Exploring the Synthesis and the Reactivity of 4-[4-(Chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole in TDAE Strategy

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Abstract: We describe herein the preparation of 4-[4-(chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole via a Stille cross-coupling reaction. After determining the best reaction conditions, we investigated the reactivity of this activated chloromethyl compound in a TDAE [tetrakis(dimethylamino)ethylene] strategy toward 10 various electrophiles, obtaining 4-(4-substituted)styryl-1,2-dimethyl-5-nitro-1*H*-imidazoles in moderate to good yields.

Key words: nitroimidazole, Stille reaction, TDAE, carbanions, cross-coupling

The discovery of the trichomonacide properties of azomycin (2-nitroimidazole) in 1956[1] led to the development of the 5-nitroimidazole series, well known for their wide spectrum of anti-infectious activity.[2] The first-in-class molecule is metronidazole (1961),[3] which is widely used for the treatment of infections caused by protozoa such as *Trichomonas vaginalis*, *Entamœba histolytica*, and *Giardia intestinalis*, and infections induced by anaerobic bacteria. Several 5-nitroimidazoles are also currently used in drugs, such as secnidazole or ornidazole. These chemotherapeutic agents inhibit the growth of both anaerobic bacteria and some anaerobic protozoa.[4] However, 5-nitroimidazoles have been found to exhibit mutagenic activity in prokaryotic microorganisms.[5] Although mutagenicity has not been demonstrated in eukaryotic cells, new nitroimidazole derivatives possessing good pharmacological activity with no mutagenicity[6] would be of great interest not only for patient care, but also to shed light on the mode of action and the mechanism of expression of mutagenicity. Moreover, the emergence of metronidazole-resistant *T. vaginalis* has resulted in decreased success of current therapies.[7] These refractory cases are usually treated with higher doses of metronidazole, which increases the occurrence of side effects.[8] Recently, small nitro-group-containing heterocyclic derivatives, including 5-nitroimidazole series (fexinidazole), have gained attention in other biological applications such as *Trypanosoma cruzi* (Chagas disease)[9] or *Mycobacterium tuberculosis*.[10] Straightforward access to new derivatives belonging to the biologically relevant 5-nitroimidazole scaffold is therefore likely to be of interest to the scientific community.

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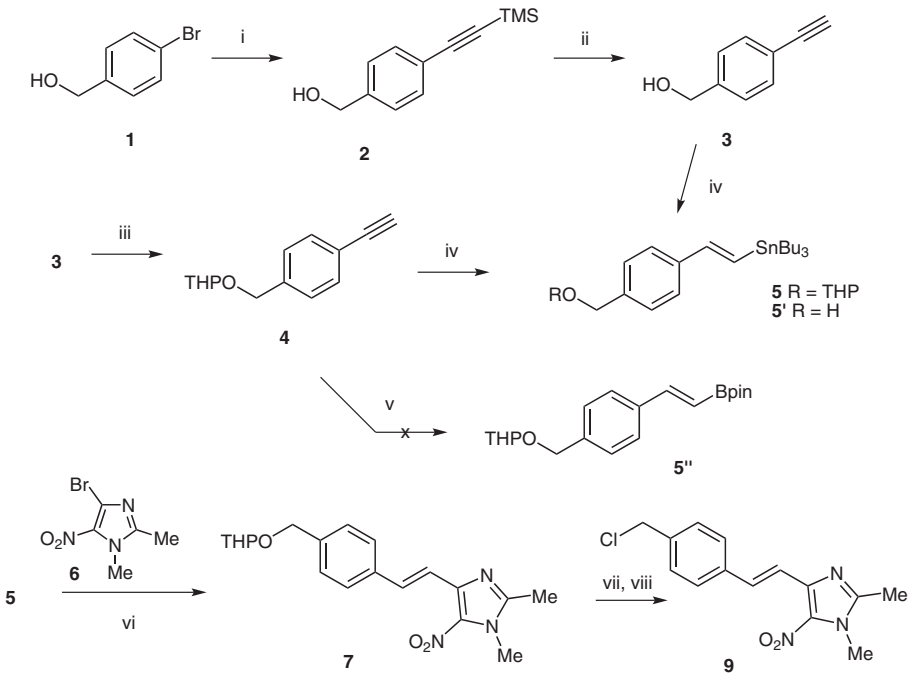
Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent that reacts with halogenated derivatives to generate a carbanion under mild conditions.[11] Since 2003, we have undertaken a program directed toward the development of original synthetic methods using TDAE methodology in medicinal chemistry.[12]

