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Unexplored Vinylic Substituted 5-Benzylidenethiazolidine-2,4-diones: Synthesis and DFT/NMR Stereochemical Assignment

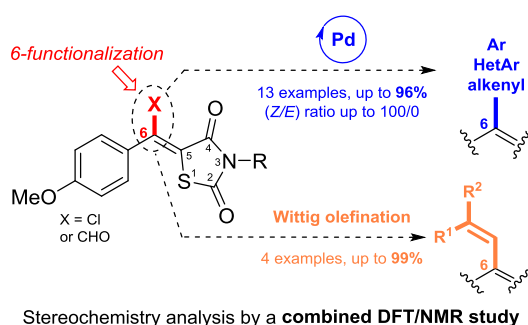
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Abstract. By exploring an efficient and versatile method for the 6-functionalization of its scaffold we investigated the opening of a new chemical space around the benzylidenethiazolidine-2,4-dione (BTZD). The 6-chloro- and 6-formyl BTZD, obtained in two steps starting from 5-lithioTZD were selected as key intermediates and involved in a Pd-catalyzed cross-coupling or Wittig olefination. A variety of aryl, heteroaryl or alkenyl substituents was successfully introduced on the vinylic position of BTZD and particular attention paid to elucidate the stereochemistry of the benzylidene derivatives by using a combined DFT/NMR study.

Graphical Abstract.



Keywords. Benzylidenethiazolidine-2,4-dione, Cross-coupling reaction, Combined DFT/NMR study, Stereochemistry, Wittig olefination, Energy calculations.

Introduction.

5-Benzylidenethiazolidine-2,4-dione (BTZD) **1** is a privileged scaffold¹ present in a wide range of bioactive molecules including antidiabetics,² antivirals,³ anti-inflammatories⁴ or antiproliferative compounds (Figure 1).⁵⁻⁹

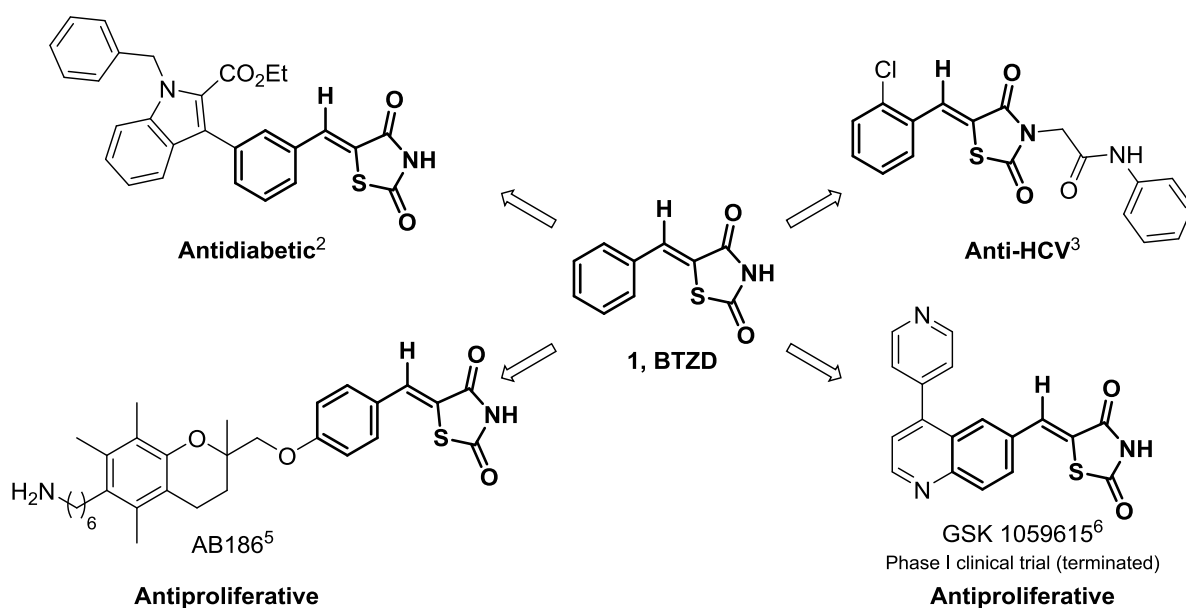
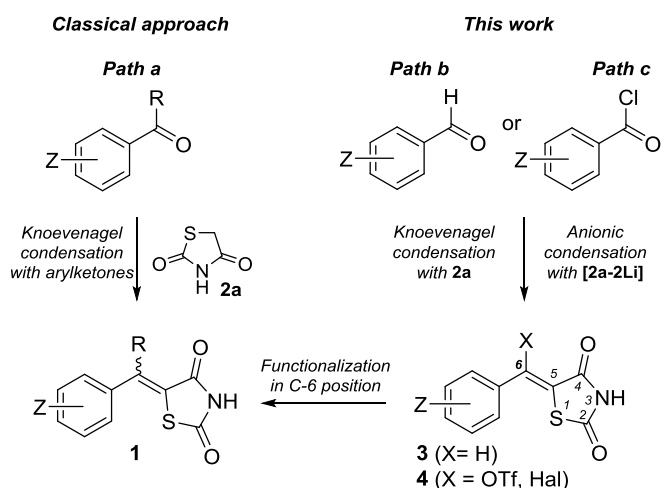


Figure 1. Examples of bioactive compounds bearing a BTZD moiety

To access new bioactive molecules, several modifications to this structure could be envisaged. *N*-alkylations of the TZD core and variation of the aryl moiety of BTZD represent the easiest and most explored methods.¹⁰⁻¹² On the other hand, the vinylic functionalization has rarely been described which is surprising considering the density of the literature dealing with this structure.^{1,10-13} Moreover, the very few reported vinylic modulations of the BTZD moiety resulted from Knoevenagel condensation involving aryl ketones (instead of aldehydes) and a thiazolidine-2,4-dione **2a** (TZD, Scheme 1, path a). This methodology has two main drawbacks. Firstly, the observed yields starting from aryl ketones are much lower than those obtained when starting from aldehydes.^{14,15} Secondly, the Knoevenagel condensation requires a large library of both substituted aryl ketones and TZD to access an important range of

compounds. Our study aimed to overcome such difficulties and we report herein on our work concerning the development of the 6-functionalization of the BTZD scaffold (for numbering, see Scheme 1) which enables the introduction of a wide functional diversity starting from three easily accessible building blocks. We envisaged two main routes to prepare the expected substituted BTZD derivatives **1** (Scheme 1, paths b and c). The first sequence (path b) is based on the 6-unsubstituted BTZDs **3** (X = H) as key-intermediates obtained by the well-known Knoevenagel condensation method using TZD **2a** and various benzaldehydes. Pd-catalyzed cross-coupling reactions are powerful tools for C-C bond formation and so the resulting compounds **3** were then involved in a Heck coupling reaction to obtain the target 6-substituted BTZDs **1**. In addition, we aimed to synthesize 6-activated BTZDs **4** (e.g. X = OTf or Halogen) to involve them in Pd-catalyzed cross couplings such as the Stille or Suzuki reactions (path c). We aimed to achieve the synthesis of the desired derivatives **4** through a condensation of bis-anionic-TZD [**2a-2Li**] with benzoyl chlorides followed by an *O*-activation.

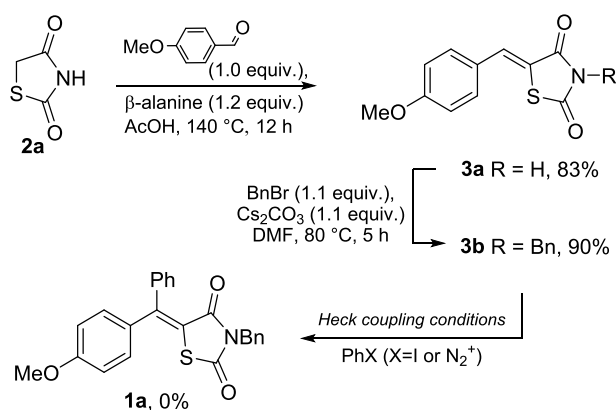
Scheme 1. Synthetic pathways to 6-functionalization of BTZDs **1.**



Results and discussion

For this study, the 3-benzyl-5-(4-methoxybenzylidene)thiazolidine-2,4-dione **3b** was selected as a model (Scheme 2). *O*- and *N*-protections were chosen to avoid side reactions and enable further functionalizations after selective deprotections.¹⁶⁻¹⁸ Thus, the Knoevenagel reaction of TZD **2a** with 4-methoxybenzaldehyde (1.0 equiv.) in the presence of an excess of β -alanine (1.2 equiv.) and in acetic acid as solvent was found to result in the expected BTZD **3a** with an excellent yield (83%).¹⁹ The *N*-benzylation of **3a** was then carried out by using benzyl bromide (1.1 equiv.) in the presence of cesium carbonate Cs₂CO₃ (1.1 equiv.) to give **3b** with an excellent yield (90%). Next, the 6-functionalization of **3b** was investigated by means of the Heck cross-coupling reaction. Unfortunately, despite numerous attempts using a wide range of Heck cross-coupling conditions in the presence of PhX, including the Heck-Matsuda conditions using an aryldiazonium salt as an alternative to aryl iodide,²⁰ no trace of the desired 6-phenyl-BTZD **1a** could be detected (Scheme 2).

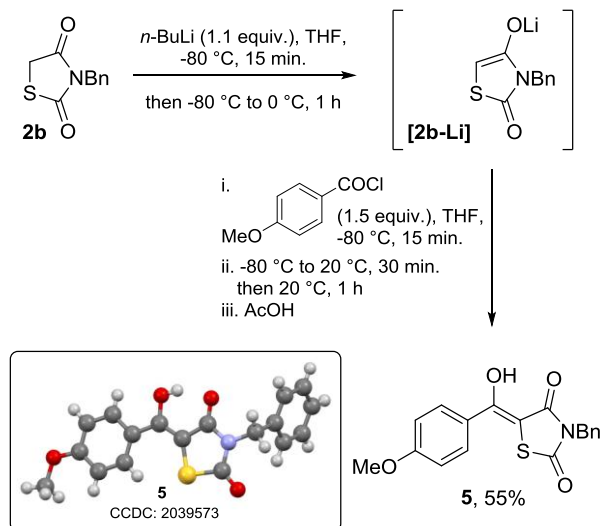
Scheme 2. 6-Functionalization of 3b involving a Heck coupling reaction.



In the light of these results, we envisaged an alternative 6-functionalization sequence starting from the activated BTZD **4**. The latter could be involved in Stille and Suzuki cross-coupling reactions (Scheme 1, path c). To access **4**, the first step was a lithiation of *N*-benzyl TZD **2b**²¹ using a slight excess of *n*-butyllithium (*n*-BuLi, 1.1 equiv.) in tetrahydrofuran (THF).²² The lithium salt [**2b**-Li] was then quenched by adding 4-methoxybenzoyl chloride as an

electrophile. A meticulous optimization of the condensation temperature was achieved to lead to the expected enol **5** with a fair yield (55%, Scheme 3).

Scheme 3. Preparation of the enol 5.



No information has been reported in the literature concerning the stereochemistry of the double bond of the reported structure²² and because the intramolecular hydrogen bond may occur in enol **5**, we assumed that it should be an (*E*)-configuration. Our hypothesis was confirmed by X-ray crystallography analysis which indeed showed the presence of an exocyclic C-C double-bond ($d_{\text{C-C}} = 1.377\text{ \AA}$) with the expected stereochemistry and a planar conjugated system (Scheme 3 and see Supplementary Information Section 1). The tautomeric equilibrium between the enol **5** and the ketone **5'** (Figure 2) was also observed by ¹H-NMR spectroscopy. In CDCl₃ as solvent, the equilibrium was fully displaced in favor of the enol form **5** similarly to the solid-state, while both **5** and **5'** tautomers were identified in more polar solvents. In particular, the α -dicarbonyl hydrogen atom H-5 was clearly observed as a strongly deshielded signal in DMSO-*d*₆, CD₃CN or acetone-*d*₆ (for ¹H-NMR spectra and details see Supplementary Information Section 2).

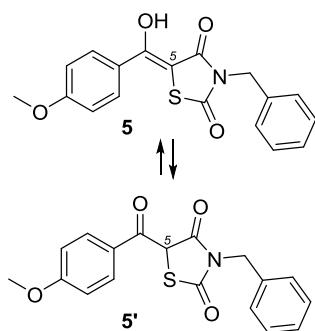
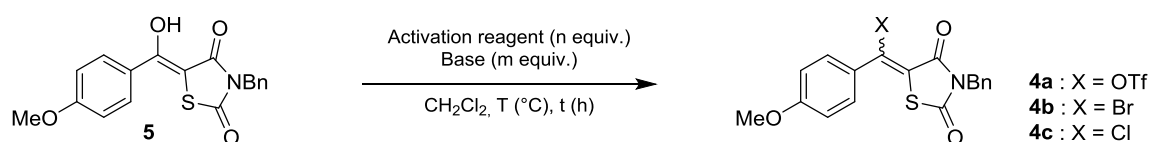


Figure 2. Tautomeric equilibrium 5/5'.

