ESI) calcd for $C_{27}H_{28}N_5O_6S$ [M + H]$^+$ 550.1760, found 550.1772.

Compound 18h. MS (ESI) calcd for $C_{28}H_{27}N_4O_6S$ [M − H]$^-$ 547.2, found 547.0; HRMS (ESI) calcd for $C_{28}H_{29}N_4O_6S$ [M + H]$^+$ 549.1808, found 549.1803.

Compound 18i. MS (ESI) calcd for $C_{30}H_{26}N_3O_5S_2$ [M − H]$^-$ 572.1, found 572.0; HRMS (ESI) calcd for $C_{30}H_{28}N_3O_5S_2$ [M + H]$^+$ 574.1470, found 574.1476.

Compound 18j. MS (ESI) calcd for $C_{30}H_{27}N_4O_5S$ [M − H]$^-$ 555.2, found 555.1; HRMS (ESI) calcd for $C_{30}H_{29}N_4O_5S$ [M + H]$^+$ 557.1859, found 557.1854.

Compound 18k. MS (ESI) calcd for $C_{29}H_{27}ClN_3O_6S$ [M − H]$^-$ 580.1, found 580.1; HRMS (ESI) calcd for $C_{29}H_{29}ClN_3O_6S$ [M + H]$^+$ 582.1465, found 582.1479.

Compound 18l. MS (ESI) calcd for $C_{29}H_{26}N_3O_6S$ [M − H]$^-$ 544.2, found 544.0; HRMS (ESI) calcd for $C_{29}H_{28}N_3O_6S$ [M + H]$^+$ 546.1699, found 546.1711.

Compound 18n. MS (ESI) calcd for $C_{28}H_{25}N_4O_7S$ [M − H]$^-$ 561.1, found 561.1; HRMS (ESI) calcd for $C_{28}H_{27}N_4O_7S$ [M + H]$^+$ 563.1600, found 563.1627.

Compound 18o. MS (ESI) calcd for $C_{32}H_{34}N_3O_6S$ [M − H]$^-$ 588.2, found 588.2; HRMS (ESI) calcd for $C_{32}H_{36}N_3O_6S$ [M + H]$^+$ 590.2325, found 590.2325.

Compound 18p. MS (ESI) calcd for $C_{30}H_{30}N_3O_7S$ [M − H]$^-$ 576.2, found 576.1; HRMS (ESI) calcd for $C_{30}H_{32}N_3O_7S$ [M + H]$^+$ 578.1961, found 578.1956.

Compound 18q. MS (ESI) calcd for $C_{30}H_{30}N_3O_7S$ [M − H]$^-$ 576.2, found 576.1; HRMS (ESI) calcd for $C_{30}H_{32}N_3O_7S$ [M + H]$^+$ 578.1961, found 578.1957.

Compound 18r. MS (ESI) calcd for $C_{29}H_{26}F_3N_3NaO_5S$ [M + Na]$^+$ 608.1, found 608.1; HRMS (ESI) calcd for $C_{29}H_{27}F_3N_3O_5S$ [M + H]$^+$ 586.1624, found 586.1620.

Compound 18s. MS (ESI) calcd for $C_{28}H_{25}Cl_2N_3NaO_5S$ [M + Na]$^+$ 608.0, found 608.0; HRMS (ESI) calcd for $C_{28}H_{26}Cl_2N_3O_5S$ [M + H]$^+$ 586.0970, found 586.0972.

Compound 18t. MS (ESI) calcd for $C_{28}H_{28}N_3O_5S$ [M − H]$^-$ 516.1, found 516.0; HRMS (ESI) calcd for $C_{28}H_{26}N_3O_5S$ [M + H]$^+$ 518.1750, found 518.1766.