In continuation of our research program centered on the design and synthesis of novel bioactive molecules using TDAE methodology[12] or $S_{RN}1$ reactions,[13] we focused our studies on the synthesis and evaluation of heterocyclic compounds displaying notably antiparasitic activity.[14] We report herein the preparation of new 5-nitroimidazoles, bearing a 4-substituted styryl group at the 4-position, in order to extend the anti-infectious pharmacomodulation in this series of compounds. The 4-styrylimidazole scaffold can have applications in inhibitors of protein farnesyltransferase,[15] ligands of histamine H-3 receptors,[16] or antiparasitic agents.[17,18] These derivatives have previously been prepared via Heck reaction,[15] Horner–Wadsworth–Emmons reaction,[16] condensation between an aromatic aldehyde with the appropriate 4-methyl-5-nitroimidazole,[17] or Suzuki–Miyaura reactions with the appropriate styrylboronic acid, respectively.[18] To the best of our knowledge, 4-(4-substituted)styryl-1,2-dimethyl-5-nitro-1*H*-imidazoles are poorly represented in the literature and in order to prepare these derivatives, we first synthesized the key intermediate 4-[4-(chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole (**9**) via a multistep synthesis. Then, we used our knowledge of the reactivity of activated chloromethyl groups in TDAE methodologies to investigate the reactivity of intermediate **9** under similar conditions.

Starting from 4-bromobenzyl alcohol (**1**), Sonogashira cross-coupling reaction with (trimethylsilyl)acetylene afforded the TMS-protected alkyne **2** which was deprotected to give 4-alkynylbenzyl alcohol **3** using tetrabutylammonium fluoride in tetrahydrofuran (Scheme 1).[19] Protection of benzyl alcohol **3** using 3,4-dihydro-2*H*-pyran afforded the O-THP alcohol **4**.[20] We first tried to prepare the corresponding styrylboronic acid pinacol ester **5″** by hydroboration of the alkyne using catecholborane in tetrahydrofuran.[21] Unfortunately, although this type of reaction was clearly reported in the literature, all attempts failed in our hands and this suitable compound was not isolated. To overcome this problem, we chose to perform an analogous procedure using tin chemistry instead of boron chemistry. Thus, radical hydrostannylation of the



Scheme 1 Preparation of key intermediate **9**. *Reagents and conditions*: (i) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, Et_3N, 70 °C, 36 h, 93%; (ii) 1 M TBAF in THF, r.t., 12 h, 95%; (iii) 3,4-dihydro-2*H*-pyran, PTSA, CH_2Cl_2, 12 h, 96%; (iv) Bu_3SnH, AIBN, toluene, 80 °C, 12 h, **5**: 65%, **5′**: 14%; (v) 1 M catecholborane in THF, 70 °C, **5″** not obtained; (vi) $PdCl_2(PPh_3)_2$, CuI, PEG-400, MW 150 °C, 1 h, 91%; (vii) PTSA, MeOH, r.t., 12 h, **8**: 98%; (viii) $SOCl_2$, r.t., 12 h, 96%.

terminal alkyne of **4** in presence of 2,2′-azobis(isobutyronitrile) provided (*E*)-styrylstannane **5** in good yield.[22] It must be pointed out that radical hydrostannylation of alcohol **3** provided the corresponding compound **5′** in only 14% yield.[23] Then, stannane **5** was engaged in a microwave-assisted Stille cross-coupling reaction[24] with 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole[25] (**6**) affording the O-THP protected compound **7**, which was further deprotected in presence of 4-toluenesulfonic acid, leading to compound **8**. Finally, chlorination of benzyl alcohol **8** was performed in thionyl chloride at room temperature to give to the expected key intermediate **9** in 47% overall yield in seven steps. The assignment of the alkene configuration was made by X-ray structural radiocrystallography.[26]