To begin the exploration of the synthetic path c, the synthesis of vinylic (pseudo)halide precursors **4a-c** was investigated (Table 1). Firstly, the reaction carried out with trifluoromethanesulfonic anhydride ($\text{ Tf}_2\text{O}$) in the presence of pyridine as base at 0 °C was unsuccessful since no conversion of **5** was observed (entry 1). A stronger base, *n*-BuLi, at -80 °C was used (entry 2) because the complete deprotonation of the enol **5** could improve the triflate formation. The modification was however disappointing and did not alter the result. Finally, the use of PhNTf_2 was envisaged (entry 3) because it is known to be a more selective *O*-triflation agent than its related anhydride. To enhance the reaction conditions, triethylamine (Et_3N) was used at 0 °C in the presence of a catalytic amount of dimethylaminopyridine (DMAP, 5 mol%). The result was once more disappointing, as no conversion was observed. Therefore, we modified our strategy and focused on the replacement of the hydroxyl group by a halide. Unfortunately, the halogenation reactions using phosphorus trihalide PX_3 ($\text{X} = \text{Cl}, \text{Br}$) and the Appel conditions (PPh_3 and CBr_4) were unsuccessful since **5** was recovered unchanged (entries 4-6). It thus appeared that the use of phosphorus oxyhalide POX_3 ($\text{X} = \text{Cl}, \text{Br}$) was a far more interesting idea. Indeed, when POCl_3 or POBr_3 were used in excess (10.0 equiv., entries 7-8) in the presence of DIPEA, partial conversion of **5** was observed (TLC monitoring). The 6-chloro-BTZD **4c** was isolated after column chromatography in moderate yield (42%) while the purification of its brominated analog led to a complete degradation of **4b**. The use of POCl_3 as both reagent and solvent²³ at 110 °C for 6 to 18 hours allowed for a

significant increase of the yield (entries 9-12). When a large excess of POCl₃ (24.0 equiv.) was used, **4c** was isolated with a good yield (71%, entry 9). However, higher excesses of POCl₃ did not lead to any improvements (60 and 63% yield respectively for 38.0 and 183.0 equiv., entries 10 and 11). Finally, to avoid the partial degradation of the 6-chloro BTZD **4c** during the column chromatography, an *in-situ* distillation of the excess of POCl₃ followed by a classical aqueous work up provided the clean **4c**, according to ¹H NMR, in an almost quantitative yield.

Table 1. Synthesis of **4a-c** precursors starting from the enol **5**.



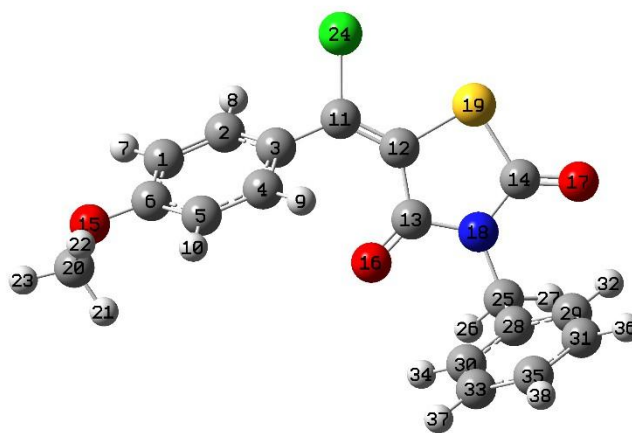
entry	Activation reagent (n equiv.)	Base (m equiv.)	T (°C)	t (h)	Isolated Yield (%) (4a-c)
1	Tf ₂ O (1.4)	Pyridine (6.0)	0	1	0 (4a) ^a
2	Tf ₂ O (1.4)	<i>n</i> -BuLi (1.1)	-80	2	0 (4a) ^{a,b}
3	PhNTf ₂ (1.4), DMAP (0.05)	Et ₃ N (1.4)	0	1	0 (4a) ^a
4	PBr ₃ (1.4)	-	rt ^c	16	0 (4b) ^a
5	PCl ₃ (1.4)	-	rt	16	0 (4c) ^a
6	PPh ₃ , CBr ₄ (1.2)	-	rt	16	0 (4b) ^a
7	POBr ₃ (10.0)	DIPEA (1.7)	rt	3	0 (4b) ^d
8	POCl ₃ (10.0)	DIPEA (1.7)	rt	3	42 (4c)
9	POCl ₃ (24.0)	DIPEA (1.7)	110	6	71 (4c) ^e
10	POCl ₃ (38.0)	DIPEA (1.7)	110	6	60 (4c) ^e
11	POCl ₃ (183.0)	DIPEA (1.7)	110	18	63 (4c) ^e

^aNo conversion. ^bTHF was used as solvent. ^crt: room temperature. ^dPartial degradation and incomplete conversion of **5**. ^ePOCl₃ was used as reagent and solvent. ^fIsolated pure without column purification.

It is noteworthy that **4c** was obtained as a mixture of inseparable isomers (ratio: 69/31 estimated by ¹H NMR based on the crude mixture, see NMR spectra in Supporting Information) while the (*E*)- and (*Z*)-isomer attribution according to NMR spectrum was deemed impossible. To overcome this problem, we computed the theoretical ¹³C NMR spectra for both (*E*)- and (*Z*)-**4c**, using the formalism described by Lodewyk, Jain, Rablen et al.²⁴⁻²⁷ and the Gaussian09 software.²⁸ For this purpose, we focused our study on the ¹H-decoupled ¹³C NMR spectra because of the higher resolution for all the signals, the absence of overlaps and the simple singlet signals when compared to the ¹H NMR spectra. The theoretical spectra were obtained in two steps for all compounds. Firstly a full geometrical optimization at the B3LYP/6-311+G(2d,p) level was performed in a vacuum, ensuring that no imaginary frequency remained. Secondly, a single point energy calculation was performed at the mPW1PW91/6-311+G(2d,p) level using the Gauge-Independent Atomic Orbital (GIAO)^{29,30} method and the universal solvent model (SMD)³¹ with a dielectric constant corresponding to chloroform ($\epsilon = 4.7113$). The raw isotropic nuclear constants obtained in this way were converted into chemical shifts using the adequate approximate linear relationships.²⁷ These data were useless because the simple linear regression following the equation $\delta_{\text{exp}} = f(\delta_{\text{th}})$ did not enable us to satisfactorily discriminate between both stereoisomers (see Supplementary Information Section 3). Therefore, the data had to be interpreted further to enable an isomer attribution. This was done simply by calculating for each carbon of **4c** (*i*) the difference between the experimental chemical shifts of the major and the minor isomers, (*ii*) the difference between the theoretical chemical shifts of the (*Z*)- and (*E*)-isomers. The sign of the product (*i*) \times (*ii*) is relevant and its absolute value was particularly high when dealing with the

carbon atoms around the double bond, such as the carbon atoms numbered C-3, C-11 and C-12 (Table 2). Indeed, the chemical shifts of these carbon atoms are directly influenced by the stereochemistry of **4c**. As a result, for these three carbons, values of $(i) \times (ii)$ were found to be high and positive which is evidence that the theoretical (*Z*)-isomer and the experimental major isomer are in fact the same compound (for full data see Supplementary Information Section 3).

Table 2. Experimental and theoretical ^{13}C NMR data for both isomers of **4c**.



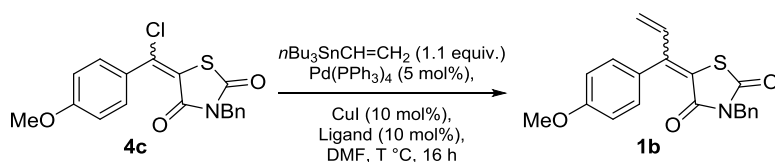
Major isomer (*Z*)-**4c**.

Carbon ^a	δ_{th}^b (ppm)		Δ_{th}	$\delta_{\text{exp}}^{c,d}$ (ppm)		Δ_{exp}	$\Delta_{\text{th}} \times \Delta_{\text{exp}}$
	(<i>Z</i>)- 4c	(<i>E</i>)- 4c		$\delta(\text{Z})_{\text{th}} - \delta(\text{E})_{\text{th}}^b$	Major isomer		
1,5	111.47	112.76	-1.29	113.48	114.36	-0.88	1.14
2,4	131.93	129.76	2.175	131.35	130.17	1.18	2.57
3	125.58	129.60	-4.02	127.16	129.9	-2.74	11.02
6	161.69	161.11	0.58	161.84	162.81	-0.97	-0.56
11	152.59	144.46	8.13	143.55	136.95	6.60	53.66
12	124.67	123.45	1.22	122.38	119.68	2.70	3.29
13	159.86	160.79	-0.93	161.76	161.63	0.13	-0.12
14	166.51	166.31	0.20	166.49	166.42	0.07	0.01

^aAs numbered in the Gaussian09 input file. ^bth = theoretical. ^c ^{13}C NMR spectra realized at 100.6 MHz in CDCl_3 . ^dexp = experimental.

In summary, the chlorination of **5** gave the expected 6-chloro BTZD **4c**, as a 69/31 mixture of (*Z/E*)-isomers in 99 % yield. To reach the target 6-functionalized BTZD **1**, we opted for Stille cross-coupling starting from **4c**. The main results are reported in Table 3 (for the purpose of clarity, we chose to represent the relative positions of Cl and S held by the double-bond of **4c** as in its major form). Firstly, **4c** was reacted at room temperature (rt) for 16 hours in DMF with a slight excess of tri-*n*-butyl(vinyl)stannane (1.1 equiv.) and Pd(PPh₃)₄ (5 mol%). To enhance the reaction yield, CuI³² (10 mol%) and hindered ligands³³ (10 mol%) were added to the reaction medium. A weak result was obtained using these conditions with tricyclohexylphosphine (PCy₃) as the ligand since the expected 6-alkenyl BTZD **1b** was detected by ¹H NMR in the crude reaction mixture in a low estimated ¹H NMR yield (30%) in the presence of starting material **4c** and traces of degradation (¹H NMR yields were determined by using duroquinone as an internal standard). Moreover, only 19% of **1b** were isolated after flash chromatography, revealing the instability of this compound on silica gel (entry 1). A higher reaction temperature (80 °C, entry 2) and the replacement of Pcy₃ by the more hindered and electron-rich (2-biphenyl)di-*tert*butylphosphine (or JohnPhos ligand - entry 3) still gave moderate yields (40 and 50% estimated ¹H NMR yield respectively, 25 and 28% isolated yields). Finally, the optimized conditions were obtained by heating at 100 °C to provide a good yield of **1b** (90% estimated ¹H NMR yield and 59% isolated yield, entry 4).

Table 3. Stille cross-coupling optimization on 4c.



Entry ^a	Ligand	T (°C)	Isolated yield (%) ^b
1	Pcy ₃	rt	19
2	Pcy ₃	80	25

3	JohnPhos	80	28
4	JohnPhos	100	59

^a**4c** was used as a pure mixture of (*Z/E*)-isomers with the ratio 69/31 and was drawn as an isomer mixture (wavy bond). For the purpose of clarity, the representation of the relative positions of Cl and S held by the double-bond of **4c** as in its major form was chosen. By default, the same representation for **1b** was chosen. ^bIsolated yields after silica gel chromatography purification.

Surprisingly, starting from (*Z/E*)-**4c**, **1b** was isolated as a single isomer (for the crude ¹H NMR spectrum see Supplementary Information Section 4) showing a highly deshielded signal at 8.24 ppm in ¹H NMR (CDCl₃, 400 MHz) which was assigned to the H16 hydrogen atom (Figure 3). To explain this level of deshielding, the theoretical chemical shifts for H16 atom in both (*Z*)-**1b** and (*E*)-**1b** were computed by using the above-described calculation method. A significant difference in the theoretical chemical shifts of both isomers was highlighted ($\delta(E)_{\text{th}} = 6.52$ ppm *versus* $\delta(Z)_{\text{th}} = 8.40$ ppm, Figure 2). This level of difference could be attributed to two phenomena - the positioning of H16 inside the anisotropy cone of the TZD carbonyl in (*Z*)-**1b** compared to (*E*)-**1b** and the establishment of a hydrogen bond between this hydrogen atom and the adjacent carbonyl. This kind of unconventional H-bonding between an unactivated C-H moiety and the lone pair of an adjacent double-bonded oxygen was studied by Sureshan et al.³⁴ It should be noted that $\delta(Z)_{\text{th,H16}}$ of **1b** was very close to the experimental value ($\delta_{\text{exp}} = 8.24$ ppm, $\delta_{\text{th}} = 8.40$ ppm), while $\delta(E)_{\text{th,H16}}$ was far more shielded (6.52 ppm) which is in accordance with Sureshan's work. Additional evidence for this (*Z*) stereochemistry of **1b** was that the linear regression, following the equation $\delta_{\text{H,exp}} = f(\delta_{\text{H,th}})$ showed a very good correlation coefficient for the (*Z*)-isomer, while the values were quite lower for the (*E*)-isomer, indicating a lower correlation trend (for details see Supplementary Information Section 3.2). After study of these computed results, the Stille-resulting derivative **1b** was unambiguously assigned to be the (*Z*)-isomer. It should be emphasized that, according

to the CIP rules, the priority of the substituents between (**Z**)-**4c** and (**Z**)-**1b** changed, suggesting an isomerization of the (**Z**)-isomer of **4c** during the Stille reaction. This means that the relative position of substituents on the BTZD double bond in (**Z**)-**4c** and (**Z**)-**1b** was inverted, although the (**Z**)-designation was maintained in both compounds.

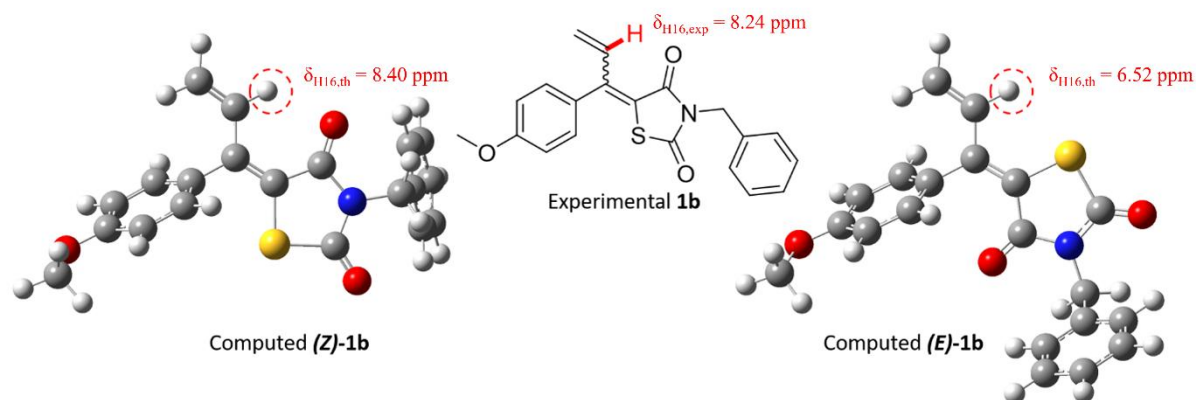


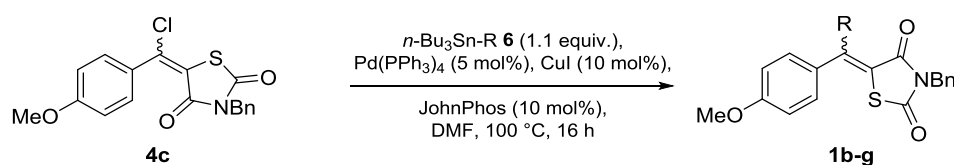
Figure 3. Comparison between the computed chemical shifts for H16 in (**E/Z**)-**1b** and the experimental one.