NMR Data for Selected Suzuki Cross-Coupling Products. Compound 17c. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.48–8.21 (m, 2H), 8.12 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.26–7.11 (m, 5H), 4.98 (d, J = 6.6 Hz, 1H), 4.62–4.47 (m, 1H), 4.07 (t, J = 7.4 Hz, 1H), 3.78 (d, J = 5.8 Hz, 2H), 3.34 (d, J = 16.5 Hz, 1H), 3.07 (dd, J = 13.9 Hz, J = 3.8 Hz, 1H), 2.94–2.72 (m, 2H), 2.62–2.33 (m, 2H), 2.32–2.15 (m, 1H), 1.70–1.53 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.3, 170.9, 170.8, 168.4, 148.3, 138.0, 137.9, 137.2, 135.1, 132.4, 131.0, 130.6, 128.9, 127.8, 125.9, 122.5, 121.7, 118.8, 54.0, 52.7, 48.8, 41.6, 36.5, 30.7, 26.1, 25.2.

Compound 17f. ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.57 (s, 1H), 8.35 (t, J = 5.8 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 1.8 Hz, 2H), 7.51 (t, J = 1.8 Hz, 1H), 7.30 (s, 1H), 7.25–7.12 (m, 5H), 4.97 (d, J = 6.6 Hz, 1H), 4.60–4.45 (m, 1H), 4.03 (t, J = 7.4 Hz, 1H), 3.78 (dd, J = 5.8 Hz, J = 1.1 Hz, 2H), 3.31 (d, J = 16.7 Hz, 1H), 3.07 (dd, J = 13.8 Hz, J = 3.9 Hz, 1H), 2.94–2.71 (m, 2H), 2.62–2.09 (m, 3H), 1.70–1.48 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.3, 170.9, 168.4, 137.8, 137.2, 137.1, 136.9, 134.6, 132.6, 128.9, 127.8, 126.4, 125.9, 123.1, 122.8, 54.0, 52.6, 48.8, 41.3, 36.6, 30.6, 26.0, 25.1.

Compound 17h. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.34 (t, J = 5.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.30–7.12 (m, 5H), 7.15 (d, J = 1.7 Hz, 1H), 7.02 (dd, J = 8.1 Hz, J = 1.7 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.05 (s, 2H), 4.95 (d, J = 6.5 Hz, 1H), 4.60–4.45 (m, 1H), 4.02 (t, J = 7.5 Hz, 1H), 3.78 (dd, J = 5.8 Hz, J = 1.9 Hz, 2H), 3.27 (d, J = 16.4 Hz, 1H), 3.06 (dd, J = 13.9 Hz, J = 3.9 Hz, 1H), 2.87 (dd, J = 13.8,, J = 11.1 Hz, 1H), 2.84–2.67 (m, 1H), 2.56–2.14 (m, 3H), 1.70–1.45 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.3, 170.9, 170.7, 168.5, 147.8, 146.6, 140.7, 137.9, 136.5, 129.4, 128.9, 127.8, 126.0, 119.5, 118.6, 118.6, 108.6, 105.4, 101.1, 54.1, 52.7, 48.9, 41.9, 36.5, 30.7, 30.7, 26.2, 25.0.

Compound 17i. ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.53 (bs, 1H), 8.35 (t, J = 5.8 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.26–7.09 (m, 5H), 6.99 (s, 1H), 4.96 (d, J = 6.5 Hz, 1H), 4.61–4.45 (m, 1H), 4.04 (t, J = 7.5 Hz, 1H), 3.79 (dd, J = 5.7 Hz, J = 1.9 Hz, 2H), 3.29 (d, J = 16.4 Hz, 1H), 3.07 (dd, J = 13.8 Hz, 3.9 Hz, 1H), 2.87 (dd, J = 13.8 Hz, J = 11.3 Hz, 1H), 2.86–2.66 (m, 1H), 2.63–2.32 (m, 2H), 2.50 (s, 3H), 2.32–2.14 (m, 1H), 1.70–1.47 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.3, 171.0, 168.5, 140.3, 137.9, 137.3, 136.7, 130.1, 130.0, 128.9, 127.8, 126.3, 125.9, 125.3, 119.7, 54.1, 52.7, 48.9, 41.3, 36.5, 30.7, 26.2, 25.1, 14.5.

