A Simple Route to New Phenanthro- and Phenanthroid-Fused Thiazoles by a PIFA-Mediated (Hetero)biaryl Coupling Reaction

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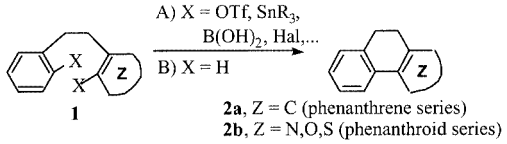
An application of the PIFA-mediated [PIFA: phenyliodine(III) bis(trifluoroacetate)] biaryl coupling reaction is presented and extended to the formation of heterobiaryl connections. A preliminary study of the scope and limitations of this procedure was carried out in the synthesis of phenanthroids **11** from a series of phenethyl-substituted heterocycles **10**. It was observed that in some cases a competitive dimerization process took place. It was also found that the coupling step could be efficiently extended to a larger number of examples if an aromatic ring were situated fused to the 1,2-diarylethane skeleton, as in **23** and **30**. The synthesis of a series of 4,5-diarylthiazoles **23a**–**g** was therefore carried out to explore the electronic requirements and the regioselectivity of the PIFA-mediated non-phenolic coupling reaction. When the same procedure was applied to aryl-heteroarylthiazoles **30**, a series of phenanthroid-fused thiazoles **31** was obtained in good overall yields. To the best of our knowledge, no oxidative aryl-heteroaryl coupling reaction of this type had previously been reported.

Introduction

Biaryl bond construction has been a recurrent theme for synthetic organic chemists during recent decades. With this as a goal, different powerful methodologies have been developed in order to synthesize different natural products of interest.[1] Some of these methodologies require substrates bearing suitable functionalization (approach A in Scheme 1) and, in this context, the procedures introduced by Stille,[2a,2b] Ullmann,[2c] Semmelhack,[2d] Negishi,[2e] Suzuki,[2f] Meyers,[2g] Lipshutz[2h] and Kharasch,[2i] among others, have become classic tools in the organic chemist's repertoire. On the other hand, biomimetic (oxidative) approaches to the synthesis of biaryl moieties have been exploited[2j] both with phenolic and with non-phenolic compounds, with the advantage that, in these cases, no additional functionalization on the aromatic rings (approach B in Scheme 1) is needed.



Scheme 1

In this context, considerable attention during the last decade has been devoted to the chemistry of hypervalent iodine reagents as a powerful tool for synthetic organic chemists.[3] The easily handled PIFA [phenyliodine(III) bis(trifluoroacetate)] and PIDA [(phenyliodine(III) diacetate] reagents have been used for the production of aryl radical cations by an SET mechanism,[4] displaying a reactivity similar to those of other oxidants such as, for example, Tl^{III}, V^{V}, Ru^{IV} and Fe^{III} salts, but with diminished toxicity. By this strategy, a series of nucleophiles (azides,[4a,5] acetates,[4] dicarbonyl compounds,[4] thiophenolates[6] and thiocyanates[6b]) has been introduced onto electron-enriched benzene rings. In the particular case of aryl rings with high nucleophilic character (high Nu), this methodology would give rise to a new biaryl connection in an elegant and simple way[7] (see Scheme 2, **3** → **4** → **6**). This methodology has in fact been employed, by ourselves[8] and by others,[9] for the preparation of different synthetic and naturally occurring products containing the biaryl moiety; in our opinion this approach should be extended in depth. In this paper we therefore wish to report our synthetic results on the PIFA-mediated preparation of phenanthrene building blocks.

According to the general proposal shown in Scheme 2, the stilbene-like substrates of type **3** must fulfil two preliminary conditions in order to be transformed into the corresponding phenanthrenes or phenanthroids **6**. Hence, the success of the reaction would probably rely firstly on the ease of formation of the radical cation intermediate located on one of the rings, and secondly on the nucleophilic character of the other ring. In the absence of such nucleophilic character in the aromatic ring (low Nu), dimerization processes

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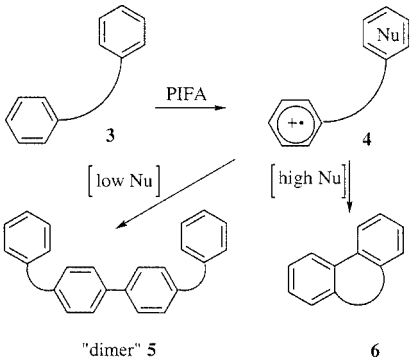
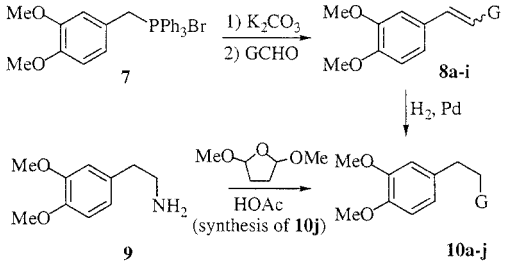


Scheme 2

may result (see Scheme 2, **3** → **4** → **5**).[10] Surprisingly, despite its tremendous potential, this methodology has not, as far as we know, been extended to the action of different simple heterocycles that would, eventually, give rise to a series of heteroaromatic phenanthroids of great interest by a short and efficient route.

Results and Discussion

In order to evaluate the scope and limitations of the proposed strategy, a series of 1,2-diarylethanes of type **10**, with varying nucleophilicity in one of the rings, was prepared (see Scheme 3).[11] Precursors **10a**−**i**[12] were obtained by standard procedures, in two steps by a Wittig reaction with the corresponding aromatic or heteroaromatic aldehyde[13] and the (3,4-dimethoxybenzyl)triphenylphosphonium bromide **7**,[14] followed by catalytic hydrogenation of the obtained *cis*/*trans* mixtures of stilbenes **8a**−**i**.[15] On the other hand, pyrrole **10j** was prepared by condensation of the phenethylamine **9** with 2,5-dimethoxytetrahydrofuran in acetic acid.[16]



G = 3,4-dimethoxyphenyl (**8/10a**); phenyl (**8/10b**); 2-thienyl (**8/10c**); 3-thienyl (**8/10d**); 2-furyl (**8/10e**); 3-furyl (**8/10f**); 6-methoxy-2-pyridyl (**8/10g**); 6-methoxy-3-pyridyl (**8/10h**); *N*-methyl-2-pyrrolyl (**8/10i**); *N*-pyrrolyl (**10j**)

Scheme 3. Synthesis of phenethyl derivatives **10a**−**j**

With compounds **10a**−**j** in hand, the oxidative biaryl coupling step was accomplished by use of the commercially available PIFA in the presence of $BF_3{\cdot}OEt_2$ as the activating agent (the cyclization process did not take place when the reaction was carried out in the absence of the Lewis acid). Figure 1 compiles the tricyclic compounds obtained. From these results we were able to deduce that only electron-rich aromatic rings were able to provide the corresponding fused systems. Thus, the fully aromatic tetramethoxyphenanthrene[17] **11a**, the naphthothiophene[18] **11c**, and the pyrroloisoquinoline[19] **11j**, which was not subject to further dehydrogenation, were prepared in moderate to high yields. Conversely, in those cases in which the aryl ring was not nucleophilic enough (as in **10g**), the dimeric material **12** was the only product detected, as a result of a homocoupling biaryl process.