To explain the high observed stereoselectivity of **1b** we proposed a mechanism based on Visentin et al. work involving the isomerization from dimethylmaleate to dimethylfumarate through an oxo-palladacycle intermediate (for our mechanism proposal, see Supplementary Information Section 5).^{35,36}

Based on the latter results, we extended the scope of the 6-functionalization using various tri-*n*-butylstannane derivatives **6** as Stille coupling partners (see Experimental Section for the preparation of commercially unavailable stannanes **6**). The optimized procedure gave good isolated yields of alkenyl- or (het)aryl derivatives **1b-g** (50-67%, Table 4) except for **1c** (21%, entry 2). As mentioned above, a partial degradation of **1b** was observed during the purification step, even when a reverse phase column was used. In addition to the isolated yield of **1**, we also evaluated the efficiency of the coupling sequence, prior to column chromatography, by directly measuring the yield on the crude mixture using duroquinone as internal reference.³⁷ As a result, such ¹H NMR analyses displayed much better yields for

derivatives **1b,d-e** compared to isolated yields, showing that some degradation occurred on the silica gel (entries 1, 3-4). By contrast, no trace of degradation was observed for **1f-g** (entries 5-6). The (*Z/E*) ratio of **1b-g** was next investigated by using quantum chemical calculations previously described for **4c** or **1b** (for details see Supplementary Information Section 3). As for vinyl-BTZD **1b**, allyl analogue **1c** was found as a single (*Z*)-isomer concerning the BTZD moiety, while the stereochemistry of the introduced protected allylamine was found to be unchanged, as evidenced by the coupling constant ($J = 15.6$ Hz, see Experimental Section). Regarding the (*Z/E*) ratio of the (hetero)aromatic compounds **1d-g**, partial changes were observed compared to ratio of **4c**.

Table 4. Extended Stille cross-coupling conditions.



Entry ^a	Product	R	Yield (%)	
			isolated (NMR) ^b	(<i>Z/E</i>) ratio ^c
1	1b		59 (90)	100/0
2	1c		21 (30)	100/0
3	1d		60 (95)	45/55
4	1e		50 (76)	86/14
5	1f		67 (69)	48/52
6	1g		59 (60)	58/42

4c was used as a pure mixture of (*Z/E*)-isomers with the ratio 69/31. For the purpose of clarity, the representation of the relative positions of the double-bond substituents was depicted as in its major form except for **1e** and **1g**.^b Yields were determined by ¹H NMR using duroquinone as an internal standard. ^c(*Z/E*) ratio was determined by ¹H NMR based on the crude mixture.

A main drawback of the Stille reaction conditions is the use of toxic tin reagents,³⁸ which are difficult to get rid of and need fastidious purifications. On the opposite, Suzuki cross-coupling,^{39,40} frequently used in pharmaceutical industry,⁴¹ is a related reaction that involves organoboron compounds which are often easier to remove and show low toxicities. To assess the efficiency of this reaction, **4c** was involved in a Suzuki cross-coupling (Table 5). Firstly, common conditions were explored using the (4-formylbenzene)boronic acid as coupling partner and Pd(PPh₃)₄ (5 mol%) as a catalyst in toluene/EtOH/water (6:3:2 v/v) which allowed the complete dissolution of **4c**, at 50 °C, in the presence of sodium carbonate (Na₂CO₃, entry 1). The observed result was quite disappointing with only 33% of 6-formylphenyl-BTZD **1h** (measured yield by ¹H NMR) in the presence of unchanged **4c**. Using twice the initial amount of Na₂CO₃ led to a slight yield improvement of **1h** (39%, entry 2), while the replacement of Na₂CO₃ by K₂CO₃ or KF showed no significant effect on the result (31 and 30% respectively, entries 3 and 4). When the solvent mixture (toluene/EtOH/water) was replaced by DMF/H₂O (1:1 v/v), no trace of **1h** was detected and the substrate **4c** was recovered unchanged (entry 5). The use of an additional ligand (PPh₃ or XPhos, 10 mol%) only resulted in poor results (9 and 10% ¹H NMR yield respectively, entries 6, 7). Next, a few catalysts were assessed as a replacement of Pd(PPh₃)₄ (entries 8-11). The use of the 2nd generation Buchwald catalyst PdXPhos G2 gave rise to a by-product **7a** (17% ¹H NMR yield, entry 8), while no increase in yield of **1h** was observed. According to MS and NMR spectra, **7a** was suggested to result from the addition of the co-solvent EtOH on the chlorinated position in **4c**. In contrast, very good results were observed by using Pd(dppf)Cl₂ as catalyst. In this case, the conversion of **4c** was almost complete and **1h** was obtained in 92% ¹H NMR yield in the presence of traces of **7a** (5% ¹H NMR yield, entry 9). We next studied the influence of the reactional temperature.

Firstly, when the temperature of initial conditions was increased to 110 °C, the yield of **1h** was significantly improved (33 vs 67% ¹H NMR yield, entries 1 and 10 respectively). Nevertheless, the byproduct **7a** was also obtained with an increased yield (33% ¹H NMR yield). Finally, the best conditions were based on the conditions stated in entry 9, by using Pd(dppf)Cl₂ as a catalyst to reduce the formation of **7a**, and at 110 °C to enhance the yield of **1h** (entry 11). As a result, and according to TLC monitoring, the expected 6-formylphenyl-BTZD **1h** was obtained after only 3 hours in quantitative ¹H NMR yield without any trace of **7a**.

Table 5. Optimization of the Suzuki cross-coupling on 4c.

Entry ^a	Pd-catalyst	Base	Ligand	T (°C)	t (h)	¹ H-NMR Yield, % ^b	
						1h	7a
1	Pd(PPh ₃) ₄	Na ₂ CO ₃ ^c	-	50	18	33	0
2	Pd(PPh ₃) ₄	Na ₂ CO ₃ ^{c,d}	-	50	18	39	0
3	Pd(PPh ₃) ₄	Cs ₂ CO ₃ ^c	-	50	18	31	0
4	Pd(PPh ₃) ₄	KF ^c	-	50	18	30	0
5 ^e	Pd(PPh ₃) ₄	Na ₂ CO ₃ ^c	-	50	18	0	0
6	Pd(PPh ₃) ₄	Na ₂ CO ₃ ^c	PPh ₃	50	18	9	0
7	Pd(PPh ₃) ₄	Na ₂ CO ₃ ^c	XPhos	50	18	10	0
8	PdXPhos G2	Na ₂ CO ₃ ^c	-	50	18	27	17
9	Pd(dppf)Cl ₂	Na ₂ CO ₃ ^c	-	50	18	92	5
10	Pd(PPh ₃) ₄	Na ₂ CO ₃ ^c	-	110	18	67	33
11	Pd(dppf)Cl ₂	Na ₂ CO ₃ ^c	-	110	3 ^f	100	0

^a**4c** was used as a pure mixture of (*Z/E*)-isomers with the ratio 69/31. For the purpose of clarity, the representation of the relative positions of the double-bond substituents was depicted as in its major form. ^bYields were determined by ¹H NMR using duroquinone as internal standard.


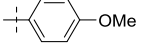
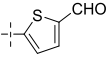

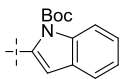
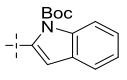
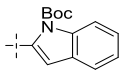


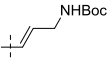
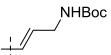
^c1 M aqueous solution. ^d3.0 equiv. of base. ^eReaction solvent: DMF/H₂O. ^fTime of completion.

We next extended the scope of the Suzuki coupling to various boronic acid and esters (Table 6). Derivative **1h** was thus prepared as previously stated (Table 5, entry 11) and isolated in an excellent 96% yield as a pure compound after classical washing work up without further purification. The (*Z/E*) ratio of **1h** was assigned as a 63/37 mixture by using quantum chemical calculations as previously described for **4c** (for details see Supplementary Information Section 3.8). It should be noted that, considering the CIP rules, the major stereoisomer of **1h** identified as (*Z*)-**1h** holds the same double bond geometry as (*E*)-**4c**, the minor stereoisomer of the substrate **4c**. Functionalization of BTZD moiety using phenyl- or *p*-methoxyphenylboronic acids as coupling partners also gave good results. **1a,i** were prepared with a very good ¹H-NMR yield (90 and 76% respectively, entries 2 and 3) but showed a lower isolated yield (76 and 49% isolated yields respectively) because of partial degradation upon silica gel purification and the formation of the by-product **7a**. The introduction of heteroaryl units was explored using thienyl-, indolyl- or pyridinylboronic acids (entries 4-6, and 9). With EtOH as the co-solvent, the expected thienyl derivatives **1j-k** were obtained in quite modest isolated yields (26 and 29% respectively) while **7a** was found to be the main product (62 and 58% isolated yields respectively) which highlights the low reactivity of these two thienylboronic acids in these cross-coupling conditions. The case of the reaction leading to **1l** when using *N*-Boc-indolylboronic acid as the coupling partner was far more critical in that no trace of this product was detected (entry 6, quantitative yield for **7a**). In contrast, the preparation of (2-fluoropyridin-3-yl) compound **1m** occurred efficiently with a good 61% isolated yield (entry 9) but still with a significant amount of **7a** (35% isolated yield). To reduce the formation of **7a** and increase the yield of expected compounds **1**, the replacement of EtOH by a more hindered alcohol was investigated. The use of *isopropanol* (*i*-PrOH) as the co-solvent was found to have a very low effect on the preparation of the indolyl derivative **1l**, since **7b** remained the main product (90% isolated yield) with only 10% of **1l** (¹H NMR yield,

entry 7). In more efficient conditions, the use of *t*-butanol (*t*-BuOH) enables **1l** to be obtained with an impressive increased ¹H NMR yield (61%) which was successfully isolated as a pure mixture of (*Z*)- and (*E*)-isomers (54% isolated yield, *Z*/*E*: 30/70, entry 8). Moreover, as expected, no trace of **7c** resulting from the addition of *t*-BuOH to **4c** was detected. In pyridine series, the replacement of EtOH by *i*-PrOH afforded **1m** in a drastically increased yield (91 and 85% ¹H NMR and isolated yields respectively, entry 10) without any trace of **7b**. Finally, in order to compare the efficiency of the Stille and the Suzuki cross-couplings, a preparation of aminoallylic derivative **1c** was examined by involving the pinacolboronic ester⁴² (**E**)-**8**. According to the optimized conditions, **1c** was prepared with very good yields depending on the nature of the alcohol co-solvent (66 and 71% isolated yields, entries 11 and 12) while only 21% of **1c** were obtained by using the Stille coupling (entry 2, table 4). It should be noted that no trace of adduct **7a** or **7c** was detected whether with EtOH or *t*-BuOH. As well as with the Stille reaction, **1c** was isolated as a single (*Z*)-isomer on the exocyclic TZD unsaturation (for the crude NMR spectrum see Supporting Information Section 4) while the stereochemistry of the introduced protected allylamine was also unchanged. Overall, Suzuki cross-coupling allowed the preparation of various 6-aryl or heteroaryl BTZD **1a,c,h-m** in modest to excellent isolated yields (up to 96%) and the use of a more hindered alcohol as co-solvent seems to allow an easier formation of **1**.

Table 6. Extended Suzuki cross-coupling conditions to various boronic derivatives.

Entry ^a	R ¹	R ²	R ³	Isolated (NMR) Yield, % ^b		
				Product	(<i>Z</i> / <i>E</i>) ratio ^c	by-product 7
1		H	Et	1h, 96 (100)	63/37	7a, 0

2		H	Et	1a, 76 (90)	72/28	7a, 10
3		H	Et	1i, 49 (76)	- ^d	7a, 24
4		H	Et	1j, 26 (38)	ND ^e	7a, 62
5		H	Et	1k, 29 (42)	50/50	7a, 58
6		H	Et	1l, 0 (0)	- ^f	7a, 100
7		H	<i>i</i> -Pr	1l, 0 (10)	27/73	7b, 90
8		H	<i>t</i> -Bu	1l, 54 (61)	30/70	7c, 0
9		H	Et	1m, 61 (65)	NA ^g	7a, 35
10		H	<i>i</i> -Pr	1m, 85 (91)	NA ^h	7b, 0
11		Bpin ⁱ	Et	1c, 66 (75)	100/0	7a, 0
12		Bpin ⁱ	<i>t</i> -Bu	1c, 71 (90)	100/0	7c, 0

^a**4c** was used as a pure mixture of (*Z/E*)-isomers with the ratio 69/31. For the purpose of clarity, the representation of the relative positions of the double-bond substituents was depicted as in its major form. ^bYields were determined by ¹H NMR using duroquinone as internal standard. ^c(*Z/E*) ratio was determined by ¹H NMR based on the crude mixture. ^dNo stereochemistry around this double-bond. ^eNot determined because of overlapping of signals. ^fNo product obtained. ^gNA: non-attributed ratio: 81/19. ^hNA: non-attributed ratio: 85/15. ⁱBPIn = pinacolboronate.

Having obtained these results, our next step was to rationalize the selectivity of the reaction for each of these products. To this end, we computed the $\Delta_r H^0$ of the isomerization of **1a-m** from the (*E*)- to the (*Z*)-isomer. This was carried out on Gaussian09²⁸ by the means of a full geometrical optimization followed by a frequency calculation (T = 373.15K, P=1atm) with the DFT functionals B3LYP, M06-2X⁴³ or wB97X-D⁴⁴ and the universal solvent model (SMD)³¹ with a dielectric constant corresponding to toluene ($\epsilon = 2.3741$) or DMF ($\epsilon = 37.219$). The obtained enthalpies were then transformed into (*Z/E*) ratio using the Boltzmann equation (see Supplementary Information Section 7). The results of these calculations were in

good agreement with the stereoselectivity obtained for the products, especially with the recommended level ω B97X-D/Def2TZVP,⁴⁵ even if the ratios of **1d**, **1f** and **1g** were less accurate than the others (Figure 4).