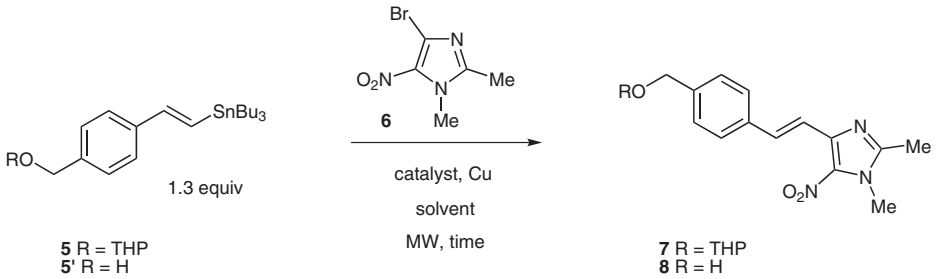
Table 1 summarizes the optimization of the Stille coupling reaction between styrylstannane **5** and 4-bromo-5-nitroimidazole **6**.

Our first attempt to perform the Stille reaction was under typical conditions in dimethylformamide using dichlorobis(triphenylphosphine)palladium(II) (2 mol%) as the palladium source and without any base or co-catalyst under microwave heating in a sealed vial. Under these conditions, starting from stannane **5′** the yield was promising (Table 1, entry 1). Since **5′** was obtained in a very low yield, further experiments were based on the more accessible stannane **5**. Under the same conditions, the yield was only 46% (entry 2). Increasing the temperature of the reaction appeared to us crucial to improve the reaction yield. In order to avoid the thermal decomposition of dimethylformamide, we chose PEG-400 as solvent.[27] Using 3% of catalyst and microwave heating at 150 °C for 1.5 hours, the target compound was obtained in 70% yield (entry 3). Addition of copper(I) iodide as co-catalyst slightly improved the yield (entry 4). With 3 mol% of catalyst instead of 2 mol%, the reaction yield reached 86% (entry 5). The use of lithium chloride as co-catalyst[24] decreased the yield (entry 6), whereas the use of tetrakis(triphenylphosphine)palladium(0) as catalyst was disappointing (entry 7). In the end, the best reaction conditions were obtained by using 4 mol% of dichlorobis(triphenylphosphine)palladium(II) in presence of 4 mol% of copper(I) iodide in PEG-400 at 150 °C under microwave heating for one hour (entry 8).

Having secured a good access to the key intermediate 4-[4-(chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole (**9**), we next investigated its reactivity with TDAE methodology.

The first attempt was made using three equivalents of *N*-tosylbenzylimine[28] as electrophile in presence of one equivalent of TDAE in anhydrous dimethylformamide at –20 °C for one hour followed by stirring at room temperature for 1.5 hours. The expected addition compound **10a** was isolated in 47% yield (Table 2, entry 1). If the amount of TDAE was increased to 1.3 equivalents, the yield of

Table 1 Optimization of the Stille Coupling Reaction of Styrylstannane **5** and **5′** with 4-Bromo-5-nitroimidazole **6**



5 R = THP
5' R = H

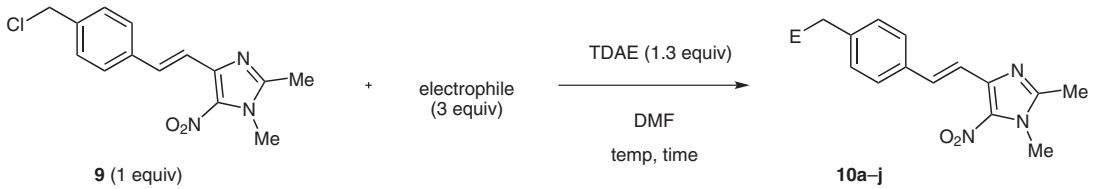
7 R = THP
8 R = H

Entry	Catalyst (mol%)	Co-catalyst (mol%)	Solvent	Temp[a] (°C)	Time (h)	Yield (%) of **7**
1	$PdCl_2(PPh_3)_2$ (2)	–	DMF	100	1	79[b]
2	$PdCl_2(PPh_3)_2$ (2)	–	DMF	100	1	46
3	$PdCl_2(PPh_3)_2$ (3)	–	PEG-400	150	1.5	70
4	$PdCl_2(PPh_3)_2$ (2)	CuI (4)	PEG-400	150	1	75
5	$PdCl_2(PPh_3)_2$ (3)	CuI (4)	PEG-400	150	1	86
6	$PdCl_2(PPh_3)_2$ (3)	LiCl (6)	PEG-400	150	1	71
7	$Pd(PPh_3)_4$ (3)	–	PEG-400	150	1.5	57
8	$PdCl_2(PPh_3)_2$ (4)	CuI (4)	PEG-400	150	1	91

[a] Microwave heating at the specified temperature.
[b] Starting from unprotected styrylstannane **5′** to afford **8**.