Compound 17t. ^{1}H NMR (250 MHz, DMSO-d_6): δ 12.57 (bs, 1H), 8.35 (t, J = 5.7 Hz, 1H), 8.14–7.99 (m, 1H), 7.28–7.13 (m, 5H), 7.17 (s, 2H), 6.99 (s, 1H), 6.93 (s, 1H), 4.96 (d, J = 6.6 Hz, 1H), 4.60–4.45 (m, 1H), 4.04 (t, J = 7.4 Hz, 1H), 3.78 (dd, J = 5.7 Hz, J = 1.9 Hz, 2H), 3.29 (d, J = 16.4 Hz, 1H), 3.07 (dd, J = 13.8 Hz, J = 3.9 Hz, 1H), 2.87 (dd, J = 13.8 Hz, J = 11.2 Hz, 1H), 2.84–2.69 (m, 1H), 2.59–2.13 (m, 3H), 2.30 (s, 6H), 1.69–1.46 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.3, 171.0, 168.5, 141.0, 137.9, 137.9, 136.5, 133.3, 130.0, 128.9, 127.8, 125.9, 122.6, 119.8, 54.0, 52.7, 48.9, 41.3, 36.5, 30.7, 26.1, 25.0, 20.7.

Compound 18a. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.38 (t, J = 5.5 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.33–7.12 (m, 5H), 7.01 (t, J = 7.8 Hz, 1H), 6.95 (s, 1H), 6.74 (t, J = 1.6 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.49 (dd, J = 7.9 Hz, J

= 1.2 Hz, 1H), 4.89 (d, J = 6.8 Hz, 1H), 4.61–4.45 (m, 1H), 4.09 (t, J = 7.1 Hz, 1H), 3.76 (d, J = 5.7 Hz, 2H), 3.17 (d, J = 16.2 Hz, 1H), 3.08 (dd, J = 13.9 Hz, J = 3.9 Hz, 1H), 2.88 (dd, J = 13.5 Hz, J = 11.5 Hz, 1H), 2.67–2.15 (m, 4H), 1.76–1.51 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.1, 171.3, 170.9, 168.8, 149.0, 141.8, 137.9, 134.1, 133.8, 132.2, 129.3, 128.9, 127.9, 126.0, 122.4, 113.2, 112.5, 110.2, 54.0, 52.1, 48.7, 40.7, 36.5, 30.5, 27.3, 25.6.

Compound 18e. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.41 (t, J = 5.5 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.84–7.51 (m, 9H), 7.36 (s, 1H), 7.29–7.15 (m, 5H), 4.93 (d, J = 6.8 Hz, 1H), 4.63–4.48 (m, 1H), 4.12 (t, J = 7.2 Hz, 1H), 3.77 (d, J = 5.6 Hz, 2H), 3.23 (d, J = 16.5 Hz, 1H), 3.09 (dd, J = 13.8 Hz, J = 3.8 Hz, 1H), 2.89 (dd, J = 13.4 Hz, J = 11.6 Hz, 1H), 2.74–2.17 (m, 4H), 1.82–1.55 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 194.7, 173.0, 171.4, 170.8, 168.7, 139.3, 137.9, 137.3, 137.0, 136.9, 135.2, 133.1, 132.4, 130.6, 129.3, 128.9, 128.4, 127.9, 126.1, 125.3, 124.7, 54.0, 52.2, 48.6, 40.6, 36.5, 30.5, 27.2, 25.7.

Compound 18f. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.40 (t, J = 5.7 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.32–7.08 (m, 5H), 7.04–6.95 (m, 3H), 6.85 (d, J = 8.2 Hz, 1H), 4.89 (d, J = 6.9 Hz, 1H), 4.60–4.45 (m, 1H), 4.25 (s, 4H), 4.09 (t, J = 7.4 Hz, 1H), 3.77 (dd, J = 5.5 Hz, J = 1.7 Hz, 2H), 3.16 (d, J = 16.4 Hz, 1H), 3.07 (dd, J = 13.9 Hz, J = 3.9 Hz, 1H), 2.88 (dd, J = 13.6 Hz, J = 11.4 Hz, 1H), 2.67–2.15 (m, 4H), 1.76–1.51 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.1, 171.3, 170.8, 168.8, 143.4, 143.0, 140.5, 137.9, 134.0, 132.4, 128.9, 127.9, 126.9, 126.1, 122.5, 118.1, 117.4, 113.3, 64.0, 54.0, 52.1, 48.6, 40.6, 36.5, 30.5, 27.2, 25.7.