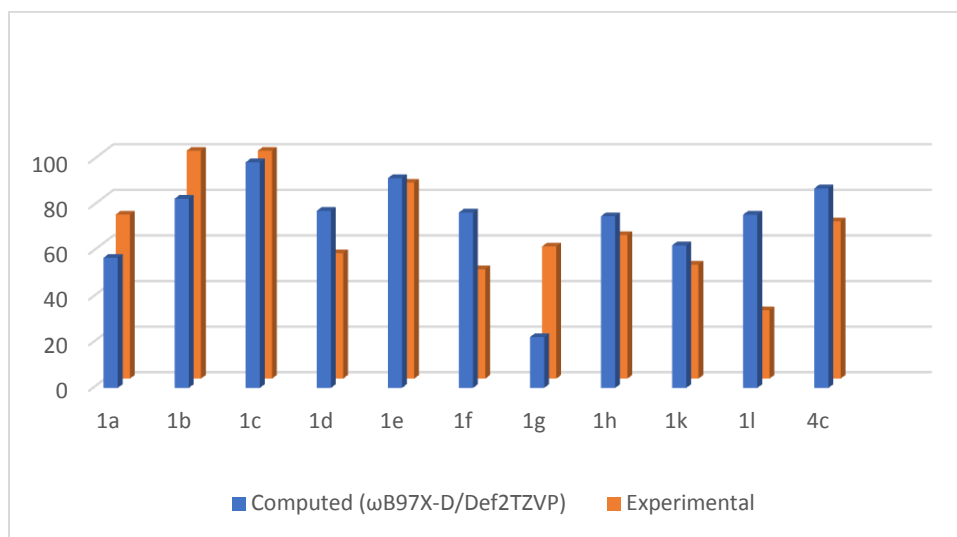
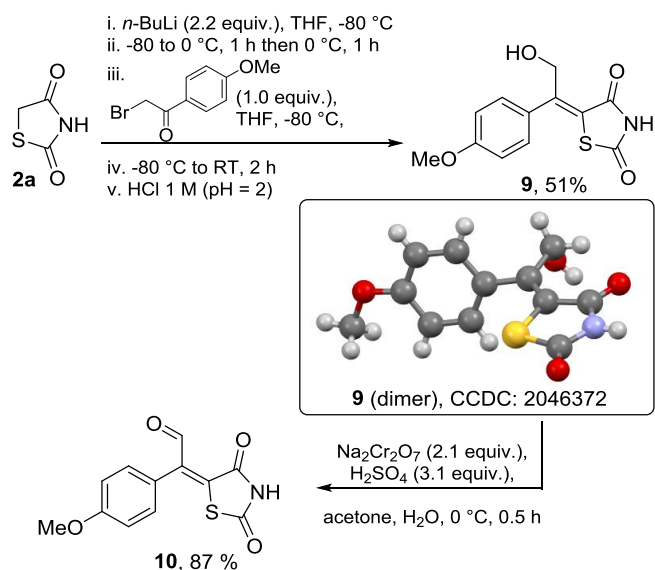


Figure 4. Comparison between the computed and experimental (*Z*) fraction of the BTZD products.

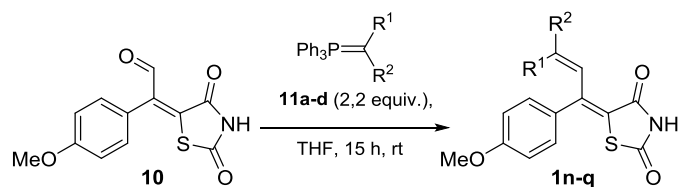
Finally, a totally different strategy was explored involving a Wittig olefination as key step for the preparation of 6-alkenyl BTZD derivatives. The hydroxymethyl BTZD **9** was synthesized with a fair 51% yield by electrophile trapping of the dilithiothiazolidine-2,4-dione [**2a-2Li**] with 2-bromo-*para*-methoxyacetophenone (1.0 equiv.) in THF (Scheme 4).⁴⁶ The (*E*)-stereochemistry was attributed to compound **9** through X-ray diffraction analysis (see Supplementary Information Section 1). The chemo-controlled oxidation by sodium dichromate of **9**⁴⁷ afforded the expected aldehyde **10** in 87% yield.

Scheme 4. Synthesis of the target aldehyde **10**.



Next, the Wittig olefination of **10** with phosphonium ylides **11a-d** in THF at rt for 15 hours (see Experimental Section for the preparation of phosphonium ylides) successfully led to the desired 6-alkenyl BTZD **1n-q** with good to excellent isolated yields (56 to 99% isolated yield, Table 7). The stereochemistry of **1n-q** was assigned as a single (*E*)-stereoisomerism for the formed alkenyl double bond according to the ¹H NMR coupling constants (*J*~16 Hz) and as a single (*Z*)-stereoisomerism for the benzylidene double bond by using the previously described method for **1b** and comparing quantum chemical calculations to experiment NMR values (for details see Supplementary Information Section 3).

Table 7. Synthesis of 6-alkenyl BTZD 1n-q.



Entry	Product	Isolated Yield, %
1	1n , R ¹ = H, R ² = CO ₂ Me	99
2	1o , R ¹ = H, R ² = COMe	56
3	1p , R ¹ = Me, R ² = CO ₂ Me	76

Conclusion.

In this paper, we have proposed two strategies including a Pd-catalyzed coupling reaction or a Wittig olefination as key-steps to prepare a library of 6-aryl-, heteroaryl- or alkenyl BTZD scaffolds **1a-m** and **1n-q**. After the development of the synthesis of the chlorinated precursor **4c**, the 6-functionalization of BTZD was proved more efficient using the Suzuki cross-coupling than the Stille reaction. Particular care was taken to assign the stereochemistry of those derivatives **1a-m** through a combined experimental/DFT-simulated NMR spectra methodology. On the other hand, the Wittig reaction led to the targeted 6-alkenyl BTZD **1n-q** with excellent yields and with a high stereoselectivity since only the (2*E*,4*Z*)-diastereoisomers were detected. With this work, we have opened up a new unexplored chemical direction and hope that this will pave the way for the discovery of new bioactive BTZD compounds.

Experimental Section.

All reactions were performed under argon atmosphere. Melting points (M.p.) were measured on a Kofler bench and were uncorrected. ¹H, ¹³C and ¹⁹F NMR spectroscopic data were recorded on a Bruker Advance III 200 (200, 50.3 and 188.2 MHz respectively), a Bruker Advance III 400 (400, 100.6 and 376.4 MHz respectively) or a Bruker Advance III HD 300 (300.1 and 75.5 MHz respectively). Chemical shifts were reported in ppm (δ) and were measured related to the signals for the residual solvents⁴⁸ or the signal for CFC₃ for ¹⁹F.⁴⁹ The NMR quantification were carried out in the presence of an internal standard (duroquinone TraceCERT[®] for spectra recorded in CDCl₃). (*Z/E*) ratios of compounds were estimated by ¹H NMR based on the crude mixture. Note that variation of this (*Z/E*) ratio could be observed after purification step, consequently, NMR spectra given in Supplementary Information could

display a modified ratio. High resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOFq ESI/QqTOF apparatus and low-resolution spectra in electronic impact (GC-EI) were recorded on a Shimadzu QP2010 coupled with a gas chromatography apparatus equipped with a DB5-MS UI column (length: 30 m, width: 0.25 mm, thickness of the film: 0.25 μm). Infrared spectra (IR) were recorded on a Shimadzu IRAffinity-1 equipped with an ATR PIKE Technologies model gladiAT. Heat-On™ block systems were used for reaction that required heating. Reaction completion was checked by TLC using 60 F₂₅₄ or 60-RP-18 F₂₅₄S (Merck) plates and were revealed with UV light (254 nm). Flash column chromatography were achieved on a Grace Reveleris® equipped with 40 μm silica or C₁₈-grafted silica cartridges. Anhydrous THF and MeOH were freshly collected on a MBRAUN MB-SPS-800 solvent purification system. Dichloromethane was distilled over CaH₂ and stocked on 4 Å molecular sieve. DMF was also stocked on 4 Å molecular sieve. *n*-BuLi was used as a commercial 1.6 M solution in hexanes (always titrated prior to use). Other commercial reagents were used without further purification.

3-Benzylthiazolidine-2,4-dione (2b): To a solution of thiazolidine-2,4-dione **2a** (TZD, 5.00 g, 42.69 mmol) in DMF (150 mL) were added K₂CO₃ (11.80 g, 85.38 mmol) and BnBr (5.60 mL, 46.96 mmol). The reaction mixture was stirred 3 hours at room temperature. After filtration of the suspended solid, the filtrate was diluted with EtOAc (360 mL), washed with water (3 \times 300 mL) then with an aqueous saturated solution of NaCl (300 mL). The aqueous layer was saturated using NaCl and extracted with EtOAc (3 \times 20 mL). The organic layers were combined and were dried (MgSO₄), the solvents were removed under reduced pressure. After purification by flash column chromatography (eluent: cyclohexane/EtOAc 100/0 to 20/80 in 20 minutes, then isocratic mode for 20 minutes) the expected benzylated TZD **2b** was obtained as a white powder (6.64 g, 32.0 mmol, 75%). ¹H NMR (CDCl₃, 400 MHz) δ

7.45-7.27 (m, 5H, H_{Ar}) , 4.77 (s, 2H, CH₂Ph), 3.94 (s, 2H, CH₂). Other analyses were in accordance with the literature.²¹

(Z)-5-(4-Methoxybenzylidene)thiazolidine-2,4-dione (3a): To a suspension of TZD **2a** (2.00 g, 17.09 mmol) in AcOH (40 mL) were added β-alanine (1.82 g, 20.51 mmol) and 4-methoxybenzaldehyde (2.33 g, 17.09 mmol). The reaction mixture was heated at 140 °C for 12 hours, allowed to come back to room temperature and filtered. The precipitate was washed with a water/AcOH 1/1 mixture (3 × 48 mL) and dried under vacuum to yield **3a** as a yellow powder (3.335 g, 14.18 mmol, 83%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.70 (s, 1H, CH), 7.51 (d, 2H, *J* = 8.7 Hz, H_{Ar}), 7.06 (d, 2H, *J* = 8.7 Hz, H_{Ar}), 3.81 (s, 3H, CH₃) Other analyses were in accordance with the literature.⁵⁰

(Z)-3-Benzyl-5-(4-methoxybenzylidene)thiazolidine-2,4-dione (3b): To a solution of **3a** (5.00 g, 21.52 mmol) in DMF (50 mL) were added Cs₂CO₃ (7.69 g, 23.60 mmol) and BnBr (2.80 mL, 23.65 mmol). The reaction mixture was heated at 80 °C for 5 hours and then diluted with EtOAc (75 mL). The obtained precipitate was filtered and the filtrate was washed with water (3 × 50 mL). The organic layer was dried (MgSO₄) and the solvents were removed under vacuum. After evaporation, the yellow powder was suspended in a minimal amount of EtOAc and filtered to give **3b** as a yellow powder (6.29 g, 19.35 mmol, 90%). ¹H NMR (CDCl₃, 200 MHz) δ 7.86 (s, 1H, CH), 7.52-7.27 (m, 7H, H_{Ar}), 6.98 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 4.90 (s, 2H, CH₂), 3.86 (s, 3H, CH₃). Other analyses were in accordance with the literature.¹⁹

(E)-3-Benzyl-5-(hydroxy(4-methoxyphenyl)methylene)thiazolidine-2,4-dione (5): To a solution of **2b** (6.00 g, 28.95 mmol) in THF (60 mL) was added dropwise at -80 °C *n*-BuLi (1.6 M in hexanes, 19.9 mL, 31.8 mmol). After stirring for 15 minutes, the reaction was allowed to warm to 0 °C over 1 hour, then cooled again at -80 °C. 4-Methoxybenzoyl chloride (5.87 mL, 43.3 mmol) was then added dropwise, while maintaining the temperature at -80 °C

for 15 minutes. It was allowed to warm up to room temperature over 30 minutes and the temperature was hold for 1 additional hour. The reaction was then quenched with AcOH (3 mL) and the solvents were removed under reduced pressure. The obtained yellow gum was rinsed twice with cold MTBE, yielding **5** as a yellow powder (2.70 g, 7.91 mmol, 55%). M.p. 134-136 °C. IR (ATR): ν (cm⁻¹) 3011, 1732, 1668, 1256. ¹H NMR (CDCl₃, 400 MHz) δ 13.22 (s, 1H, OH), 7.76-7.71 (m, 2H, H_{Ar}), 7.47-7.28 (m, 5H, H_{Ar}), 7.01-6.95 (m, 2H, H_{Ar}), 4.90 (s, 2H, CH₂), 3.87 (s, 3H, CH₃O). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 170.6 (C_{quat}), 168.1 (C_{quat}), 165.5 (C_{quat}), 162.6 (C_{quat}), 135.3 (C_{quat}), 129.9 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.3 (CH_{Ar}), 124.9 (C_{quat}), 114.4 (CH_{Ar}), 92.9 (C_{quat}), 55.6 (CH₃), 44.8 (CH₂). HRMS-ESI (pos. mode) m/z : [M+Na]⁺ Calcd for C₁₈H₁₅NO₄SNa 364.0614; Found 364.0644.