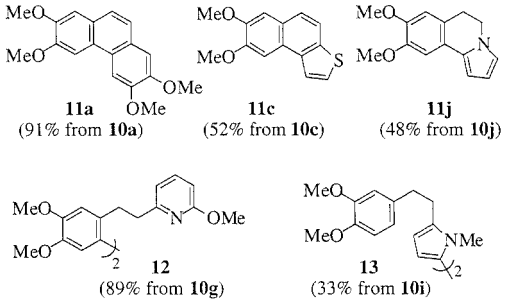
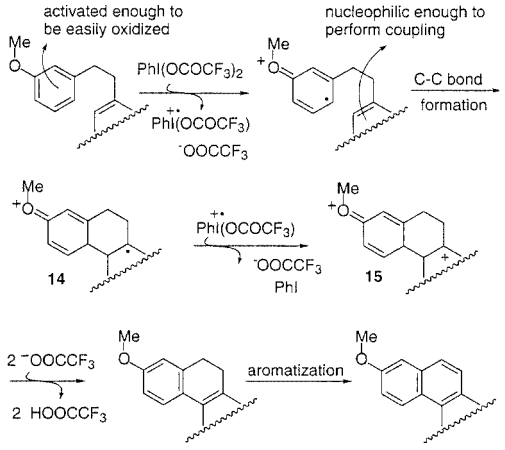


Figure 1. Phenanthrenes and phenanthroids **11**, and dimers **12** and **13** obtained from **10**

The particular behaviour of pyrrole **10i** deserves a more detailed inspection. In this case, pyrrole−pyrrole dimerization took place, in preference to the geometrically prevented cyclization, through the 5-position to afford dimer **13**. The higher nucleophilicity of this site with respect to the 3-position (the one required for the target heterocyclization) accounted for the experimental result, and it also revealed that the radical cation intermediate was generated in the pyrrole ring, with a second pyrrole ring acting as the nucleophilic partner in the reaction. In contrast, the availability of the 2(= 5)-position in pyrrole **10j** allowed the desired intramolecular cyclization, providing the corresponding pyrroloisoquinoline **11j**. Finally, under the same reaction conditions, substrates **10b**, **10d**, **10e**, **10f** and **10h** decomposed to give complex mixtures of unidentified compounds.[20]

Although, as mentioned, the chemistry of hypervalent iodine has for the first time been extended through these experiments to promote oxidative heterobiaryl coupling reactions, starting from simple and nonfunctionalized stilbene-like precursors, we were not completely satisfied with the obtained results, since certain limitations (dimer formation and degradation processes) had arisen. We therefore decided to have a closer look at the proposed mechanism of the coupling step (see Scheme 4).

The assumption that weakly nucleophilic rings were not able to undergo the desired coupling was reflected in the fact that dimer **12** was formed instead of the target benzoquinoline derivative. In view of the previous results, and in order to expand the scope of our strategy to a higher number of examples, it was possible to speculate that the reaction rate might be increased by avoidance of the dimerization pathway, if an aromatic ring were to be situated fused



Scheme 4. Proposed mechanism for the cyclization step

to the 1,2-diarylethane skeleton in such a way that the resulting benzylic intermediate of type **16** (see Figure 2) would be formed through a more stabilized transition state. In addition, the closer proximity of the two rings should make the biaryl connection more likely to occur. A new series of 4,5-diarylthiazoles of type **19** (see Scheme 5) was therefore prepared, in order to be transformed into the corresponding phenanthro- and phenanthroid-fused thiazoles.

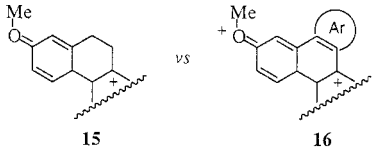
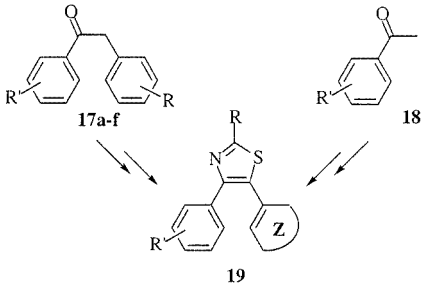


Figure 2. Proposed intermediates **15** and **16**

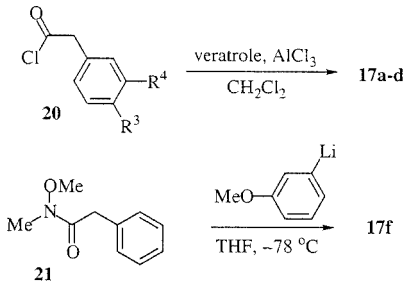


Scheme 5

We considered two reasons to select and focus on the thiazole system, aside from the simplicity of its projected preparation. Firstly, since the thiazole moiety is present in a number of important natural products,[21] we should reach a series of heterocyclic derivatives with a presumably high potential pharmacological activity. Secondly, the behaviour of the thiazole system under oxidative coupling conditions has so far been unknown.

As already shown, radical cations have been proposed as intermediates in oxidative coupling reactions,[4] and so the yield and regioselectivity of such a step might be highly influenced by the electronic nature and location of the aryl substituents. In order to study both factors,[8b] the synthesis of a series of 4,5-diarylthiazoles **23** − including highly activated (**23a**, **23b**, **23g**), moderately activated (**23c**), nonactivated (**23e**, **23f**) and deactivated (**23d**) aromatic rings − was planned. Moreover, the projected approach had to be amenable to easy extension to the preparation of different 4-aryl-5-heteroarylthiazoles of type **19** (Z = N, O, S) (vide infra). A schematic representation of the selected synthons **17** and **18** is therefore included in Scheme 5.

The construction of the selected precursors started from bromo ketones **22a**−**f**, easily accessible by bromination of the corresponding deoxybenzoins **17a**−**f** under standard conditions. Because of the severe electronic and regioselective constraints of the Friedel−Crafts acylation[22] used to prepare deoxybenzoins **17a**−**d**, an alternative approach had to be developed to prepare **17f**. Consequently, as shown in Scheme 6, the anion derived from lithiation of 3-bromoanisole was prepared and treated with commercially available amide **21** to afford deoxybenzoin **17f** in acceptable yield. The transformation of bromo ketones into thiazoles **23a**−**f** and **23g** was carried out in good to excellent yields (78−97%) by use of thioacetamide and thiourea, in DMF as solvent (see Scheme 7).



Scheme 6. Synthesis of deoxybenzoins **17**

At this stage of the research, the diarylthiazoles **23a**−**g** were submitted to our oxidative coupling conditions, affording the corresponding series of phenanthro-fused thiazoles **24** in variable yields. From the obtained results, the following conclusions can be proposed:

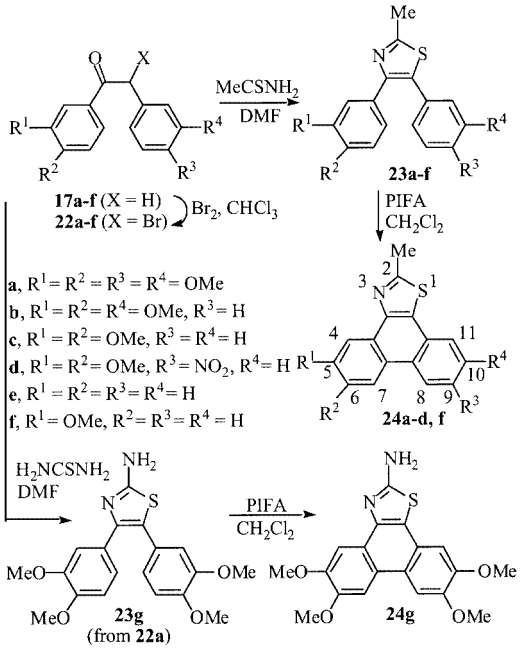
1) activation with electron-donating groups is needed in at least one of the rings,

2) the reaction takes place in moderate to good yield (63−83%), provided that at least two methoxy groups are present in one of the rings (**23a**, **23b**, **23c**, **23d**, **23g**),

3) if only one methoxy group is present, the yield decreases dramatically (less than 5% for **23f**),[23]