Compound 18i. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.42 (t, J = 5.6 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.0 Hz, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.55 (s, 1H), 7.43–7.28 (m, 2H), 7.28–7.14 (m, 5H), 7.09 (s, 1H), 4.92 (d, J = 6.9 Hz, 1H), 4.62–4.47 (m, 1H), 4.11 (t, J = 7.3 Hz, 1H), 3.77 (d, J = 5.1 Hz, 2H), 3.21 (d, J = 16.4 Hz, 1H), 3.09 (dd, J = 13.8 Hz, J = 3.8 Hz, 1H), 2.89 (dd, J = 13.4 Hz, J = 11.6 Hz, 1H), 2.72–2.15 (m, 4H), 1.81–1.55 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.1, 171.3, 170.8, 168.7, 139.9, 138.0, 137.9, 136.0, 133.8, 132.7, 128.9, 127.9, 126.1, 125.2, 124.8, 124.6, 123.4, 122.2, 119.5, 54.0, 52.1, 48.6, 40.7, 36.5, 30.5, 27.2, 25.7, 25.7.

Compound 18p. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.41 (t, J = 5.7 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.30–7.12 (m, 5H), 7.18 (s, 1H), 6.68 (d, J = 2.1 Hz, 2H), 6.43 (t, J = 2.1 Hz, 1H), 4.90 (d, J = 6.8 Hz, 1H), 4.63–4.45 (m, 1H), 4.12 (t, J = 7.0 Hz, 1H), 3.77 (s, 6H), 3.77 (m, 2H), 3.19 (d, J = 16.2 Hz, 1H), 3.08 (dd, J = 13.8 Hz, J = 3.9 Hz, 1H), 2.88 (dd, J = 13.6 Hz, J = 11.4 Hz, 1H), 2.68–2.15 (m, 4H), 1.74–1.54 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 173.1, 171.4, 170.9, 168.8, 160.7, 140.6, 137.9, 135.3, 135.0, 132.4, 128.9, 127.9, 126.1, 124.0, 103.1, 99.4, 55.1, 54.0, 52.1, 48.6, 40.6, 36.5, 30.5, 27.2, 25.7.

Characterization of Alkyl-Substituted Thienoindolizines 23–26. Compound 23. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.23–8.10 (m, 2H), 7.54 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.33–7.13 (m, 6H), 6.92 (s, 1H), 5.69 (d, J = 5.2 Hz, 1H), 4.63–4.46 (m, 1H), 3.84–3.63 (m, 2H), 3.60 (dd, J = 10.0 Hz, 3.0 Hz, 1H), 3.30 (d, J = 16.1 Hz, 1H), 3.08 (dd, J = 13.7 Hz, 3.3 Hz, 1H), 2.91 (dd, J = 13.4 Hz, 11.9 Hz, 1H), 2.65 (dd, J = 14.8 Hz, 6.0 Hz, 1H), 2.46–2.08 (m, 3H), 1.94–1.56 (m, 2H), 1.44–1.20 (m, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 171.9, 171.7, 169.9, 169.2, 140.8, 138.7, 137.2, 134.1, 132.4, 129.6, 129.5, 128.5, 127.9, 126.7, 125.4, 121.1, 54.8, 52.8, 50.3, 41.9, 36.9, 33.0, 30.3, 24.9, 18.7; MS (ESI) calcd for $C_{29}H_{28}N_3O_5S$ $[M - H]^-$ 530.2, found 530.3; HRMS (ESI) calcd for $C_{29}H_{30}N_3O_5S$ $[M + H]^+$ 532.1906, found 532.1906.