(Z/E)-3-Benzyl-5-(chloro(4-methoxyphenyl)methylene)thiazolidine-2,4-dione (4c): To a solution of **5** (2.19 g, 6.41 mmol) in POCl₃ (14.70 mL) was added DIPEA (1.90 mL, 10.91 mmol). The reaction mixture was heated at 110 °C for 6 hours, then POCl₃ was distilled off at 110 °C under reduced pressure. The obtained brown residue was diluted with EtOAc (150 mL), washed with water (3 × 100 mL) and with a saturated aqueous solution of NaCl (100 mL). The organic layer was dried (MgSO₄) and the solvents were removed under reduced pressure, yielding the **(Z)-enriched 4c** as a brown oil (2.28 g, 6.35 mmol, 99%, *Z/E* ratio = 69/31). IR (ATR): ν (cm⁻¹) 2837, 1736, 1676, 1256. ¹H NMR (CDCl₃, 400 MHz) δ 7.56-7.50 (m, 2x2H, H_{Ar}), 7.50-7.27 (m, 2x5H, H_{Ar}), 6.97-6.90 (m, 2x2H, H_{Ar}), 4.88 and 4.78 (2s, 2x2H, CH₂), 3.86 (s, 2x3H, CH₃O). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 166.5 (C_{quat}), 166.4 (C_{quat}), 162.8 (C_{quat}), 161.8 (2 peaks, C_{quat}), 161.6 (C_{quat}), 143.6 (C_{quat}), 136.9 (C_{quat}), 135.2 (2 peaks, C_{quat}), 131.4 (CH_{Ar}), 130.2 (CH_{Ar}), 129.9 (C_{quat}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (2 peaks, CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.2 (C_{quat}), 122.4 (C_{quat}), 119.7 (C_{quat}), 114.4 (CH_{Ar}), 113.5 (CH_{Ar}), 55.6 (CH₃), 55.5 (CH₃), 45.3 (2 peaks, CH₂). HRMS-ESI (pos. mode) m/z : [M+Na]⁺ Calcd for C₁₈H₁₄ClNO₃SNa 382.0275; Found 382.0290.

General procedure for Stille cross-coupling: To Pd(PPh₃)₄ (0.032 g, 0.028 mmol) and CuI (0.010 g, 0.056 mmol) were added a solution of **4c** (0.200 g, 0.555 mmol) in DMF (2 mL), JohnPhos ligand (0.016 g, 0.056 mmol) and a solution of the appropriate tri-*n*-butylstannane **6** (0.610 mmol) in DMF (2 mL). The reaction mixture was heated at 100 °C for 16 hours then allowed to cool down at room temperature and was diluted with EtOAc (25 mL). A 1 M aqueous solution of KF (20 mL) was added, the obtained biphasic mixture was vigorously stirred for 5 minutes and filtered over a Celite[®] pad. The organic layer was washed with water (3 × 25 mL) and with an aqueous saturated solution of NaCl (25 mL), dried (MgSO₄) and the solvents were removed under reduced pressure. The afforded brown residue was dissolved with acetonitrile (CH₃CN) (20 mL), washed with *n*-hexane (2 × 20 mL) and CH₃CN was evaporated under reduced pressure.

(Z)-3-Benzyl-5-(1-(4-methoxyphenyl)allylidene)thiazolidine-2,4-dione (1b): This compound was prepared according to the general procedure for the Stille reaction starting from the commercial tri-*n*-butyl(vinyl)stannane. After CH₃CN evaporation, the residue was purified by flash chromatography on neutral alumina (eluent: cyclohexane/EtOAc 100/0 to 95/5 in 20 minutes then isocratic mode for 10 minutes) yielding **(Z)-1b** (pure *(Z)*-isomer) as a yellow oil (0.115 g, 0.327 mmol, 59%). IR (ATR): ν (cm⁻¹) 2926, 1732, 1668, 1246. ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (dd, *J* = 17.2 Hz, *J* = 10.6 Hz, 1H, CH=CH₂), 7.47-7.42 (m, 2H, H_{Ar}), 7.37-7.27 (m, 3H, H_{Ar}), 7.16 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.95 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 5.60 (dd, *J* = 10.6 Hz, *J* = 1.4 Hz, 1H, CH=CH_{cis}H), 5.21 (dd, *J* = 17.2 Hz, *J* = 1.4 Hz, 1H, CH=CH_{trans}H), 4.85 (s, 2H, CH₂), 3.85 (s, 3H, OCH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 167.9 (C_{quat}), 164.5 (C_{quat}), 160.4 (C_{quat}), 149.8 (C_{quat}), 135.6 (C_{quat}), 134.3 (CH₂=CH), 130.2 (CH_{Ar}), 129.6 (C_{quat}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.2 (CH_{Ar}), 126.3 (CH₂=CH), 122.5 (C_{quat}), 114.3 (CH_{Ar}), 55.4 (CH₃), 44.8 (CH₂); (the NMR spectra showed slight excess of

aliphatic signal, attributed to *n*-Bu₃SnCl). HRMS-ESI (pos. mode) *m/z*: [M+Na]⁺Calcd for C₂₀H₁₇NO₃SNa 374.0821; Found 374.0827.

***tert*-Butyl ((2*E*,4*Z*)-4-(3-benzyl-2,4-dioxothiazolidin-5-ylidene)-4-(4-methoxyphenyl)but-2-en-1-yl)carbamate (**1c**):**

*Preparation of tert-butyl (E)-(3-(tri-*n*-butylstannyl)allyl)carbamate (6a).*⁵¹ To a suspension of CuCN (0.58 g, 6.44 mmol) in THF (20 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 8.5 mL) at -80 °C. After stirring for 10 minutes, *n*-Bu₃SnH (3.66 mL, 13.59 mmol) was added dropwise. After 15 minutes, a solution of *N*-Boc-propargylamine (1.00 g, 6.44 mmol) in THF (3 mL) was slowly added. After 2 hours at -80 °C, the reaction was quenched by the addition of a buffered NH₄OH/NH₄Cl solution (20 mL). The reaction mixture was diluted with EtOAc (50 mL), washed with water (3 × 30 mL) and with an aqueous saturated solution of NaCl. The organic layer was dried (MgSO₄) and the solvents were removed under reduced pressure. After flash column chromatography (eluent: cyclohexane/EtOAc 100/0 for 20 minutes then to 95/5 in 20 minutes) **6a** was afforded as a colourless oil (0.975 g, 2.18 mmol, 34%). ¹H NMR (CDCl₃, 400 MHz): δ 0.85-0.91 (m, 15H, SnCH₂, CH₃), 1.24-1.35 (m, 6H, CH₂CH₃), 1.39-1.52 (m, 15H, CH₂CH₂CH₃, *t*-Bu), 3.78 (br s, 2H, CH₂NH), 4.59 (br s, 1H, NH), 5.92-6.00 (m, 1H, CH₂-CH=CH), 6.05-6.12 (m, 1H, CH=CH). Other analyses were in accordance with the literature.⁵²

The compound **1c** was prepared according to the general procedure for the Stille reaction with the tri-*n*-butylstannane **6a**. After CH₃CN removal, the residue was purified by flash column chromatography in reverse phase (eluent: H₂O/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 20 minutes). The expected derivative (**Z**)-**1c** (pure (**Z**)-isomer) was obtained as a yellow solid (0.056 g, 0.116 mmol, 21%). M.p. 83-85 °C. IR (ATR): ν (cm⁻¹) 3348, 2972, 1722, 1668, 1248. ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (td, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H, CH=CH-CH₂), 7.46-7.26 (m, 5H, H_{Ar}), 7.12 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.94 (d, *J* = 8.7

Hz, 2H, H_{Ar}), 5.68 (td, $J = 15.6$ Hz, $J = 5.7$ Hz, 1H, CH=CHCH₂), 4.84 (s, 2H, CH₂Ph), 4.66 (br s, 1H, NH), 3.93-3.86 (m, 2H, CH₂NH), 3.85 (s, 3H, CH₃O), 1.45 (s, 9H, *t*-Bu). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 167.9 (C_{quat}), 164.5 (C_{quat}), 160.4 (C_{quat}), 155.7 (C_{quat}), 149.0 (C_{quat}), 140.3 (CH=CH-CH₂), 135.6 (C_{quat}), 130.1 (CH_{Ar}), 130.0 (C_{quat}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH=CH-CH₂), 128.2 (CH_{Ar}), 121.7 (C_{quat}), 114.4 (CH_{Ar}), 79.9 (C_{quat}), 55.5 (CH₃-O), 44.8 (CH₂-Ph), 42.7 (CH₂-NH), 28.5 (CH₃,*t*-Bu). HRMS-ESI (pos. mode) m/z : [M+Na]⁺ Calcd for C₂₆H₂₈N₂O₅SNa 503.1611; Found 503.1666.

(*Z/E*)-3-Benzyl-5-((4-methoxyphenyl)(3,4,5-trimethoxyphenyl)methylene)thiazolidine-2,4-dione (1d):

*Preparation of the tri-*n*-butyl(3,4,5-trimethoxyphenyl)stannane (6b):* To a solution of 1-bromo-3,4,5-trimethoxybenzene (2.00 g, 8.09 mmol) in THF (20 mL) at -80 °C was added *n*-BuLi solution (1.6 M in hexanes, 5.6 mL, 8.90 mmol). After 30 minutes, the temperature was allowed to warm up to room temperature and *n*-Bu₃SnCl (2.4 mL, 8.90 mL) was added. After refluxing for 30 minutes, the reaction mixture was hydrolyzed. EtOAc (30 mL) was added and the organic layer was washed with an aqueous HCl 1 M solution and water (pH=4). The organic layer was dried (MgSO₄) and solvents were removed under reduced pressure. After purification by flash column chromatography (eluent: cyclohexane/EtOAc 100/0 to 90/10 in 20 minutes, then isocratic mode for 20 minutes) **6b** was obtained as a colourless oil (1.40 g, 3.07 mmol, 38%). ¹H NMR (CDCl₃, 400 MHz) δ 6.64 (s, 2H, H_{Ar}), 3.87 (s, 6H, CH₃O), 3.85 (s, 3H, CH₃O), 1.60-1.51 (m, 6H, CH₂), 1.41-1.27 (m, 6H, CH₂), 1.12-0.98 (m, 6H, CH₂), 0.90 (t, $J = 7.2$ Hz, 9H, CH₃). Other analyses were in accordance with the literature.⁵³

The compound **1d** was prepared according to the general procedure for the Stille reaction with the tri-*n*-butylstannane **6b**. After purification of the crude product ((*Z/E*) ratio = 45/55) by flash chromatography in reverse phase (eluent: H₂O/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 20 minutes), **1d** was isolated (yellow oil, 0.165 g, 0.33 mmol, 60%) as

an (*E*)-enriched isomer fraction of **1d** (0.055 g, 0.11 mmol, 20%, (*Z/E*) ratio = 22/78 for (*E*)-enriched **1d**) and a pure mixture of the two stereoisomers (0.110 g, 0.22 mmol, 40%).
Analysis for the pure mixture of isomers 1d: IR (ATR): ν (cm⁻¹) 2930, 1728, 1676, 1236. HRMS-ESI (pos. mode) *m/z*: [M+H]⁺ Calcd for C₂₇H₂₆NO₆S 492.1475; Found 492.1464.
Analysis for the (E)-enriched 1d: ¹H NMR (CDCl₃, 400 MHz) δ 7.45-7.38 (2m, 2x2H, H_{Ar}), 7.34-7.19 (2m, 2x5H, H_{Ar}), 6.92-6.87 (2m, 2x2H, H_{Ar}), 6.47 and 6.39 (2s, 2x2H, H_{Ar}), 4.82 and 4.81 (2s, 2x2H, CH₂), 3.91 and 3.89 (2s, 2x3H, CH₃), 3.85 and 3.84 (2s, 2x3H, CH₃), 3.77 and 3.74 (2s, 2x6H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 168.4 (C_{quat}), 164.0 (C_{quat}), 161.1 (C_{quat}), 160.8 (C_{quat}), 153.3 (C_{quat}), 152.9 (C_{quat}), 152.2 (C_{quat}), 151.8 (C_{quat}), 139.1 (C_{quat}), 136.7 (C_{quat}), 135.8 (C_{quat}), 135.7 (C_{quat}), 134.4 (C_{quat}), 133.1 (C_{quat}), 131.9 (CH_{Ar}), 131.3 (C_{quat}), 130.7 (C_{quat}), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 122.4 (C_{quat}), 119.5 (C_{quat}), 114.2 (CH_{Ar}), 113.5 (CH_{Ar}), 107.5 (CH_{Ar}), 107.1 (CH_{Ar}), 61.1 (CH₃), 56.5 (CH₃), 56.4 (CH₃), 56.3 (CH₃), 55.5 (CH₃), 55.4 (CH₃), 44.9 (2 peaks, CH₂).

(*Z/E*)-5-(Benzo[*b*]furan-2-yl(4-methoxyphenyl)methylene)-3-benzylthiazolidine-2,4-dione (1e):

*Preparation of the 2-tri-*n*-butylstannylbenzo[*b*]furane (6c)*: To a solution of benzo[*b*]furane (1.00 g, 8.46 mmol) in THF (25 mL) at 0 °C was added *n*-BuLi solution (1.6 M in hexanes, 5.8 mL, 9.31 mmol). After stirring for 1 hour, the temperature was cooled down to -80 °C and *n*-Bu₃SnCl (2.5 mL, 9.2 mmol) was added. After stirring for additional 30 minutes, the reaction mixture was hydrolyzed, diluted with EtOAc (50 mL) and washed with water (3 × 30 mL). The organic layer was dried (MgSO₄) and the solvents were removed under reduced pressure. After purification by flash column chromatography (eluent: cyclohexane/EtOAc 100/0), **6c** was given as a colourless oil (3.11 g, 7.64 mmol, 90%). ¹H NMR (CDCl₃, 400

MHz) δ 7.59-7.47 (m, 2H, H_{Ar}), 7.26-7.14 (m, 2H, H_{Ar}), 6.91 (d, $J = 0.9$ Hz, 1H, H_{furane}), 1.68-1.53 (m, 6H, CH₂), 1.44-1.29 (m, 6H, CH₂), 1.22-1.12 (m, 6H, CH₂), 0.91 (t, $J = 7.2$ Hz, 9H, CH₃). Other analyses were in accordance with the literature.⁵⁴

The compound **1e** was prepared according to the general procedure for the Stille reaction with the tri-*n*-butylstannane **6c**. After the purification of the crude compound ((*Z/E*) ratio = 14/86) by flash chromatography in reverse phase (eluent: H₂O/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 20 minutes) **1e** was obtained as an (*E*)-enriched isomer of **1e** (yellow amorphous solid, 0.122 g, 0.28 mmol, (*Z/E*) ratio = 5/95, 50%). IR (ATR): ν (cm⁻¹) 3030, 1724, 1668, 1242. HRMS-ESI (pos. mode) m/z : [M+Na]⁺ Calcd for C₂₆H₁₉NO₄SNa 464.0927; Found 464.1011. ¹H NMR (CDCl₃, 400 MHz) δ 7.71-7.21 (m, 2x11H, H_{Ar}, H_{benzofurane}), 7.04-6.94 (m, 2x2H, H_{Ar}), 6.57 (d, $J = 0.9$ Hz, 2x1H, H_{benzofurane}), 4.89 and 4.79 (2s, 2x2H, CH₂), 3.89 and 3.87 (2s, 2x3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 169.1 (C_{quat}), 164.5 (C_{quat}), 160.2 (C_{quat}), 156.2 (C_{quat}), 155.1 (C_{quat}), 136.7 (C_{quat}), 135.6 (C_{quat}), 130.6 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (C_{quat}), 128.1 (CH_{Ar}), 127.9 (C_{quat}), 127.3 (CH_{Ar}), 124.0 (CH_{Ar}), 122.3 (CH_{Ar}), 118.8 (C_{quat}), 115.6 (CH_{Ar}), 114.0 (CH_{Ar}), 111.9 (CH_{Ar}), 55.4 (CH₃), 44.8 (CH₂).