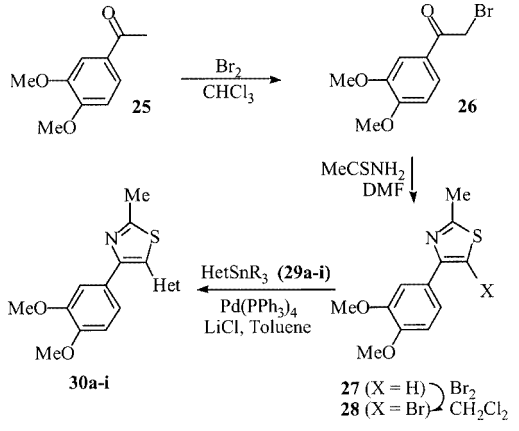
4) finally, no regioisomers other than those described, which are the result of a *para*−*para* interaction, are detected.[24]

Once we had completed the preparation of phenanthro-fused thiazoles **24**, we moved to a next objective: the preparation of phenanthroid-fused thiazoles of type **31**. For this purpose, a new route had to be optimized in order to construct the skeleton of the required 4-aryl-5-heteroaryl-



Scheme 7. Synthesis of phenanthrothiazoles **24**

thiazoles **30a**−**i**. As shown in Scheme 8, bromo ketone **26**, obtained from acetophenone **25**, reacted with thioacetamide in DMF, and the obtained 4-arylthiazole **27** was regioselectively brominated to afford bromothiazole **28**, which in turn was coupled under Stille conditions with a series of commercially available (**29a**, **29c**) or known (**29b**, **29d**, **29e**, **29f**, **29i**, **29g**, **29h**)[25] trialkylstannyl heterocyclic derivatives **29** (see Figure 3) giving rise to the corresponding 4-aryl-5-heteroarylthiazoles **30a**−**i**.



Scheme 8. Synthesis of 4-aryl-5-heteroarylthiazoles **30**

When the PIFA-mediated coupling reaction was carried out on thiazoles **30a**−**d**, the corresponding phenanthroid-fused thiazoles **31a**−**d** were isolated in moderate to high yields (see Figure 4), as one would expect from such nucleophilic heterocycles. In addition, no regioisomers other than those shown were detected. This is in agreement with the

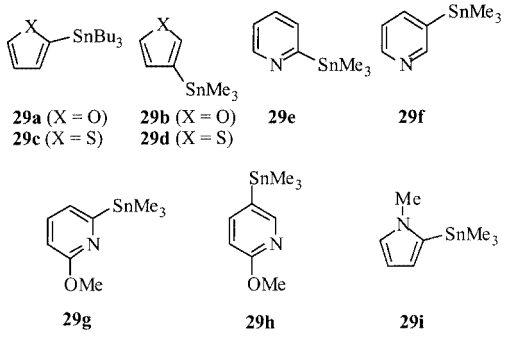


Figure 3. Trialkyltin-substituted heterocycles **29** employed

fact that the 2-position in furans and thiophenes is more nucleophilic than the 3-position. On the other hand, all attempts to promote cyclization in substrates **30e** and **30f** resulted in the recovery of the starting materials completely unchanged. In order to balance the pyridine ring deactivation, to our minds the reason for the lack of reactivity in the thiazoles **30e** and **30f**, a new derivative bearing a methoxy group located *para* to the cyclization point was prepared. Pyridine **29g**, synthesized from 2-methoxypyridine by metallation with *n*BuLi and treatment of the resulting anion with Me_3SnCl in the presence of the lithium salt of 2-(dimethylamino)ethanol,[26] was therefore coupled with bromothiazole **28**. To our delight, the action of PIFA on the obtained thiazole **30g** afforded the desired benzoquinoline **31g** in good yield. Later, we found that thiazole **30h**, which bears a pyridine ring with the electron-donating group located *meta* with respect to the cyclization point, could be also transformed regioselectively into the corresponding benzoquinoline **31h** in a similar yield, provided

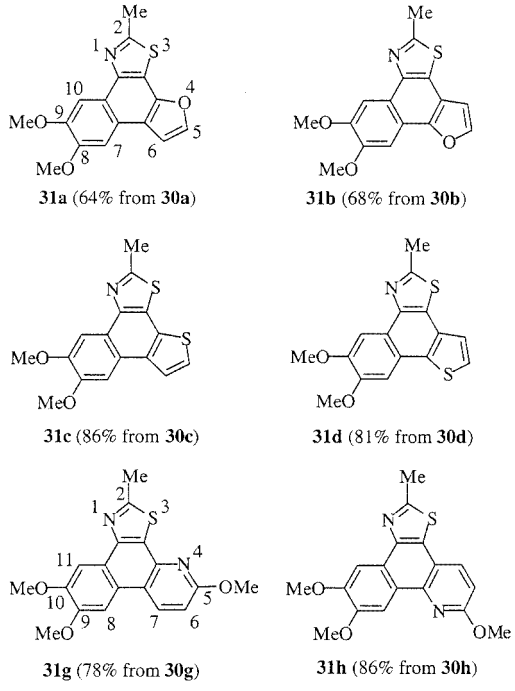


Figure 4. Naphthothiazoles **31a**−**d** and thiazoloquinolines **31g** and **31h**

that the temperature was raised (refluxing solvent).[27] Finally, and as the only exception, reductive cleavage of the pyrrole-substituted thiazole **30i** was found to yield derivative **27** under the typical cyclization conditions.

Conclusion

In summary, new synthetic applications of PIFA-mediated biaryl and aryl-heteroaryl coupling reactions have been presented. The judicious combination of Stille and oxidative intramolecular coupling procedures with suitably activated substrates has allowed us to prepare a series of phenanthro- and phenanthroid-fused thiazoles in very good overall yields. Apart from mechanistic insights, our investigations should provide preparative approaches to interesting new and more complex heterocyclic compounds, a line of research now underway in our group.

Experimental Section

General: See ref.[28]

Typical Procedure for the Oxidative Coupling Reaction with 1,2-Diarylethanes 10. Synthesis of 2,3,6,7-Tetramethoxyphenanthrene (11a): A solution of PIFA (165 mg, 0.38 mmol) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.76 mmol) in CH_2Cl_2 (8 mL) was added at −20 °C to a solution of ethane **10a** (100 mg, 0.33 mmol) in 5 mL of the same solvent. The mixture was stirred at the same temperature for 40 min, and the solvent was removed in vacuo to provide, after crystallisation, 89 mg of pure phenanthrene **10a** in 91% yield. M.p. 178−180 °C (hexanes), m.p. 180−181 °C (toluene/hexanes, 1:1); see ref.[29]

7,8-Dimethoxynaphtho[2,1-*b*]thiophene (11c): Thiophene **11c** was obtained by the typical procedure, from ethane **10c** in 52% yield. M.p. 127−129 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 3 H), 4.08 (s, 3 H), 7.26 (s, 1 H), 7.55 (d, *J* = 5.5 Hz, 1 H), 7.61 (s, 1 H), 7.63 (d, *J* = 8.7 Hz, 1 H), 7.77 (d, *J* = 8.7 Hz, 1 H), 7.86 (d, *J* = 5.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.8, 55.9, 103.2, 107.6, 118.9, 121.5, 123.8, 124.5, 125.4, 126.1, 135.0, 135.9, 148.5, 149.4 ppm. $C_{14}H_{12}O_2S$ (244.31): calcd. C 68.83, H 4.95; found C 68.79, H 4.99.

8,9-Dimethoxypyrrolo[2,1-*a*]-5,6-dihydroisoquinoline (11j):[19] Isoquinoline **11j** was obtained by the typical procedure, from pyrrole **10j** in 48% yield. M.p. 132−133 °C (Et_2O). ^{1}H NMR ($CDCl_3$): δ = 3.00 (t, *J* = 6.7 Hz, 2 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 4.02 (t, *J* = 6.7 Hz, 2 H), 6.20 (dd, *J* = 3.5, 2.6 Hz, 1 H), 6.39 (dd, *J* = 3.5, 1.6 Hz, 1 H), 6.65 (dd, *J* = 2.6, 1.6 Hz, 1 H), 6.70 (s, 1 H), 7.02 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.0, 44.2, 55.9, 102.2, 108.2, 111.2, 120.3, 120.5, 122.7, 129.9, 132.5, 147.1, 149.0 ppm.