Compound 24 (1:1 Epimeric Mixture). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.34–8.04 (m, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.44–6.93 (m, 14H), 5.01 (dd, J = 6.4, 4.0 Hz, 1H), 4.64–4.41 (m, 1H), 3.99 (t, J = 6.6, 6.6 Hz, 1H), 3.76 (s, 2H), 3.42–3.20 (m, 1H), 3.22–2.56 (m, 5H), 2.41–2.27 (m, 1H), 2.14–1.99 (m, 0.5H), 1.90–1.74 (m, 0.5H), 1.37–1.13 (m, 1H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 175.7, 174.5, 169.2, 169.1, 141.4, 141.2, 140.2140.0, 138.6, 138.5, 137.3, 136.9, 134.0, 131.7, 130.7, 129.6, 129.5, 129.3, 129.2, 129.0, 128.9, 128.5, 128.4, 127.9, 126.7, 126.6, 125.5, 121.0, 120.9, 51.8, 51.6, 50.1, 49.6, 44.2, 43.3, 40.5, 40.3, 37.4, 37.1, 37.0, 36.3, 34.3, 30.7, 25.9, 25.2; MS (ESI) calcd for $C_{35}H_{32}N_3O_5S$ $[M - H]^-$ 606.2, found 606.4; HRMS (ESI) calcd for $C_{354}H_{34}N_3O_5S$ $[M + H]^+$ 608.2219, found 608.2189.

Compound 25. ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.27 (t, J = 5.1 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.4 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.31–7.20 (m, 6H), 7.12 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 4.67–4.51 (m, 1H), 3.74 (d, J = 2.9 Hz, 2H), 3.62 (dd, J = 8.9 Hz, 4.6 Hz, 1H), 3.26–3.03 (m, 2H), 3.00–2.83 (m, 1H), 2.47–1.33 (m, 7H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 172.1, 171.7, 169.6, 169.4, 141.2, 138.7, 135.9, 134.5, 134.1, 129.6, 129.5, 128.6, 128.0, 126.7, 125.4, 124.0, 54.7, 51.7, 50.1, 40.5, 36.9, 33.1, 32.2, 25.5, 18.7; MS (ESI) calcd for $C_{29}H_{28}N_3O_5S$ $[M - H]^-$ 530.2, found 530.3; HRMS (ESI) calcd for $C_{29}H_{30}N_3O_5S$ $[M + H]^+$ 532.1906, found 532.1913.

Compound 26 (1:1 Epimeric Mixture). ^{1}H NMR (250 MHz, DMSO-d_6): δ 8.33–8.07 (m, 2H), 7.55 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.33–7.11 (m, 7H), 4.91 (d, J = 6.8 Hz, 1H), 4.63–4.41 (m, 1H), 4.11–3.91 (m, 1H), 3.86–3.57 (m, 2H), 3.28–3.00 (m, 2H), 2.88 (dd, J = 13.3 Hz, 11.5 Hz, 1H), 2.73–2.52 (m, 2H), 2.41–0.99 (m, 5H), 1.00–0.73 (m, 6H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 176.8, 175.2, 169.5, 169.4, 141.4, 138.7, 138.6, 135.6, 134.0, 132.9, 129.6, 128.5, 128.1, 126.7, 125.5, 124.3, 124.0, 51.4, 51.0, 50.0, 49.2, 40.6, 40.5, 40.3, 39.6, 37.2, 37.1, 36.3, 33.4, 26.6, 26.0, 25.6, 23.8, 23.7, 22.0; MS (ESI) calcd for $C_{32}H_{34}N_4O_5S$ $[M - H]^-$ 572.2, found 572.4; HRMS (ESI) calcd for $C_{32}H_{36}N_3O_5S$ $[M + H]^+$ 574.2375, found 574.2371.

Characterization of Aryl-Substituted Thiophenes 32 and 34. Compound 32 (1:1 Epimeric Mixture). ^{1}H NMR (800 MHz, DMSO-d_6): δ 8.68 (d, J = 7.1 Hz, 0.5H), 8.63 (d, J = 7.5 Hz, 0.5H), 8.58–8.47 (m, 2H), 8.30 (d, J = 13.4 Hz, 1H), 8.12 (t, J = 7.4 Hz, 1H), 8.03 (t, J = 7.0 Hz, 1H), 7.70 (dd, J = 8.5 Hz, J = 17 Hz, 1H), 7.52 (s, 0.5H), 7.45 (s, 0.5H), 7.29–7.13 (m, 5H), 6.93 (s, 0.5H), 6.78 (s, 0.5H), 5.42–5.31 (m, 1H), 4.54 (bs, 1H), 3.69 (bs, 2H), 3.05 (t, J = 12 Hz, 1H), 2.80–2.59 (m, 3H), 1.83 (s, 1.5H), 1.81 (s, 1.5H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 169.3, 169.2, 169.0, 148.9, 148.7, 148.7, 139.1, 139.0, 138.6, 138.5, 135.9,