(*Z/E*)-3-Benzyl-5-((4-methoxyphenyl)(thiophen-2-yl)methylene)thiazolidine-2,4-dione

(1f): This compound was prepared according to the general procedure for the Stille reaction with the commercially available tri-*n*-butyl(thiophen-2-yl)stannane. The crude compound **1f** ((*Z/E*) ratio = 48/52) was diluted with CH₃CN to give an (*Z*)-enriched isomer fraction of **1f** as a yellow precipitate (0.025 g, 0.06 mmol, 11%, *Z/E* ratio = 93/7). After evaporation of the filtrate, the residue was purified by flash chromatography in reverse phase (eluent: H₂O/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 20 minutes) to afford **1f** as a pure mixture of the two stereoisomers (yellow solid, 0.126 g, 0.31 mmol, 56%). *Analysis for the pure mixture of isomers 1f*: M.p. 93-95 °C. IR (ATR): ν (cm⁻¹) 2928, 1722, 1688, 1248.

HRMS-ESI (pos. mode) m/z : $[M+Na]^+$ Calcd for $C_{22}H_{17}NO_3S_2Na$ 430.0542; Found 430.0579.

Analysis for the (Z)-enriched 1f: 1H NMR ($CDCl_3$, 400 MHz) δ 7.57 and 7.51 (2dd, $J = 5.1$ Hz, $J = 1.1$ Hz, 2x1H, $H_{thiophene}$), 7.47-7.14 (m, 2x8H, $H_{thiophene}$, H_{Ar}), 7.10 and 7.05 (2dd, $J = 3.9$ Hz, $J = 5.1$ Hz, 2x1H, $H_{thiophene}$), 6.97-6.91 (m, 2x2H, H_{Ar}), 4.87 and 4.78 (2s, 2x2H, CH_2), 3.87 and 3.86 (2s, 2x3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 167.7 (C_{quat}), 164.2 (C_{quat}), 160.4 (C_{quat}), 144.4 (C_{quat}), 143.5 (C_{quat}), 135.6 (C_{quat}), 132.9 (CH_{Ar}), 131.6 (CH_{Ar}), 131.4 (C_{quat}), 130.8 (2 peaks, CH_{Ar}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 113.8 (CH_{Ar}), 55.4 (CH_3), 45.1 (CH_2).

(Z/E)-3-Benzyl-5-((4-methoxyphenyl)(2-methoxypyridin-4-yl)methylene)thiazolidine-2,4-dione (1g): This compound was prepared according to the general procedure for the Stille reaction with the commercially available 2-methoxy-4-(tri-*n*-butylstannyl)pyridine. After purification of the mixture ((*Z/E*) ratio = 58/42) of the two isomers of **1g** by reverse phase flash column chromatography (eluent: water/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 10 minutes), the (*E*)-enriched isomer and the (*Z*)-enriched isomer were isolated as yellow oils (0.072 g, 0.166 mmol, 30%, (*Z/E*) ratio = 7/93 for (*E*)-enriched **1g** and 0.070 g, 0.161 mmol, 29%, (*Z/E*) ratio = 93/7 for (*Z*)-enriched **1g**). *Analysis for the mixture of isomers*: IR (ATR): ν (cm^{-1}) 2947, 1736, 1681, 1259. HRMS-ESI (pos. mode) m/z : $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O_4S$ 433.1217; Found 433.1254. *Analysis for the (E)-enriched 1g*: 1H NMR ($CDCl_3$, 400 MHz) δ 8.20 (br d, $J = 4.9$ Hz, 1H, $H_{pyridine}$), 7.41-7.28 (m, 5H, H_{Ar}), 7.25-7.20 (m, 2H, H_{Ar}), 6.91-6.86 (m, 2H, H_{Ar}), 6.72 (br d, $J = 4.9$ Hz, 1H, $H_{pyridine}$), 6.58 (br s, 1H, $H_{pyridine}$), 4.78 (s, 2H, CH_2), 3.97 (s, 3H, CH_3), 3.83 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz) δ 167.8 (C_{quat}), 164.3 (C_{quat}), 163.8 (C_{quat}), 161.2 (C_{quat}), 150.6 (C_{quat}), 147.5 (C_{quat}), 146.7 ($CH_{pyridine}$), 135.4 (C_{quat}), 131.4 (C_{quat}), 130.7 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.3 (CH_{Ar}), 121.4 (C_{quat}), 117.1 ($CH_{pyridine}$), 114.5 (CH_{Ar}), 111.0 ($CH_{pyridine}$), 55.6 (CH_3), 53.9 (CH_3), 45.1 (CH_2). *Analysis for the (Z)-enriched 1g*: 1H NMR ($CDCl_3$, 400 MHz)

δ 8.20 (br d, $J = 5.3$ Hz, 1H, H_{pyridine}), 7.44-7.27 (m, 5H, H_{Ar}), 7.21-7.16 (m, 2H, H_{Ar}), 6.90-6.86 (m, 2H, H_{Ar}), 6.73 (dd, $J = 5.3$ Hz, $J = 1.4$ Hz, 1H, H_{pyridine}), 6.63 (br s, 1H, H_{pyridine}), 4.81 (s, 2H, CH₂), 3.95 (s, 3H, CH₃), 3.84 (s, 3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 167.3 (C_{quat}), 164.7 (C_{quat}), 163.7 (C_{quat}), 160.9 (C_{quat}), 151.7 (C_{quat}), 148.6 (C_{quat}), 147.8 (CH_{pyridine}), 135.4 (C_{quat}), 131.5 (CH_{Ar}), 129.5 (C_{quat}), 129.2 (CH_{Ar}), 128.8 (CH_{Ar}), 128.3 (CH_{Ar}), 122.1 (C_{quat}), 116.3 (CH_{pyridine}), 113.7 (CH_{Ar}), 110.9 (CH_{pyridine}), 55.4 (CH₃), 54.0 (CH₃), 45.2 (CH₂).

General procedure for Suzuki cross-coupling: To a reaction medium of **4c** (0.200 g, 0.555 mmol) in toluene (4 mL) and Pd(dppf)Cl₂.CH₂Cl₂ (0.023 g, 0.028 mmol) was added a solution of the boronic acid derivative (0.832 mmol) in a mixture of the selected alcohol (EtOH, *i*-PrOH or *t*-BuOH) and toluene (3/2 v/v, 5 mL). After stirring for 1 minute, water (2 mL) and a 1 M aqueous solution of Na₂CO₃ (832 μ L, 0.832 mmol) were added. The reaction mixture was heated at 110 °C for 3 hours, allowed to cool down at rt and diluted with EtOAc (30 mL). The organic layer was washed with water (3 \times 20 mL) and with an aqueous saturated solution of NaCl (20 mL), dried (MgSO₄) and the solvents were removed under reduced pressure.

(*Z/E*)-4-((3-Benzyl-2,4-dioxothiazolidin-5-ylidene)(4-methoxyphenyl)methyl)

benzaldehyde (1h): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available (4-formylbenzene)boronic acid and EtOH as a co-solvent. After the purification of the crude compound ((*Z/E*) ratio = 63/37) by flash chromatography (eluent: cyclohexane/EtOAc 100/0 for 20 minutes then to 85/15 in 20 minutes) **1h** was isolated as a pure mixture of the two stereoisomers as a yellow oil (0.228 g, 0.533 mmol, (*Z/E*) ratio = 74/26, 96%). IR (ATR): ν (cm⁻¹) 2931, 1732, 1672, 1250. ¹H NMR (CDCl₃, 400 MHz) δ 10.05 and 10.04 (2s, 2x1H, CHO), 7.92-7.87 (m, 2x2H, H_{Ar}), 7.47-7.16 (m, 2x9H, H_{Ar}), 6.92-6.87 (m, 2x2H, H_{Ar}), 4.83 and 4.78 (2s, 2x2H, CH₂), 3.84 and 3.83 (2s,

2x3H, CH₃O). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 191.8 (CHO), 191.4 (CHO), 167.9 (C_{quat}), 167.4 (C_{quat}), 164.0 (C_{quat}), 163.7 (C_{quat}), 161.2 (C_{quat}), 160.9 (C_{quat}), 150.3 (C_{quat}), 149.4 (C_{quat}), 147.2 (C_{quat}), 145.8 (C_{quat}), 136.9 (C_{quat}), 136.3 (C_{quat}), 135.3 (2 peaks, C_{quat}), 132.1 (C_{quat}), 131.7 (CH_{Ar}), 131.0 (CH_{Ar}), 130.1 (CH_{Ar}), 130.0 (CH_{Ar}), 129.6 (CH_{Ar}), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.3 (CH_{Ar}), 121.9 (C_{quat}), 121.2 (C_{quat}), 114.4 (CH_{Ar}), 113.7 (CH_{Ar}), 55.5 (CH₃), 55.4 (CH₃), 45.2 (CH₂), 45.0 (CH₂). HRMS-ESI (pos. mode) *m/z*: [M+Na]⁺ Calcd for C₂₅H₁₉NO₄SNa 452.0927; Found 452.0907. GC-MS (EI): 429 (36), 268 (10), 152 (9), 91 (26).

(E)-3-Benzyl-5-(ethoxy(4-methoxyphenyl)methylene)thiazolidine-2,4-dione (7a): Yellow oil obtained as a by-product of functionalization using Suzuki cross-couplings within various yields (10-100%). IR (ATR): ν (cm⁻¹) 2976, 1722, 1666, 1248. ¹H NMR (CDCl₃, 400 MHz) δ 7.36 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.37-7.27 (m, 5H, H_{Ar}), 6.99 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 3.86 (s, 3H, CH₃O), 4.74 (s, 2H, CH₂Ph), 3.85 (q, *J* = 7.1 Hz, 2H, OCH₂), 1.23 (t, *J* = 7.1 Hz, 3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 168.5 (C_{quat}), 164.1 (C_{quat}), 162.9 (C_{quat}), 161.6 (C_{quat}), 136.0 (C_{quat}), 131.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.7 (CH_{Ar}), 127.9 (CH_{Ar}), 122.6 (C_{quat}), 114.1 (CH_{Ar}), 104.1 (C_{quat}), 66.8 (CH₂O), 55.5 (CH₃O), 44.6 (CH₂Ph), 15.4 (CH₃). HRMS-ESI (pos. mode) *m/z*: [M+Na]⁺ Calcd for C₂₀H₁₉NO₄SNa 392.0927; Found 392.0929.

(Z/E)-3-Benzyl-5-((4-methoxyphenyl)(phenyl)methylene)thiazolidine-2,4-dione (1a): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available phenylboronic acid and EtOH as a co-solvent. (*Z/E*) ratio of the crude reaction mixture = 72/28. After purification by flash column chromatography in reverse phase (eluent: water/MeOH 50/50 to 10/90 in 20 minutes then isocratic mode for 10 minutes) **1a** was isolated as a pure mixture of the two stereoisomers as a yellow oil (0.169 g, 0.421 mmol, 76%, (*Z/E*) ratio = 74/26). IR (ATR): ν (cm⁻¹) 3055, 1730, 1670, 1248. ¹H NMR (CDCl₃, 400 MHz) δ 7.44-7.17 (m, 2x12H, H_{Ar}), 6.88 (d, *J* = 8.9 Hz, 2x2H, H_{Ar}), 4.82 and 4.79 (2s, 2x2H,

CH₂), 3.84 and 3.83 (2s, 2x3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 168.3 (C_{quat}), 168.2 (C_{quat}), 164.0 (C_{quat}), 161.0 (C_{quat}), 160.7 (C_{quat}), 152.2 (C_{quat}), 151.8 (C_{quat}), 141.6 (C_{quat}), 139.5 (C_{quat}), 135.7 (C_{quat}), 133.3 (C_{quat}), 131.8 (CH_{Ar}), 131.1 (CH_{Ar}), 131.0 (C_{quat}), 130.0 (CH_{Ar}), 129.6 (CH_{Ar}), 129.4 (CH_{Ar}), 129.2 (CH_{Ar}), 129.1 (2 peaks, CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.2 (3 peaks, CH_{Ar}), 120.5 (C_{quat}), 119.9 (C_{quat}), 114.2 (CH_{Ar}), 113.5 (CH_{Ar}), 55.5 (CH₃), 55.4 (CH₃), 45.0 (CH₂), 44.9 (CH₂). HRMS-ESI (pos. mode) *m/z*: [M+H]⁺ Calcd for C₂₄H₂₀NO₃S 402.1158; Found 402.1145.