1,1′-{2,2′-[2-(6-Methoxy-2-pyridyl)ethyl]-4,4′,5,5′-tetramethoxy}-biphenyl (12):[30] Biphenyl **12** was obtained by the typical procedure, from pyridine **10g** in 89% yield as an oil. ^{1}H NMR ($CDCl_3$): δ = 2.77−2.82 (m, 8 H), 3.81 (s, 6 H), 3.83 (s, 6 H), 3.86 (s, 6 H), 6.45 (d, *J* = 6.9 Hz, 2 H), 6.48 (d, *J* = 8.3 Hz, 2 H), 6.66 (s, 2 H), 6.75 (s, 2 H), 7.36 (dd, *J* = 8.3, 6.9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 32.7, 39.5, 53.1, 55.8, 55.9, 107.4, 111.9, 113.1, 115.1, 132.1, 132.7, 138.6, 146.4, 147.8, 159.1, 163.5 ppm.

2,2′-Bis[5-(3,4-dimethoxyphenylethyl)-1-methylpyrrole] (13):[30] Pyrrole **13** was obtained by the typical procedure, from pyrrole **10i** in 33% yield as an oil. ^{1}H NMR ($CDCl_3$): δ = 2.91 (s, 8 H), 3.79 (s, 6 H), 3.83 (s, 6 H), 3.87 (s, 6 H), 6.13 (d, *J* = 4.8 Hz, 2 H), 6.60 (d, *J* = 2.0 Hz, 2 H), 6.60 (dd, *J* = 7.9, 2.0 Hz, 2 H), 6.80 (d, *J* = 7.9 Hz, 2 H), 7.18−7.20 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.8, 33.2, 34.1, 55.8, 55.9, 109.9, 111.2, 111.4, 120.1, 123.9, 124.6, 132.6, 146.7, 147.6, 148.9 ppm.

Typical Procedure for the Synthesis of Deoxybenzoins 17a−f. Synthesis of 1-(3,4-Dimethoxyphenyl)-2-(3-methoxyphenyl)ethanone (17b): Thionyl chloride (1.1 mL, 15.1 mmol) was added to a suspension of 3-methoxyphenylacetic acid (1.0 g, 6.0 mmol) in CH_2Cl_2 (30 mL). The mixture was heated under reflux for 4 h, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), veratrole (913 mg, 6.6 mmol) was added, and the mixture was cooled on an ice bath. $AlCl_3$ (2.0 g, 15.0 mmol) was then added, and the solution was heated under reflux for 3 h. After cooling, the reaction mixture was quenched with HCl (1 M, 30 mL) and decanted, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with Na_2SO_4 and the solvent was removed under reduced pressure. Deoxybenzoin **17b** was purified by crystallization of the obtained oil from MeOH (1.32 g, 77% yield). M.p. 57−60 °C (MeOH). IR (KBr): $\tilde{\nu}$ = 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.74 (s, 3 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 4.18 (s, 2 H), 6.74−6.91 (m, 4 H), 7.18−7.26 (m, 1 H), 7.53 (d, *J* = 2.0 Hz, 1 H), 7.63 (dd, *J* = 8.3, 2.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.0, 54.9, 55.6, 55.8, 109.7, 110.3, 114.7, 121.4, 123.3, 129.4, 136.3, 148.7, 153.0, 159.5, 195.0 ppm. $C_{17}H_{18}O_4$ (286.32): calcd. C 71.31, H 6.34; found C 71.28, H 6.31.

1-(3,4-Dimethoxyphenyl)-2-(4-nitrophenyl)ethanone (17d): Deoxybenzoin **17d** was obtained by the typical procedure, in 81% yield. M.p. 116−119 °C (MeOH). IR (KBr): $\tilde{\nu}$ = 1676 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3 H), 3.90 (s, 3 H), 4.33 (s, 2 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 7.61 (dd, *J* = 8.3, 2.0 Hz, 1 H), 8.09 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.2, 55.7, 55.9, 109.8, 110.0, 123.1, 123.4, 129.0, 130.3, 142.4, 148.9, 153.5, 194.5 ppm. $C_{16}H_{15}NO_5$ (301.29): calcd. C 63.78, H 5.02, N 4.65; found C 63.81, H 5.12, N 4.61.

Synthesis of 1-(3-Methoxyphenyl)-2-phenylethanone (17f): *n*BuLi (1.56 M in hexane, 5.14 mL) was added at −78 °C to a solution of 3-bromoanisole (1.0 g, 5.4 mmol) in THF (10 mL). The mixture was stirred at the same temperature for 20 min, and a solution of the commercially available amide **21** (320 mg, 1.8 mmol) in THF (10 mL) was then added. The mixture was stirred for 5 min at −78 °C and allowed to warm up to room temp. over 30 min. The reaction mixture was quenched with HCl (1 M, 10 mL) and decanted, the organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was column chromatographed (hexanes/EtOAc, 95:5) to afford ethanone **17f** as a colourless oil (301 mg, 74%). IR (neat): $\tilde{\nu}$ = 1672 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3 H), 4.28 (s, 2 H), 7.08−7.63 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.4, 55.2, 112.6, 119.5, 121.1, 126.7, 129.3, 129.4, 134.4, 137.7, 159.6, 197.3 ppm. MS (EI): *m*/*z* = 226 (9) [M^+], 135 (100).

Typical Procedure for the Synthesis of 2-Bromoethanones 22a−f. Synthesis of 2-Bromo-1,2-bis(3,4-dimethoxyphenyl)ethanone (22a): Bromine (0.2 mL, 3.8 mmol) was added dropwise to a solution of ethanone **17a**[31] (800 mg, 2.52 mmol) in 10 mL of freshly distilled $CHCl_3$. The mixture was heated under reflux until conversion was complete (NMR, 3 h). After the mixture had cooled, the solvent was evaporated under reduced pressure to provide a residue that was column-chromatographed (CH_2Cl_2) to yield pure bromoe-

thanone **22a** (935 mg, 94%) as a yellowish solid. M.p. 78−80 °C. IR (KBr): $\tilde{\nu}$ = 1675 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.82 (s, 3 H), 3.86 (s, 3 H), 3.93 (s, 6 H), 6.86 (s, 1 H), 6.90−7.10 (m, 3 H), 7.52 (s, 1 H), 7.62 (s, 1 H), 7.63 (dd, *J* = 8.2, 0.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.6, 55.9, 56.0, 56.1, 110.2, 110.9, 112.5, 113.6, 115.0, 123.6, 126.6, 127.6, 149.0, 150.1, 189.5 ppm. $C_{18}H_{19}BrO_5$ (395.24): calcd. C 54.70, H 4.85; found C 54.66, H 4.82.

2-Bromo-1-(3,4-dimethoxyphenyl)-2-(3-methoxyphenyl)ethanone (22b): Bromoethanone **22b** was obtained by the typical procedure, from ethanone **17b** in 91% yield. M.p. 149−152 °C (CH_2Cl_2/hexanes, 1:1). IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.74 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 6.71−6.90 (m, 4 H), 7.10 (d, *J* = 3.0 Hz, 1 H), 7.44−7.51 (m, 2 H), 7.59−7.63 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.3, 55.4, 55.9, 56.0, 110.2, 111.0, 113.3, 115.9, 116.9, 123.6, 126.5, 133.9, 136.9, 149.0, 153.8, 159.4, 189.1 ppm. $C_{17}H_{17}BrO_4$ (365.22): calcd. C 55.91, H 4.69; found C 55.65, H 4.92.