131.8, 131.2, 129.6, 129.5, 128.5, 126.6, 126.5, 125.9, 125.8, 125.7, 122.2, 119.5, 54.5, 45.9, 45.7, 41.9, 41.8, 40.5, 40.4, 38.0, 37.9, 23.1, 23.0; MS (ESI) calcd for $C_{26}H_{25}N_4O_7S$ $[M - H]^-$ 537.1, found 537.2; HRMS (ESI) calcd for $C_{26}H_{27}N_4O_7S$ $[M + H]^+$ 539.1600, found 539.1602.

Compound 34 (1:1 Epimeric Mixture). ^{1}H NMR (800 MHz, DMSO-d_6): δ 8.62 (bs, 1H), 8.56 (bs, 1H), 8.35 (d, J = 11.5 Hz, 1H), 8.13 (m, 1H), 8.09 (d, J = 7.0 Hz, 1H), 7.70 (dd, J = 7.9 Hz; J = 15.7 Hz, 1H), 7.61 (s, 0.5H), 7.52 (s, 0.5H), 7.28–7.18 (m, 5H), 7.02 (s, 0.5H), 6.77 (s, 0.5H), 4.67–4.61 (m, 1H), 4.46–4.43 (m, 1H), 3.69 (bs, 2H), 3.09–2.54 (m, 12H); ^{13}C NMR (200 MHz, DMSO-d_6): δ 170.0, 169.8, 148.9, 145.1, 144.7, 140.0, 139.9, 138.5, 138.3, 135.8, 131.9, 131.2, 129.7, 128.5, 127.7, 127.3, 126.8, 126.7, 125.9, 122.4, 119.6, 60.7, 60.4, 51.9, 51.7, 47.3, 40.5, 40.4, 38.4, 38.0, 37.9, 37.7,; MS (ESI) calcd for $C_{28}H_{29}N_4O_8S_2$ $[M - H]^-$ 613.1, found 613.2; HRMS (ESI) calcd for $C_{28}H_{31}N_4O_8S_2$ $[M + H]^+$ 615.1583, found 615.1580.

Acknowledgment. The Danish National Research Foundation is gratefully acknowledged for financial support.