3-Benzyl-5-(bis(4-methoxyphenyl)methylene)thiazolidine-2,4-dione (1i): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available (4-methoxybenzene)boronic acid and EtOH as a co-solvent. It was obtained by flash column chromatography (eluent: cyclohexane/EtOAc 100/0 to 80/20 in 20 minutes then isocratic mode for 10 minutes) and then by flash column chromatography in reverse phase (eluent: water/MeOH 50/50 to 10/90 in 20 minutes then isocratic mode for 10 minutes) as a yellow solid (0.109 g, 0.253 mmol, 49%). M.p. 83-85 °C. IR (ATR): ν (cm⁻¹) 1728, 1668, 1248. ¹H NMR (CDCl₃, 400 MHz) δ 7.43-7.37 (m, 2H, H_{Ar}), 7.33-7.27 (m, 3H, H_{Ar}), 7.24-7.20 (m, 2H, H_{Ar}), 7.19-7.15 (m, 2H, H_{Ar}), 6.90-6.85 (m, 4H, H_{Ar}), 4.81 (s, 2H, CH₂), 3.84 (s, 3H, CH₃), 3.83 (s, 3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 168.5 (C_{quat}), 164.2 (C_{quat}), 161.0 (C_{quat}), 160.7 (C_{quat}), 152.2 (C_{quat}), 135.8 (C_{quat}), 133.8 (C_{quat}), 131.8 (CH_{Ar}), 131.4 (CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Ar}), 128.1 (CH_{Ar}), 118.9 (C_{quat}), 114.1 (CH_{Ar}), 113.5 (CH_{Ar}), 55.5 (CH₃), 55.4 (CH₃), 44.9 (CH₂). HRMS-ESI (pos. mode) *m/z*: [M+Na]⁺ Calcd for C₂₅H₂₁NO₄SNa 454.1083; Found 454.1131.

(Z/E)-5-((3-Benzyl-2,4-dioxothiazolidin-5-ylidene)(4-methoxyphenyl)methyl)thiophene-2-carbaldehyde (1j): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available (5-formylthiophen-2-yl)boronic acid and EtOH as a co-solvent. The purification of the crude reaction mixture ((Z/E) ratio was not

determined because of overlapping of signals in ^1H NMR spectrum of the crude mixture) was done by flash column chromatography in reverse phase (eluent: water/MeOH 50/50 to 10/90 in 20 minutes then isocratic mode for 10 minutes), giving **1j** as a pure mixture of the two stereoisomers (yellow oil, 0.063 g, 0.144 mmol, 26%, non-attributed ratio = 62/38). IR (ATR): ν (cm^{-1}) 2978, 1719, 1665, 1248. ^1H NMR (CDCl_3 , 400 MHz) δ 9.92 and 9.91 (2s, 2x1H, CHO), 7.73-7.69 (m, 2x1H, $\text{H}_{\text{thiophene}}$), 7.49-7.15 (m, 2x8H, H_{Ar} , $\text{H}_{\text{thiophene}}$), 6.99-6.91 (m, 2x2H, H_{Ar}), 4.85 and 4.79 (2s, 2x2H, CH_2), 3.87 and 3.86 (2s, 2x3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.6 MHz) δ 183.2 (CHO), 182.9 (CHO), 167.2 (C_{quat}), 166.6 (C_{quat}), 163.8 (C_{quat}), 163.6 (C_{quat}), 161.2 (C_{quat}), 160.7 (C_{quat}), 152.6 (C_{quat}), 149.3 (C_{quat}), 146.6 (C_{quat}), 145.7 (C_{quat}), 141.9 (C_{quat}), 141.5 (C_{quat}), 135.5 ($\text{CH}_{\text{thiophene}}$), 135.3 (C_{quat}), 135.2 (C_{quat}), 135.2 ($\text{CH}_{\text{thiophene}}$), 132.7 (C_{quat}), 132.6 ($\text{CH}_{\text{thiophene}}$), 132.4 ($\text{CH}_{\text{thiophene}}$), 130.7 (CH_{Ar}), 130.5 (CH_{Ar}), 130.4 (C_{quat}), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 124.2 (C_{quat}), 121.4 (C_{quat}), 114.6 (CH_{Ar}), 114.1 (CH_{Ar}), 55.6 (CH_3), 55.4 (CH_3), 45.3 (CH_2), 45.2 (CH_2). HRMS-ESI (pos. mode) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{18}\text{NO}_4\text{S}_2$ 436.0672; Found 436.0790.

(Z/E)-3-Benzyl-5-((4-methoxyphenyl)(thiophen-3-yl)methylene)thiazolidine-2,4-dione

(1k): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available (thiophen-3-yl)boronic acid and EtOH as a co-solvent. After the solvent removal, the organic residue ((Z/E) ratio = 50/50) was purified by flash chromatography on neutralized silica (silica neutralization: elution of cyclohexane + 1 % Et_3N , 200 mL, rinsed with a cyclohexane/EtOAc 80/20, 200 mL; purification eluent: cyclohexane/EtOAc 100/0 to 93/7 in 20 minutes then isocratic mode for 20 minutes). The expected thienyl derivative **1k** was isolated as a pure mixture of the two stereoisomers (yellow solid, 0.065 g, 0.159 mmol, 29%, non-attributed ratio = 37/63). M.p. 69-71 °C. IR (ATR): ν (cm^{-1}) 2833, 1726, 1668, 1246. ^1H NMR (CDCl_3 , 400 MHz) δ 7.46-7.01 (m, 2x10H,

$H_{\text{thiophene}}$, H_{Ar}), 6.93-6.88 (m, 2x2H, H_{Ar}), 4.83 and 4.80 (2s, 2x2H, CH_2), 3.85 and 3.84 (2s, 2x3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.6 MHz) δ 168.2 (C_{quat}), 168.0 (C_{quat}), 164.2 (C_{quat}), 164.0 (C_{quat}), 160.9 (C_{quat}), 160.6 (C_{quat}), 146.0 (C_{quat}), 145.9 (C_{quat}), 142.3 (C_{quat}), 139.2 (C_{quat}), 135.7 (2 peaks, C_{quat}), 133.7 (C_{quat}), 131.3 (C_{quat}), 131.2 (CH_{Ar}), 131.0 (CH_{Ar}), 129.7 (2 peaks, $\text{CH}_{\text{thiophene}}$), 129.1 (CH_{Ar} , $\text{CH}_{\text{thiophene}}$), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 ($\text{CH}_{\text{thiophene}}$), 128.2 (2 peaks, CH_{Ar}), 126.5 ($\text{CH}_{\text{thiophene}}$), 124.5 ($\text{CH}_{\text{thiophene}}$), 120.1 (C_{quat}), 118.9 (C_{quat}), 114.2 (CH_{Ar}), 113.6 (CH_{Ar}), 55.5 (CH_3), 55.4 (CH_3), 45.0 (CH_2), 44.9 (CH_2). HRMS-ESI (pos. mode) m/z : $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_3\text{S}_2$ 425.0988; Found 425.0968.

(Z/E)-tert-Butyl 2-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)(4-methoxyphenyl)methyl)-1H-indole-1-carboxylate (11): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available (1-(*tert*-butoxycarbonyl)-1H-indol-2-yl)boronic acid and *t*-BuOH as a co-solvent at the 0.300 g scale for **4c**. The purification of the crude reaction mixture ((*Z/E*) ratio = 30/70) was done by flash chromatography in reverse phase (eluent: water/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 20 minutes) to give **11** as a pure mixture of the two stereoisomers (yellow solid, 0.242 g, 0.448 mmol, 54%, (*Z/E*) ratio = 30/70). M.p. 89-91 °C. IR (ATR): ν (cm^{-1}) 2970, 1732, 1678, 1254. ^1H NMR (CDCl_3 , 400 MHz) δ 8.17 and 8.00 (2dd, $J = 0.7$ Hz, $J = 8.4$ Hz, 2x1H, H_{Ar}), 7.59 and 7.50 (2d, $J = 7.6$ Hz, 2x1H, H_{Ar}), 7.45-7.21 (m, 2x9H, H_{Ar}), 6.90-6.81 (m, 5H, H_{Ar}), 6.49 (d, $J = 0.7$ Hz, 1H, H_{Ar}), 4.86-4.76 (m, 2x2H, CH_2), 3.82 and 3.81 (2s, 2x3H, CH_3), 1.39 and 1.37 (2s, 2x9H, *t*-Bu). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.6 MHz) δ 168.0 (C_{quat}), 167.8 (C_{quat}), 163.8 (C_{quat}), 163.6 (C_{quat}), 161.0 (C_{quat}), 149.4 (C_{quat}), 148.9 (C_{quat}), 144.3 (C_{quat}), 141.5 (C_{quat}), 138.1 (C_{quat}), 136.8 (C_{quat}), 136.0 (C_{quat}), 135.6 (C_{quat}), 135.5 (C_{quat}), 132.2 (CH_{Ar}), 131.2 (C_{quat}), 131.0 (CH_{Ar}), 129.1 (C_{quat}), 129.1 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (2 peaks, C_{quat}), 128.1 (CH_{Ar}), 126.1 (CH_{Ar}), 125.1 (CH_{Ar}), 123.4 (CH_{Ar}), 123.0 (CH_{Ar}), 121.7 (CH_{Ar}), 121.1 (CH_{Ar}), 120.8 (2 peaks, C_{quat}), 115.7 (CH_{Ar}), 115.3

(CH_{Ar}), 114.1 (CH_{Ar}), 114.0 (CH_{Ar}), 112.9 (CH_{Ar}), 111.3 (CH_{Ar}), 84.8 (C_{quat}), 83.8 (C_{quat}), 55.4 (CH₃O), 55.3 (CH₃O), 45.0 (CH₂), 44.9 (CH₂), 28.0 (CH₃), 27.8 (CH₃). HRMS-ESI (pos. mode) *m/z*: [M+H]⁺ Calcd for C₃₁H₂₉N₂O₅S 541.1792; Found 541.1831.

(Z/E)-3-Benzyl-5-((2-fluoropyridin-3-yl)(4-methoxyphenyl)methylene)thiazolidine-2,4-dione (1m): This compound was prepared according to the general procedure for the Suzuki reaction with the commercially available (2-fluoropyridin-3-yl)boronic acid and *i*-PrOH as a co-solvent. The crude reaction mixture (non-attributed ratio = 85/15) was purified by flash column chromatography in reverse phase (eluant: water/MeOH 50/50 to 10/90 in 20 minutes then isocratic mode for 10 minutes) to give the fluoropyridine **1m** as a pure mixture of the two stereoisomers (yellow solid, 0.198 g 0.472 mmol, 85%, non-attributed ratio = 85/15). M.p. 150-152 °C. IR (ATR): ν (cm⁻¹) 3057, 1736, 1674, 1252. ¹H NMR (CDCl₃, 400 MHz) δ 8.28-8.21 (2m, 2x1H, H_{pyridine}), 7.70-7.62 and 7.52-7.45 (2m, 2x1H, H_{pyridine}), 7.40-7.15 (m, 2x8H, H_{Ar}, H_{pyridine}), 6.91- 6.82 (m, 2x2H, H_{Ar}), 4.79 and 4.76 (2s, 2x2H, CH₂), 3.80 (2s, 2x3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 167.7 (C_{quat}), 164.0 (C_{quat}), 161.2 (C_{quat}), 160.2 (d, *J* = 239.2 Hz, C_{quat}), 149.3 (d, *J* = 14.8 Hz, CH_{pyridine}), 147.9 (d, *J* = 14.8 Hz, CH_{pyridine}), 141.4 (d, *J* = 3.6 Hz, CH_{pyridine}), 141.2 (d, *J* = 3.6 Hz, CH_{pyridine}), 140.9 (d, *J* = 4.5 Hz, C_{quat}), 135.3 (C_{quat}), 131.3 (C_{quat}), 131.2 (CH_{Ar}), 130.7 (CH_{Ar}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 123.0 (d, *J* = 50.8 Hz, C_{quat}), 122.4 (C_{quat}), 121.8 (d, *J* = 4.2 Hz, CH_{pyridine}), 121.4 (d, *J* = 4.2 Hz, CH_{pyridine}), 114.6 (CH_{Ar}), 113.7 (CH_{Ar}), 55.6 (CH₃), 55.4 (CH₃), 45.3 (CH₂), 45.1 (CH₂). ¹⁹F NMR (CDCl₃, 376.4 MHz) δ -66.05 and -69.63. HRMS-ESI (pos. mode) *m/z*: [M+H]⁺ Calcd for C₂₃H₁₈FN₂O₃S 421.1017; Found 421.1000.

***tert*-Butyl ((2*E*,4*Z*)-4-(3-benzyl-2,4-dioxothiazolidin-5-ylidene)-4-(4-methoxyphenyl)but-2-en-1-yl)carbamate (1c)**:

Preparation of tert-butyl (E)-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)carbamate ((E)-8): The reaction mixture constituted of Schwartz reagent (zirconocene chloride hydride, 0.165 g, 0.64 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (1.000 g, 4.50 mmol), pinacolborane (1.40 mL, 9.66 mmol) and Et₃N (0.10 mL, 0.64 mmol) was heated at 65 °C for 18 hours. After dilution with EtOAc (25 mL) and hydrolysis with an aqueous saturated solution of NH₄Cl, the organic layer was washed with a NaHCO₃ 5% aqueous solution (2 × 20 mL), a saturated NaCl aqueous solution (20 mL) and dried (MgSO₄). The solvents were removed under reduced pressure. The crude residue was purified by flash column chromatography (eluant: cyclohexane/EtOAc 100/0 to 90/10 in 20 minutes then isocratic mode for 20 minutes) to yield the pinacolborane (**(E)-8**) as a colourless solid (0.835 g, 2.95 mmol, 46%). ¹H NMR (400 MHz, CDCl₃) δ 6.58 (td, *J*₁ = 18.0 Hz, *J*₂ = 4.6 Hz, 1H, CH-CH₂), 5.57 (td, *J*₁ = 18.0 Hz, *J*₂ = 1.8 Hz, 1H, CH-B), 4.62 (br s, 1H, NH), 3.84 (m, 2H, CH₂), 1.44 (s, 9H, *t*-Bu), 1.26 (s, 12H, CH₃). Other analyses were in accordance with the literature.⁴²

The derivative **1c** was prepared according to the general procedure of the Suzuki cross-coupling starting from the pinacolborane (**(E)-8**) in *t*-BuOH as co-solvent. The expected derivative (**(Z)-1c**) (pure (*Z*)-isomer) was isolated by flash chromatography in reverse phase (eluent: H₂O/MeOH 50/50 to 10/90 in 20 minutes, then isocratic mode for 10 minutes) as a yellow solid (0.189 g, 0.394 mmol, 71%).