2-Bromo-1-(3,4-dimethoxyphenyl)-2-phenylethanone (22c): Bromoethanone **22c** was obtained by the typical procedure, from ethanone **17c**[31] in 97% yield. M.p. 104−106 °C (MeOH). IR (KBr): $\tilde{\nu}$ = 1675 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.90 (s, 3 H), 3.93 (s, 3 H), 6.39 (s, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 7.33−7.36 (m, 3 H), 7.51−7.55 (m, 3 H), 7.61 (dd, *J* = 8.5, 2.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 50.9, 55.4, 55.6, 109.7, 110.7, 123.4, 126.4, 128.5, 128.6, 136.0, 148.6, 153.3, 189.2 ppm. $C_{16}H_{15}BrO_3$ (335.19): calcd. C 57.33, H 4.51; found C 57.55, H 4.72.

2-Bromo-1-(3,4-dimethoxyphenyl)-2-(4-nitrophenyl)ethanone (22d): Bromoethanone **22d** was obtained by the typical procedure, from ethanone **17d** in 65% yield. M.p. 48−51 °C (hexanes). IR (KBr): $\tilde{\nu}$ = 1675 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.87 (s, 3 H), 3.91 (s, 3 H), 6.39 (s, 1 H), 6.86 (d, *J* = 8.7 Hz, 1 H), 7.51 (d, *J* = 2.1 Hz, 1 H), 7.62 (dd, *J* = 8.7, 2.1 Hz, 1 H), 7.70 (d, *J* = 8.7 Hz, 2 H), 8.16 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 46.9, 55.8, 56.0, 110.0, 111.0, 123.6, 126.3, 130.2, 142.9, 147.6, 149.2, 154.1, 188.7 ppm. $C_{16}H_{14}BrNO_5$ (380.19): calcd. C 50.55, H 3.71, N 3.68; found C 50.51, H 3.68, N 3.65.

2-Bromo-1,2-diphenylethanone (22e): Bromoethanone **22e** was obtained by the typical procedure, from commercially available deoxybenzoin **17e** in 98% yield. M.p. 44−46 °C (hexanes). IR (KBr): $\tilde{\nu}$ = 1682 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.40 (s, 1 H), 7.35−7.61 (m, 8 H), 7.91−8.01 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.1, 128.3, 128.5, 128.6, 128.7, 133.3, 135.4, 190.6 ppm. $C_{14}H_{11}BrO$ (275.14): calcd. C 61.11, H 4.03; found C 61.35, H 4.22.

2-Bromo-1-(3-methoxyphenyl)-2-phenylethanone (22f): Bromoethanone **22f** was obtained by the typical procedure, from ethanone **17f** in 71% yield as a colourless oil after purification by column chromatography (hexanes/EtOAc, 6:4). IR (neat): $\tilde{\nu}$ = 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.83 (s, 3 H), 6.37 (s, 1 H), 7.08−7.12 (m, 1 H), 7.31−7.41 (m, 4 H), 7.51−7.56 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 51.3, 55.6, 113.5, 120.5, 129.0, 129.1, 129.8, 135.3, 135.9, 159.8, 190.8 ppm. MS (EI): *m*/*z* = 226 (1), 135 (100).

2-Bromo-1-(3,4-dimethoxyphenyl)ethanone (26): Bromoethanone **26** was obtained by the typical procedure, from commercially available acetophenone **25** in 97% yield. M.p. 45−47 °C (Et_2O). IR (KBr): $\tilde{\nu}$ = 1669 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.91 (s, 3 H), 3.94 (s, 3 H), 4.38 (s, 2 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 7.57 (dd, *J* = 8.5, 2.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.5, 55.5, 55.7, 109.6, 110.2, 123.4, 126.4, 148.7, 153.5, 189.5 ppm. $C_{10}H_{11}BrO_3$ (259.10): calcd. C 46.36, H 4.28; found C 46.21, H 4.32.

Typical Procedure for the Synthesis of Thiazoles 23a−g. Synthesis of 4,5-Bis(3,4-dimethoxyphenyl)-2-methylthiazole (23a): A solution of bromo ketone **22a** (1 g, 2.5 mmol) and thioacetamide (280 mg, 3.0 mmol) [or thiourea for **23g**] in 20 mL of DMF was heated at 65 °C until total consumption of the starting material (TLC, 8 h). After this had cooled, ethyl acetate (40 mL) was added and the mixture was washed with H_2O (3 × 20 mL). The organic extracts were dried with Na_2SO_4 and the solvent was removed in vacuo. Thiazole **23a** was purified by crystallization from Et_2O (0.86 g, 93%). M.p. 67−69 °C. ^1H NMR ($CDCl_3$): δ = 2.73 (s, 3 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 6.75−6.90 (m, 3 H), 7.04−7.08 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 55.4, 55.6, 56.0, 56.1, 110.6, 111.0, 114.8, 115.4, 115.6, 120.6, 125.2, 127.4, 128.7, 148.2, 148.3, 149.7, 150.5, 164.4 ppm. $C_{20}H_{21}NO_4S$ (371.45): calcd. C 64.67, H 5.70, N 3.77; found C 64.77, H 5.59, N 3.67.

4-(3,4-Dimethoxyphenyl)-5-(3-methoxyphenyl)-2-methylthiazole (23b): Thiazole **23b** was obtained by the typical procedure, from bromo ketone **22b** in 89% yield. M.p. 149−152 °C (hexanes/CH_2Cl_2, 1:1). ^1H NMR ($CDCl_3$): δ = 2.74 (s, 3 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 6.76−6.94 (m, 4 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 7.10 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.21(d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 55.1, 55.4, 55.7, 110.6, 111.8, 113.5, 114.8, 121.5, 122.0, 127.4, 129.6, 130.9, 133.5, 148.4, 149.1, 159.4, 163.6 ppm. $C_{19}H_{19}NO_3S$ (341.43): calcd. C 66.84, H 5.61, N 4.10; found C 66.81, H 5.55, N 4.21.

4-(3,4-Dimethoxyphenyl)-2-methyl-5-phenylthiazole (23c): Thiazole **23c** was obtained by the typical procedure, from bromo ketone **22c** in 92% yield. M.p. 78−80 °C (hexanes). ^1H NMR ($CDCl_3$): δ = 2.74 (s, 3 H), 3.65 (s, 3 H), 3.85 (s, 3 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 1.9 Hz, 1 H), 7.10 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.28−7.34 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.8, 55.1, 55.4, 110.4, 111.6, 121.2, 127.1, 127.5, 128.2, 130.7, 132.0, 148.0, 148.1, 148.7, 163.2 ppm. $C_{18}H_{17}NO_2S$ (311.40): calcd. C 69.43, H 5.50, N 4.50; found C 69.51, H 5.42, N 4.31.

4-(3,4-Dimethoxyphenyl)-2-methyl-5-(4-nitrophenyl)thiazole (23d): Thiazole **23d** was obtained by the typical procedure, from bromo ketone **22d** as a colourless oil in 78% yield, after purification by column chromatography (hexanes/EtOAc, 1:1). ^1H NMR ($CDCl_3$): δ = 2.78 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.99 (dd, *J* = 8.3, 2.0 Hz, 1 H), 7.05 (d, *J* = 2.0 Hz, 1 H), 7.47 (d, *J* = 9.1 Hz, 2 H), 8.14 (d, *J* = 9.1 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.3, 55.7, 55.8, 110.9, 111.9, 121.9, 123.9, 126.6, 128.6, 128.7, 130.0, 139.4, 146.7, 148.8, 149.3, 151.3, 165.6 ppm. MS (EI): *m*/*z* = 354 (100) [M^+], 339 (12), 311 (12), 265 (23).

2-Methyl-4,5-diphenylthiazole (23e): Thiazole **23e** was obtained by the typical procedure, from bromo ketone **22e** in 97% yield. M.p. 44−46 °C (Et_2O). ^1H NMR ($CDCl_3$): δ = 2.76 (s, 3 H), 7.27−7.40 (m, 8 H), 7.49−7.53 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 127.6, 127.8, 128.2, 128.6, 128.9, 129.5, 132.1, 134.8, 163.8 ppm. $C_{16}H_{13}NS$ (251.35): calcd. C 76.46, H 5.21, N 5.57; found C 76.41, H 5.42, N 5.31.