Supporting Information Available. Analytical data (HPLC, MS, and NMR) for building blocks and compounds cleaved from the solid support. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Discov. Dev.* **2005**, *8*, 723–740.
(2) Schatz, J. Thiophenes, Thiophene 1,1-Dioxides and Thiophene 1-Oxides. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations. Hetarenes and Related Ring Systems*; Maas, G., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Chapter *9.10*, pp 287–422.
(3) Bubenik, M.; Meerovitch, K.; Bergeron, F.; Attardo, G.; Chan, L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 503–506.
(4) Lütjens, H.; Zickgraf, A.; Figler, H.; Linden, J.; Olsson, R. A.; Scammels, P. J. *J. Med. Chem.* **2003**, *46*, 1870–1877.
(5) Wan, Y.; Wallinder, C.; Johansson, B.; Holm, M.; A. K., M.; Wu, X.; Botros, M.; Karlén, A.; Pettersoon, A.; Nyberg, F.; Fändriks, L.; Hallberg, A.; Alterman, M. *J. Med. Chem.* **2004**, *47*, 1536–1546.
(6) Tamagnan, G.; Alagille, D.; Fu, X.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B.; Baldwin, R. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1131–1133.
(7) Michaelides, M. R.; Hong, Y.; DiDomenico, S.; Bayburt, E. K.; Asin, K. E.; Britton, D. R.; Wel Lin, C.; Shiosaki, K. *J. Med. Chem.* **1997**, *40*, 1585–1599.
(8) Lohray, B. B.; Lohray, V. B.; Srivastava, B. K.; Kapadanis, P. B.; Pandya, P. *Bioorgan. Med. Chem.* **2004**, *12*, 4557–4564.
(9) Torrado, A.; Lamas, C.; Agejas, J.; Jimenéz, A.; Díaz, N.; Gilmore, J.; Boot, J.; Findlay, J.; Hayhurst, L.; Wallace, L.; Brodamore, R.; Tomlinson, R. *Bioorg. Med. Chem.* **2004**, *12*, 5277–5295.
(10) Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Santos, J. S. O.; Pierré, A.; Atassi, G.; Caignard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448–1464.
(11) Kumar, P. J.; Raju, S.; Goud, S.; Sailaja, M.; Sarma, M. R.; Reddy, G. O.; Kumar, M. P.; Reddy, V. V. R. M. K.; Surash, T.; Hegde, P. *Bioorg. Med. Chem.* **2004**, *12*, 1221–1230.
(12) Roncali, J. *Chem. Rev.* **1992**, *92*, 711–738.
(13) Horowitz, G. *Adv. Mater.* **1998**, *10*, 365–377.
(14) Noma, N.; Tsuzuki, T.; Shirota, Y. *Adv. Mater.* **1995**, *7*, 647–648.
(15) Nielsen, T. E.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765–3773.
(16) Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2005**, *7*, 599–610.
(17) Nielsen, T. E.; Le Quement, S.; Meldal, M. *Org. Lett.* **2005**, *7*, 3601–3604.
(18) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 2004.
(19) Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748–5749.
(20) Atherton, E.; Fox, H.; Harkiss, D.; Logan, C. J.; Sheppard, R. C.; Williams, B. J. *J. Chem. Soc. Chem. Commun.* **1978**, 537–529.
(21) Atherton, E.; Fox, H.; Harkiss, D.; Sheppard, R. C. *J. Chem. Soc. Chem. Commun.* **1978**, 539–540.
(22) Meldal, M. *Tetrahedron Lett.* **1992**, *33*, 3077–3080.
(23) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927–1930.
(24) Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701–1704.
(25) Malenfant, P. R. L.; Fréchet, J. M. J. *Chem. Commun.* **1998**, 2657–2658.
(26) Han, Y.; Giroux, A.; Lépine, C.; Laliberté, F.; Huang, Z.; Perrier, H.; Bayly, C. I.; Young, R. N. *Tetrahedron* **1999**, *55*, 11669–11685.
(27) Briehn, C. A.; Kirschbaum, T.; Bäuerle, P. *J. Org. Chem.* **2000**, *65*, 352–359.
(28) Kirschbaum, T.; Briehn, C. A.; Bäuerle, P. *J. Chem. Soc. Perkins Trans. 1* **2000**, 1211–1216.
(29) Briehn, C. A.; Bäuerle, P. *Synth. Met.* **2001**, *119*, 121–122.
(30) Kirschbaum, T.; Bäuerle, P. *Synth. Met.* **2001**, *119*, 127–128.
(31) Briehn, C. A.; Bäuerle, P. *J. Comb. Chem.* **2002**, *4*, 457–469.
(32) Turner, D. J.; Anémian, R.; Mackie, P. R.; Cupertino, D. C.; Yeates, S. G.; Turner, M. L.; Spivey, A. C. *Org. Biomol. Chem.* **2007**, *5*, 1752–1763.
(33) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–515.
(34) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
(35) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
(36) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
(37) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145–157.
(38) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885–939.
(39) Nielsen, T. E.; Le Quement, S.; Meldal, M. *Tetrahedron Lett.* **2005**, *46*, 7959–7962.
(40) Dörwald, F. Z. *Side-Reactions in Organic Synthesis*; Wiley-VCH: New York, 2005.
(41) Groth, T.; Meldal, M. *J. Comb. Chem.* **2001**, *3*, 34–44.
(42) Le Quement, S. T.; Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2007**, *9*, 1060–1072.

CC700199N