(E)-5-(2-Hydroxy-1-(4-methoxyphenyl)ethylidene)thiazolidine-2,4-dione (9): To a solution of TZD **2a** (10.00 g, 85.4 mmol) in THF (450 mL) at -80 °C was added dropwise the solution of *n*-BuLi (1.6 M in hexanes, 121 mL, 187.9 mmol). The temperature was allowed to warm up to 0 °C (ice bath) and maintained for 1 hour. After cooling to -80 °C, a solution of 2-bromo-1-(4-methoxyphenyl)ethan-1-one (19.6 g, 85.4 mmol) in THF (25 mL) was added to the reaction mixture. The temperature media was allowed to rise to room temperature in 2 hours, then the reaction was quenched by adding an aqueous HCl 1 M solution (pH=2).

Solvents were then removed under reduced pressure. The crude reaction mixture was then dissolved in EtOAc (400 mL), washed with water (3 × 250 mL) and an aqueous NaCl solution (250 mL). The organic layer was then dried (MgSO₄) and the solvents were removed under reduced pressure. The residue was suspended in CH₂Cl₂, placed in the freezer overnight and filtered to give the allylic alcohol **9** as a white powder (11.4 g, 43.2 mmol, 51%). M.p. 170-172 °C. IR (ATR): ν (cm⁻¹) 3364, 2959, 1732, 1682, 1250. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 12.31 (br s, 1H, NH), 7.39-7.33 (m, 2H, H_{Ar}), 7.03-6.97 (m, 2H, H_{Ar}), 5.02-4.92 (m, 3H, OH, CH₂), 3.79 (s, 3H, CH₃). ¹³C{¹H} NMR (DMSO-*d*₆, 100.6 MHz) δ 163.8 (C_{quat}), 162.1 (C_{quat}), 155.7 (C_{quat}), 149.1 (C_{quat}), 127.2 (C_{quat}), 125.4 (CH_{Ar}), 118.5 (C_{quat}), 109.9 (CH_{Ar}), 55.4 (CH₂), 51.2 (CH₃). HRMS-ESI (neg. mode) *m/z*: [M-H]⁻ Calcd for C₁₂H₁₀NO₄S 264.0336, Found 264.0347.

(E)-2-(2,4-Dioxothiazolidin-5-ylidene)-2-(4-methoxyphenyl)acetaldehyde (10): *Jones reagent preparation:* A sulfuric acid solution (4.2 M, 15 mL) was slowly and carefully added at 0 °C on sodium bichromate dihydrate (6.52 g, 21.9 mmol). This Jones reagent has a Cr (VI) concentration of 2.9 M. *Jones oxidation:* To a solution of the allylic alcohol **9** (4.00 g, 15.08 mmol) in acetone (150 mL) at 0 °C was slowly added a portion of Jones reagent (11.20 mL, 32.48 mmol). After 30 minutes, *i*-PrOH (4 mL) was added and after additional 30 minutes, the solution was filtered on a pad of Celite[®]. Acetone was removed under reduced pressure and the obtained solution was diluted with EtOAc (450 mL) and filtered on a pad of Celite[®]. The organic layer was washed with water (2 × 400 mL), then dried (MgSO₄) and the solvents were removed under reduced pressure, to give the aldehyde **10** as a yellow solid, which was used without further purification (3.35 g, 13.12 mmol, 87%). M.p. 150-152 °C. IR (ATR): ν (cm⁻¹) 2959, 1746, 1682, 1258. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 12.88 (br s, 1H, NH), 10.65 (s, 1H, CHO), 7.27 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.03 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 3.80 (s, 3H, CH₃). ¹³C{¹H} NMR (DMSO-*d*₆, 100.6 MHz) δ 190.5 (CHO), 167.0 (C_{quat}), 166.2 (C_{quat}), 160.3

(C_{quat}), 143.4 (C_{quat}), 137.2 (C_{quat}), 130.7 (CH_{Ar}), 126.0 (C_{quat}), 114.2 (CH_{Ar}), 55.3 (CH₃).

HRMS-ESI (neg. mode) *m/z*: [2M-H]⁻ Calcd for C₂₄H₁₇N₂O₈S₂ 525.0432; Found 525.0446.

General procedure for the Wittig reaction: To a solution of the aldehyde **10** (0.100 g, 0.380 mmol) in THF (10 mL) was added the selected phosphonium ylide **11b-d** (0.836 mmol). The reaction mixture was stirred at rt for 15 hours. THF was then removed under reduced pressure.

Methyl (2E,4Z)-4-(2,4-dioxothiazolidin-5-ylidene)-4-(4-methoxyphenyl)but-2-enoate

(1n): This compound was prepared according the general procedure for the Wittig reaction starting from the commercially available phosphonium ylide **11a**. After purification by flash column chromatography (eluent: CH₂Cl₂/acetone 100/0 to 95/5 in 20 minutes), **1n** was obtained as a bright yellow powder (0.120 g, 0.375 mmol, 99%). M.p. 204-206 °C. IR (ATR): ν (cm⁻¹) 2920, 1732, 1682, 1246. ¹H NMR (CDCl₃, 400 MHz) δ 8.94 (d, *J* = 15.7 Hz, 1H, CH=CHCO₂Me), 8.33 (br s, 1H, NH), 7.16 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 6.98 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 5.77 (d, *J* = 15.7 Hz, 1H, CHCO₂Me), 3.86 (s, 3H, CH₃), 3.77 (s, 3H, CH₃). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 166.8 (C_{quat}), 165.9 (C_{quat}), 164.1 (C_{quat}), 160.8 (C_{quat}), 146.6 (C_{quat}), 139.6 (CH), 130.0 (CH_{Ar}), 128.8 (C_{quat}), 128.6 (C_{quat}), 128.5 (CH), 114.8 (CH_{Ar}), 55.6 (CH₃), 52.2 (CH₃). HRMS-ESI (neg. mode) *m/z*: [M-H]⁻ Calcd for C₁₅H₁₂NO₅S 318.0442; Found 318.0529.

(Z)-5-((E)-1-(4-Methoxyphenyl)-4-oxopent-2-en-1-ylidene)thiazolidine-2,4-dione (**1o**):

Preparation of (triphenylphosphanylidene)propan-2-one (11b): To a solution of PPh₃ (7.17 g, 27.35 mmol) in EtOAc (30 mL) was added 2-chloroacetone (2.00 mL, 24.86 mmol). The reaction mixture was refluxed at 90 °C for 3 hours and the formed precipitate was filtered, washed with EtOAc (2 × 10 mL) and dried under vacuum to give the chlorophosphonium salt as a white powder (5.82 g, 16.40 mmol, 60 %). The latter compound (2.00 g, 5.63 mmol) was

dissolved in CH₂Cl₂ (30 mL). This organic layer was washed with an aqueous 1 M NaOH solution (2 × 30 mL), dried (MgSO₄), filtered and the solvents were removed under reduced pressure. The expected **11b** was obtained as a white powder (1.47 g, 4.66 mmol, 82%). ¹H NMR (CDCl₃, 400 MHz) δ 7.71-7.40 (m, 15H, H_{Ar}), 3.69 (br d, *J* = 26.2 Hz, 1H, CH), 2.09 (d, *J* = 1.8 Hz, 3H, CH₃). Other analyses were in accordance with the literature.⁵⁵

The compound **1o** was prepared according the general procedure for the Wittig reaction starting from **11b**. After purification by flash column chromatography (eluent: CH₂Cl₂/acetone 100/0 to 85/15 in 20 minutes), **1o** was obtained as a yellow powder (0.064 g, 0.213 mmol, 56%). M.p. 193-195 °C. IR (ATR): ν (cm⁻¹) 3125, 2992, 1732, 1695, 1252. ¹H NMR (CDCl₃, 400 MHz) δ 8.87 (d, *J* = 16.1 Hz, 1H, CH=CHCO), 8.55 (br s, 1H, NH), 7.15 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.98 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 5.94 (d, *J* = 16.1 Hz, 1H, CH=CHCO), 3.86 (s, 3H, CH₃O), 2.39 (s, 3H, CH₃CO). ¹³C{¹H} NMR (CDCl₃, 100.6 MHz) δ 199.5 (C_{quat}), 166.4 (C_{quat}), 164.8 (C_{quat}), 160.8 (C_{quat}), 147.2 (C_{quat}), 138.7 (CH), 136.7 (CH), 130.0 (CH_{Ar}), 129.2 (C_{quat}), 128.4 (C_{quat}), 114.8 (CH_{Ar}), 55.5 (CH₃O), 27.2 (CH₃CO). HRMS-ESI (neg. mode) *m/z*: [M-H]⁻ Calcd for C₁₅H₁₂NO₄S 302.0493; Found 302.0470.

Methyl (2*E*,4*Z*)-4-(2,4-dioxothiazolidin-5-ylidene)-4-(4-methoxyphenyl)-2-methylbut-2-enoate (1p):

Preparation of methyl 2-(triphenylphosphanylidene)propanoate (11c): The phosphonium ylide **11c** was prepared according the procedure described for **11b**, starting from methyl 2-bromopropionate (3.34 mL, 29.94 mmol) and was obtained as a white powder (1.45 g, 4.16 mmol, 86% in 2 steps). ¹H NMR (CDCl₃, 400 MHz): δ 1.57-1.62 (m, 3H, CH₃), 3.30 (br s, 3H, CH₃O), 7.36-7.74 (m, 15H, H_{Ar}). Other analyses were in accordance with the literature.⁵⁶

The compound **1p** was prepared according the general procedure for the Wittig reaction starting from the phosphonium ylide **11c**. After purification by flash column chromatography (eluent: CH₂Cl₂/acetone 100/0 to 95/5 in 20 minutes), **1p** was obtained as a yellow oil (0.096

g, 0.289 mmol, 76%). IR (ATR): ν (cm^{-1}) 3179, 2955, 1734, 1690, 1244. ^1H NMR (CDCl_3 , 400 MHz) δ 8.34 (br s, 1H, NH), 8.16 (q, $J = 1.6$ Hz, 1H, CH), 7.30 (d, $J = 9.1$ Hz, 2H, H_{Ar}), 6.95 (d, $J = 9.1$ Hz, 2H, H_{Ar}), 3.86 (s, 3H, CH_3O), 3.82 (s, 3H, CH_3O), 1.45 (d, $J = 1.6$ Hz, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.6 MHz) δ 168.5 (C_{quat}), 167.0 (C_{quat}), 164.5 (C_{quat}), 161.1 (C_{quat}), 146.4 (C_{quat}), 136.3 (CH), 134.8 (C_{quat}), 131.0 (C_{quat}), 130.2 (CH_{Ar}), 124.7 (C_{quat}), 114.8 (CH_{Ar}), 55.5 (CH_3O), 52.6 (CH_3O), 15.1 (CH_3). HRMS-ESI (neg. mode) m/z : $[\text{M}-\text{H}]^-$ Calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_5\text{S}$ 332.0598; Found 332.0591.

(2E,4Z)-4-(2,4-Dioxothiazolidin-5-ylidene)-4-(4-methoxyphenyl)but-2-enitrile (1q):

Preparation of (triphenylphosphanylidene)acetonitrile (11d): The phosphonium ylide **11d** was prepared according the described procedure for **11b**, starting from the commercially available (cyanomethyl)triphenylphosphonium chloride (2.00 g, 5.92 mmol). The phosphonium ylide **11d** was obtained as a white powder (1.62 g, 4.66 mmol, 91%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.71-7.43 (m, 15H, H_{Ar}), 1.62-1.57 (m, 1H, CH). Other analyses were in accordance with the literature.⁵⁷

The compound **1q** was prepared according the general procedure for the Wittig reaction starting from the phosphonium ylide **11d**. After purification by flash column chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{acetone}$ 100/0 to 95/5 in 20 minutes) **1q** was obtained as a yellow oil (0.066 g, 0.231 mmol, 61%). IR (ATR): ν (cm^{-1}) 3175, 3071, 2216, 1738, 1693, 1244. ^1H NMR (acetone- d_6 , 400 MHz) δ 11.18 (br s, 1H, NH), 8.84 (d, $J = 16.4$ Hz, 1H, $\text{CH}=\text{CHCN}$), 7.30 (d, $J = 8.8$ Hz, 2H, H_{Ar}), 7.10 (d, $J = 8.8$ Hz, 2H, H_{Ar}), 5.44 (d, $J = 16.4$ Hz, 1H, CHCN), 3.88 (s, 3H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (acetone- d_6 , 100.6 MHz) δ 166.5 (C_{quat}), 166.1 (C_{quat}), 161.8 (C_{quat}), 145.9 (CH), 143.9 (C_{quat}), 131.9 (C_{quat}), 131.0 (CH_{Ar}), 128.4 (C_{quat}), 118.6 (C_{quat}), 115.6 (CH_{Ar}), 106.1 (CH), 55.8 (CH_3). HRMS-ESI (neg. mode) m/z : $[\text{M}-\text{H}]^-$ Calcd for $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_3\text{S}$ 285.0339; Found 285.0331.

Associated Content

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

X-ray data for **5** and **9**; NMR study of the tautomeric equilibrium between **5** and **5'**; Benzylidene double-bond assignment using the combined theoretical calculation/NMR studies for **1a-q** and **4c**; Comparison of the ^1H NMR spectra of **1b**, reaction mixture and pure (vinyl)tributyltin (Stille reaction); Comparison of the ^1H NMR spectra of **1c**, reaction mixture and pure (*E*)-**8** (Suzuki reaction); Mechanism proposal for the stereoselectivity observed for **1b**; Comparison between the computed and experimental (*Z/E*) ratios; ^1H and $^{13}\text{C}\{^1\text{H}\}$ APT NMR spectra of **1a-q**, **2d**, **3a-b**, **4c**, **5**, **6a-c**, **7a**, **9**, **10**, **11b-d**; $^{19}\text{F}\{^1\text{H}\}$ NMR spectrum of **1m**; NOESY spectrum of **1q**.

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