4-(3-Methoxyphenyl)-2-methyl-5-phenylthiazole (23f): Thiazole **23f** was obtained by the typical procedure, from bromo ketone **22f** in 86% yield as a colourless oil, after purification by column chromatography (hexanes/EtOAc, 1:1). ^1H NMR ($CDCl_3$): δ = 2.75 (s, 3 H), 3.67 (s, 3 H), 6.79−6.83 (m, 1 H), 7.04−7.32 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 55.0, 113.6, 114.1, 121.4, 127.9,

128.6, 129.2, 129.6, 132.0, 132.5, 149.1, 159.3, 163.8 ppm. MS (EI): m/z = 281 (100) [M^+], 266 (5).

2-Amino-4,5-bis(3,4-dimethoxyphenyl)thiazole (23g): Thiazole **23g** was obtained by the typical procedure, from bromo ketone **22a** in 92% yield. M.p. 164−166 °C (Et_2O). ^1H NMR ($CDCl_3$): δ = 3.68 (s, 3 H), 3.72 (s, 3 H), 3.83 (s, 3 H), 3.88 (s, 3 H), 5.44 (br. s, 2 H), 6.71 (d, J = 8.3 Hz, 1 H), 6.80 (s, 1 H), 6.94−6.98 (m, 3 H), 7.01 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.5, 55.7, 56.0, 56.2, 110.6, 111.0, 115.3, 120.6, 116.2, 125.4, 127.4, 146.5, 148.1, 148.2, 148.3, 149.6, 166.0 ppm. $C_{19}H_{20}N_2O_4S$ (372.44): calcd. C 61.27, H 5.41, N 7.52; found C 61.31, H 5.62, N 7.31.

4-(3,4-Dimethoxyphenyl)-2-methylthiazole (27): Thiazole **27** was obtained by the typical procedure, from bromo ketone **26** in 98% yield. M.p. 62−65 °C (EtOAc). ^1H NMR ($CDCl_3$): δ = 2.71 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 6.85 (d, J = 8.3 Hz, 1 H), 7.14 (s, 1 H), 7.36 (dd, J = 8.3, 1.8 Hz, 1 H), 7.42 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 55.7, 55.4, 109.4, 110.7, 110.9, 118.5, 127.6, 148.7, 148.8, 154.7, 165.5 ppm. $C_{12}H_{13}NO_2S$ (235.30): calcd. C 61.26, H 5.57, N 5.95; found C 61.31, H 5.67, N 5.81.

Synthesis of 5-Bromo-4-(3,4-dimethoxyphenyl)-2-methylthiazole (28): Bromine (0.32 mL, 6.3 mmol) was added dropwise to a solution of thiazole **27** (1.2 g, 5.25 mmol) in 15 mL of $CHCl_3$. The mixture was heated under reflux until conversion was complete (NMR, 4 h). Then, after cooling, the solvent was removed under reduced pressure and the crude bromothiazole **28** was purified by crystallization from Et_2O (1.6 g, 97%). M.p. 158−161 °C. ^1H NMR ($CDCl_3$): δ = 2.70 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 6.93 (d, J = 8.3 Hz, 1 H), 7.45 (d, J = 1.8 Hz, 1 H), 7.50 (dd, J = 8.3, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.5, 55.8, 100.8, 110.5, 111.4, 121.1, 126.1, 148.9, 151.5, 165.3 ppm. $C_{12}H_{12}BrNO_2S$ (314.20): calcd. C 45.87, H 3.85, N 4.46; found C 45.77, H 3.62, N 4.41.

Typical Procedure for the Stille Coupling Reaction. Synthesis of 4-(3,4-Dimethoxyphenyl)-5-(6-methoxypyrid-2-yl)-2-methylthiazole (30g): A solution of pyridine **29g**[25d] (122 mg, 0.45 mmol) in toluene (5 mL) was added to a suspension of bromothiazole **28** (100 mg, 0.28 mmol), LiCl (36 mg, 0.84 mmol) and $Pd(PPh_3)_4$ (33 mg, 10% mol) in 25 mL of the same solvent, and the mixture was heated under reflux for 48 h. After this had cooled to room temp., the solvent was evaporated under reduced pressure and the residue was column-chromatographed (hexanes/EtOAc, 1:1; this eluent was used for the purification of all derivatives **30**) to afford thiazole **30g** (72 mg, 78%) as an oil that was crystallised from ether. M.p. 95−97 °C (Et_2O). ^1H NMR ($CDCl_3$): δ = 2.72 (s, 3 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 6.55 (dd, J = 8.3, 0.8 Hz, 1 H), 6.80−6.88 (m, 2 H), 7.07−7.14 (m, 2 H), 7.31−7.35 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 53.3, 55.8, 109.0, 111.0, 112.1, 114.6, 121.8, 128.1, 133.5, 138.6, 148.7, 148.8, 149.0, 150.8, 163.3, 165.6 ppm. $C_{18}H_{18}N_2O_3S$ (342.41): calcd. C 63.14, H 5.30, N 8.18; found C 63.09, H 5.42, N 8.14.

4-(3,4-Dimethoxyphenyl)-5-(2-furyl)-2-methylthiazole (30a): Thiazole **30a** was obtained by the typical procedure, from bromothiazole **28** and commercially available 2-(tributylstannyl)furan (**29a**) in 86% yield. M.p. 77−79 °C (hexanes). ^1H NMR ($CDCl_3$): δ = 2.73 (s, 3 H), 3.83 (s, 3 H), 3.91 (s, 3 H), 6.26−6.27 (m, 1 H), 6.32−6.34 (m, 1 H), 6.83 (d, J = 8.5 Hz, 1 H), 7.09 (s, 1 H), 7.16 (dd, J = 8.5, 2.0 Hz, 1 H), 7.36 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.0, 55.6, 55.7, 108.4, 110.6, 111.4, 111.5, 121.3, 127.4, 142.0, 146.1, 148.4, 148.8, 150.0, 163.8 ppm. $C_{16}H_{15}NO_3S$ (301.36): calcd. C 63.77, H 5.02, N 4.65; found C 63.59, H 5.22, N 4.34.

4-(3,4-Dimethoxyphenyl)-5-(3-furyl)-2-methylthiazole (30b): Thiazole **30b** was obtained by the typical procedure, from bromothiazole **28** and 3-(trimethylstannyl)furan (**29b**),[25a] in 74% yield as a colourless oil. ^1H NMR ($CDCl_3$): δ = 2.69 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 6.27−6.28 (m, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 7.12−7.16 (m, 2 H), 7.35−7.36 (m, 1 H), 7.44−7.46 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.0, 55.6, 55.7, 110.6, 110.9, 111.7, 116.9, 121.3, 121.7, 127.5, 140.4, 143.1, 148.4, 148.6, 149.8, 162.9 ppm. HRMS calcd. for $C_{16}H_{16}NO_3S$ 301.0773, found 301.0779.

4-(3,4-Dimethoxyphenyl)-2-methyl-5-(2-thienyl)thiazole (30c): Thiazole **30c** was obtained by the typical procedure, from bromothiazole **28** and commercially available 2-(tributylstannyl)thiophene (**29c**), in 89% yield as a colourless oil. ^1H NMR ($CDCl_3$): δ = 2.73 (s, 3 H), 3.75 (s, 3 H), 3.89 (s, 3 H), 6.83 (d, J = 8.3 Hz, 1 H), 6.97−7.08 (m, 3 H), 7.17 (dd, J = 8.3, 2.0 Hz, 1 H), 7.23−7.28 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 55.5, 55.7, 110.6, 111.8, 121.6, 124.0, 126.5, 127.1, 127.2 127.9, 133.2, 148.3, 148.7, 150.3, 163.8 ppm. HRMS calcd. for $C_{16}H_{15}NO_2S_2$ 317.0544, found 317.0550.

4-(3,4-Dimethoxyphenyl)-2-methyl-5-(3-thienyl)thiazole (30d): Thiazole **30d** was obtained by the typical procedure, from bromothiazole **28** and 3-(trimethylstannyl)thiophene (**29d**),[25b] in 72% yield as a colourless oil. ^1H NMR ($CDCl_3$): δ = 2.73 (s, 3 H), 3.74 (s, 3 H), 3.89 (s, 3 H), 6.82 (d, J = 8.3 Hz, 1 H), 6.96 (dd, J = 5.1, 1.6 Hz, 1 H), 7.03 (d, J = 2.0 Hz, 1 H), 7.12 (dd, J = 8.3, 2.0 Hz, 1 H), 7.23−7.29 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 55.5, 55.7, 110.7, 111.6, 121.3, 123.8, 125.8, 125.9, 127.6, 132.1, 128.3, 148.3, 148.5, 163.0 ppm. HRMS calcd. for $C_{16}H_{15}NO_2S_2$ 317.0544, found 317.0535.

4-(3,4-Dimethoxyphenyl)-2-methyl-5-(2-pyridyl)thiazole (30e): Thiazole **30e** was obtained by the typical procedure, from bromothiazole **28** and 2-(trimethylstannyl)pyridine (**29e**),[25c] in 69% yield as a colourless oil. ^1H NMR ($CDCl_3$): δ = 2.74 (s, 3 H), 3.79 (s, 3 H), 3.91 (s, 3 H), 6.85 (d, J = 8.3 Hz, 1 H), 7.05−7.13 (m, 3 H), 7.18−7.22 (m, 1 H), 7.43−7.50 (m, 1 H), 8.56−8.59 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.3, 55.8, 55.9, 111.1, 112.1, 121.8, 121.9, 122.3, 127.8, 136.0, 148.8, 149.1, 149.6, 151.1, 151.8, 166.0 ppm. HRMS calcd. for $C_{17}H_{16}N_2O_2S$ 312.0932, found 312.0937.

4-(3,4-Dimethoxyphenyl)-2-methyl-5-(3-pyridyl)thiazole (30f): Thiazole **30f** was obtained by the typical procedure, from bromothiazole **28** and 3-(trimethylstannyl)pyridine (**29f**),[25c] in 72% yield. M.p. 99−102 °C (Et_2O). ^1H NMR ($CDCl_3$): δ = 2.77 (s, 3 H), 3.73 (s, 3 H), 3.87 (s, 3 H), 6.77 (d, J = 8.5 Hz, 1 H), 6.97−7.05 (m, 2 H), 7.19−7.31 (m, 1 H), 7.61 (d, J = 7.9 Hz, 1 H), 8.53−8.60 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.3, 55.6, 55.8, 110.9, 111.8, 121.6, 123.3, 126.9, 128.4, 128.6, 128.9, 131.1, 132.0, 136.8, 148.8, 150.1, 164.8 ppm. $C_{17}H_{16}N_2O_2S$ (312.39): calcd. C 65.36, H 5.16, N 8.97; found C 65.40, H 5.14, N 9.01.

4-(3,4-Dimethoxyphenyl)-5-(6-methoxypyrid-3-yl)-2-methylthiazole (30h): Thiazole **30h** was obtained by the typical procedure, from bromothiazole **28** and pyridine **29h**,[25e] in 77% yield as a colourless oil. ^1H NMR ($CDCl_3$): δ = 2.73 (s, 3 H), 3.74 (s, 3 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 6.67 (d, J = 8.3 Hz, 1 H), 6.77 (d, J = 8.3 Hz, 1 H), 6.98−7.03 (m, 2 H), 7.46 (dd, J = 8.7, 2.4 Hz, 1 H), 8.15 (d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 53.5, 55.6, 55.7, 110.6, 110.8, 111.8, 121.4, 139.6, 121.5, 127.3, 147.1, 148.5, 148.6, 149.7, 163.4, 163.8 ppm. HRMS calcd. for $C_{18}H_{18}N_2O_3S$ 342.1038, found 342.1039.

4-(3,4-Dimethoxyphenyl)-5-(1-methylpyrrol-2-yl)-2-methylthiazole (30i): Thiazole **30i** was obtained by the typical procedure, from bromothiazole **28** and 1-methyl-2-(trimethylstannyl)pyrrole (**29i**),[25f] in 89% yield as a colourless oil. ^1H NMR ($CDCl_3$): 2.74

(s, 3 H), 3.16 (s, 3 H), 3.67 (s, 3 H), 3.86 (s, 3 H), 6.21 (dd, J = 5.3, 2.8 Hz, 1 H), 6.29−6.31 (m, 1 H), 6.69 (dd, J = 5.3, 2.0 Hz, 1 H), 6.79 (d, J = 8.3 Hz, 1 H), 6.92 (d, J = 2.0 Hz, 1 H), 7.16 (dd, J = 8.3, 2.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.9, 33.7, 55.1, 55.4, 108.0, 109.8, 110.5, 111.2, 120.0, 120.6, 122.1, 123.0, 127.5, 148.0, 148.1, 150.6, 164.5 ppm. HRMS calcd. for $C_{17}H_{18}N_2O_2S$ 314.1089, found 314.1094.

Typical Procedure for the Oxidative Coupling Reaction. Synthesis of 5,6,9,10-Tetramethoxy-2-methylphenanthro[9,10-*d*]thiazole (24a): A solution of PIFA (139 mg, 0.32 mmol) and $BF_3{\cdot}OEt_2$ (0.08 mL, 0.65 mmol) in CH_2Cl_2 (8 mL) was added at −20 °C (at room temp. for **24f** and at 40 °C for **31h**) to a solution of thiazole **23a** (101 mg, 0.28 mmol) in 5 mL of the same solvent. The mixture was stirred at the same temperature for 40 min, and the solvent was removed in vacuo to provide, after column chromatography (hexanes/EtOAc, 1:1), pure phenanthro-thiazole **24a** (81 mg, 81%) as a solid. M.p. > 300 °C. ^{1}H NMR ($CDCl_3$): δ = 2.94 (s, 3 H), 4.05 (s, 3 H), 4.12 (s, 3 H), 4.13 (s, 3 H), 4.14 (s, 3 H), 7.14 (s, 1 H), 7.76 (s, 1 H), 7.77, (s, 1 H), 8.13 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0, 55.9, 56.0, 103.3, 103.9, 104.7, 105.9, 120.9, 122.1, 122.4, 123.1, 123.4, 148.7, 148.9, 149.0, 163.7 ppm. $C_{20}H_{19}NO_4S$ (369.44): calcd. C 65.02, H 5.18, N 3.79; found C 65.21, H 5.02, N 3.71.

5,6,10-Trimethoxy-2-methylphenanthro[9,10-*d*]thiazole (24b): Phenanthro-thiazole **24b** was obtained by the typical procedure, from thiazole **23b** in 77% yield. M.p. 193−196 °C (hexanes). ^{1}H NMR (CD_3COCD_3): δ = 2.93 (s, 3 H), 3.99 (s, 3 H), 4.03 (s, 3 H), 4.08 (s, 3 H), 7.25 (dd, J = 9.3, 2.4 Hz, 1 H), 7.33 (d, J = 2.4 Hz, 1 H), 8.23 (s, 1 H), 8.15 (s, 1 H), 8.69 (d, J = 9.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.1, 55.4, 55.8, 56.1, 103.3, 104.7, 106.4, 116.1, 121.7, 122.4, 124.7, 127.5, 148.5, 148.9, 149.1, 157.8 ppm. $C_{19}H_{17}NO_3S$ (339.41): calcd. C 67.24, H 5.05, N 4.13; found C 67.44, H 5.00, N 4.21.

5,6-Dimethoxy-2-methylphenanthro[9,10-*d*]thiazole (24c): Phenanthro-thiazole **24c** was obtained by the typical procedure, from thiazole **23c** in 74% yield. M.p. 171−174 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 3 H), 4.13 (s, 3 H), 4.15 (s, 3 H), 7.52−7.63 (m, 2 H), 7.92 (dd, J = 7.0, 1.7 Hz, 1 H), 7.99 (s, 1 H), 8.16 (s, 1 H), 8.54 (dd, J = 8.5, 1.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0, 55.9, 56.1, 103.7, 104.7, 122.9, 123.0, 125.9, 123.9, 126.2, 126.3, 128.1, 129.0, 148.1, 149.0, 149.6, 165.1 ppm. $C_{18}H_{15}NO_2S$ (309.38): calcd. C 69.88, H 4.89, N 4.53; found C 69.81, H 4.72, N 4.29.

5,6-Dimethoxy-2-methyl-9-nitrophenanthro[9,10-*d*]thiazole (24d): Phenanthro-thiazole **24d** was obtained by the typical procedure, from thiazole **23d** in 63% yield. M.p. 244−247 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 3.00 (s, 3 H), 4.17 (s, 3 H), 4.19 (s, 3 H), 7.96 (s, 1 H), 7.98 (d, J = 9.0 Hz, 1 H), 8.17 (s, 1 H), 8.34 (d, J = 9.0 Hz, 1 H), 9.40 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.3, 53.4, 56.3, 103.8, 105.1, 114.0, 119.7, 120.1, 123.6, 124.2, 127.5, 127.8, 145.3, 150.8, 163.4, 172.7 ppm. $C_{18}H_{14}N_2O_4S$ (354.38): calcd. C 61.01, H 3.98, N 7.91; found C 61.11, H 3.82, N 7.81.

2-Amino-5,6,9,10-tetramethoxyphenanthro[9,10-*d*]thiazole (24g): Phenanthro-thiazole **24g** was obtained by the typical procedure, from thiazole **23g** in 83% yield. M.p. 95−97 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 3 H), 4.11 (s, 3 H), 4.12 (s, 3 H), 4.13 (s, 3 H), 5.25 (br. s, 2 H), 6.99 (s, 1 H), 7.79 (s, 1 H), 7.81, (s, 1 H), 7.92 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.0, 56.1, 103.4, 104.2, 104.7, 104.9, 121.4, 121.5, 123.6, 147.9, 148.8, 148.9, 149.1, 164.8 ppm. $C_{19}H_{18}N_2O_4S$ (370.42): calcd. C 61.61, H 4.90, N 7.56; found C 61.51, H 4.68, N 7.41.

8,9-Dimethoxy-2-methylfuro[3,2-*a*]naphtho[4,3-*d*]thiazole (31a): Thiazole **31a** was obtained by the typical procedure, from thiazole **30a** in 64% yield as a colourless oil, after purification by column chromatography (hexanes/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$): δ = 2.97 (s, 3 H), 4.09 (s, 3 H), 4.13 (s, 3 H), 7.24 (d, J = 2.0 Hz, 1 H), 7.45 (s, 1 H), 7.77 (d, J = 2.0 Hz, 1 H), 8.17 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0, 56.0, 56.1, 103.5, 104.7, 106.1, 116.4, 119.6, 120.7, 121.3, 143.8, 145.6, 148.4, 149.5, 163.8 ppm. HRMS calcd. for $C_{16}H_{13}NO_2S_2$ 315.0388, found 315.0381.

8,9-Dimethoxy-2-methylfuro[2,3-*a*]naphtho[4,3-*d*]thiazole (31b): Thiazole **31b** was obtained by the typical procedure, from thiazole **30b** in 68% yield. M.p. 165−168 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 3 H), 4.10 (s, 3 H), 4.13 (s, 3 H), 6.94 (d, J = 2.0 Hz, 1 H), 7.65 (s, 1 H), 7.77 (d, J = 2.0 Hz, 1 H), 8.14 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.0, 56.0, 56.2, 100.2, 104.5, 106.8, 115.3, 115.5, 121.4, 123.2, 143.8, 145.9, 148.4, 149.1, 149.5, 163.3 ppm. $C_{16}H_{13}NO_3S$ (299.35): calcd. C 64.20, H 4.38, N 4.68; found C 64.12, H 4.41, N 4.72.

8,9-Dimethoxy-2-methylthieno[3,2-*a*]naphtho[4,3-*d*]thiazole (31c): Thiazole **31c** was obtained by the typical procedure, from thiazole **30c** in 86% yield. M.p. 171−174 °C (Et_2O). ^{1}H NMR ($CDCl_3$): δ = 2.92 (s, 3 H), 4.07 (s, 3 H), 4.12 (s, 3 H), 7.46 (d, J = 5.3 Hz, 1 H), 7.54 (s, 1 H), 7.80 (d, J = 5.3 Hz, 1 H), 8.07 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9, 55.8, 56.1, 103.8, 104.4, 121.4, 122.3, 122.9, 124.3, 124.7, 128.3, 133.4, 147.3, 148.8, 149.1, 163.4 ppm. $C_{16}H_{13}NO_2S_2$ (315.41): calcd. C 60.93, H 4.15, N 4.44; found C 61.09, H 4.32, N 4.14.

8,9-Dimethoxy-2-methylthieno[2,3-*a*]naphtho[4,3-*d*]thiazole (31d): Thiazole **31d** was obtained by the typical procedure, from thiazole **30d** in 81% yield. M.p. 156−159 °C (hexanes). ^{1}H NMR ($CDCl_3$): δ = 2.96 (s, 3 H), 4.08 (s, 3 H), 4.13 (s, 3 H), 7.40 (s, 1 H), 7.47 (d, J = 5.5 Hz, 1 H), 7.53 (d, J = 5.5 Hz, 1 H), 8.14 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9, 56.0, 56.2, 103.7, 104.6, 120.9, 122.5, 123.4, 125.0, 125.6, 129.1, 134.2, 147.2, 149.3, 149.4, 164.0 ppm. $C_{16}H_{13}NO_2S_2$ (315.41): calcd. C 60.93, H 4.15, N 4.44; found C 61.00, H 4.18, N 4.49.

5,9,10-Trimethoxy-2-methylbenzo[*f*]thiazolo[4,5-*h*]quinoline (31g): Benzoquinoline **31g** was obtained by the typical procedure, from thiazole **30g** as an oil, in 78% yield after purification by column chromatography (hexanes/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$): δ = 2.98 (s, 3 H), 4.12 (s, 3 H), 4.13 (s, 3 H), 4.14 (s, 3 H), 7.02 (d, J = 8.9 Hz, 1 H), 7.82 (s, 1 H), 8.12 (s, 1 H), 8.68 (d, J = 8.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.3, 53.6, 56.0, 56.2, 103.0, 104.6, 110.8, 118.2, 121.7, 123.7, 134.0, 141.1, 149.2, 149.5, 162.2, 168.1 ppm. HRMS calcd. for $C_{18}H_{16}N_2O_3S$ 340.0882, found 340.0893.

6,9,10-Trimethoxy-2-methylbenzo[*h*]thiazolo[5,4-*f*]quinoline (31h): Benzoquinoline **31h** was obtained by the typical procedure, from thiazole **30h** in 86% yield. M.p. 203−206 °C (Et_2O). ^{1}H NMR ($CDCl_3$): δ = 2.94 (s, 3 H), 4.13 (s, 3 H), 4.15 (s, 3 H), 4.18 (s, 3 H), 6.95 (d, J = 8.7 Hz, 1 H), 8.02 (d, J = 8.7 Hz, 1 H), 8.06 (s, 1 H), 8.52 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.1, 53.3, 55.8, 56.2, 103.9, 104.9, 111.2, 116.2, 124.4, 124.7, 136.1, 142.0, 146.4, 148.9, 150.7, 161.6, 164.4 ppm. $C_{18}H_{16}N_2O_3S$ (340.40): calcd. C 63.51, H 4.74, N 8.23; found C 63.41, H 4.67, N 8.21.

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