10a was slightly enhanced (entry 2). Electron-donating groups such as the methoxy group afforded **10b** with a slightly lower yield than previously, even though the reaction time was considerably increased. Under the same conditions, a similar yield of **10c** was obtained with *N*-tosyl-4-fluorobenzylimine (entry 4). Using aldehydes as electrophiles, the yield of **10d** increased using a longer reaction time (entry 6), and also by heating the reaction mixture (entry 7). The structure of this compound was confirmed by X-ray structural analysis (Figure 1). The resolution of the structure gives an average picture of the crystal showing two enantiomers based on chiral carbon C13. The major enantiomer is the structure containing the oxygen O3A and hydrogen H3A representing an abundance of about 80% of (*S*)-**10d** in the crystal.[26] In the case of 4-formylbenzonitrile, heating the reaction mixture at 70 °C resulted in a lower yield of **10e** than the same reaction conducted at room temperature (entries 8 and 9). Strong electron-withdrawing groups such as the nitro group did not improve the yield of this reaction, leading to only 42% yield of **10f** after 24 hours at room temperature. The reaction also worked with *ortho*-substituted substrates like 2-bromobenzaldehyde (entry 12). It must be pointed out that this same experiment conducted in tetrahydrofuran instead of dimethylformamide was unsuccessful: no trace of the target compound **10g** was observed by LC-MS analysis. We therefore investigated other substrates bearing carbonyl function, and found that diethyl oxomalonate afforded the expected derivative **10h** in 55% yield at room temperature in only one hour (entry 13). However, when ethyl pyruvate was used, the reaction mixture had to be heated to improve the reaction yield from 31% to 71% of **10i** (entries 14 and 15), while ethyl glyoxylate only led to the target derivative **10j** in 37% yield (entry 16). The global observed yields remained slightly lower when using 4-[4-(chloromethyl)phenyl]-1,2-dimethyl-5-nitro-1*H*-imidazole as the starting material probably due to the greater number of bonds between the nitro electron-withdrawing group and the chlorine atom which plays the role of leaving group in the formation of the benzylic anion.[29] Globally in these reactions, byproducts observed by LC-MS analysis were mainly due to the reduction of compound **9**.

Table 2 Addition of Chloromethyl **9** with Various Electrophiles Using TDAE Strategy



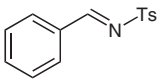
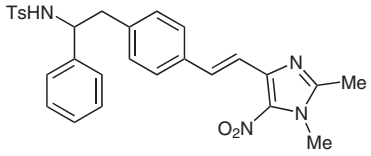
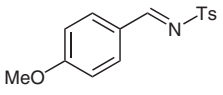
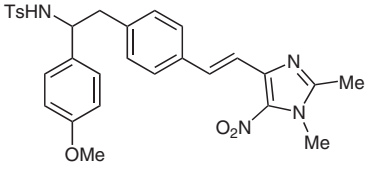
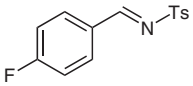
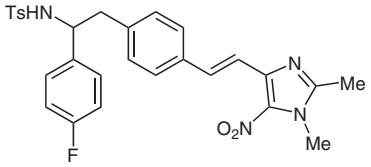
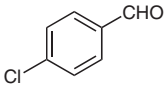
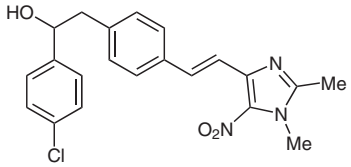
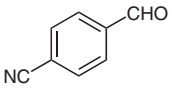
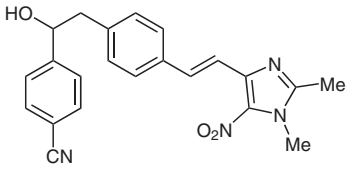
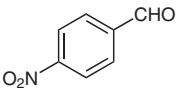
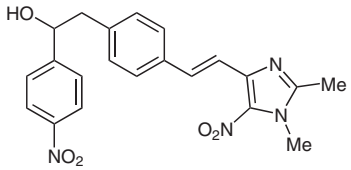
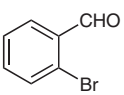
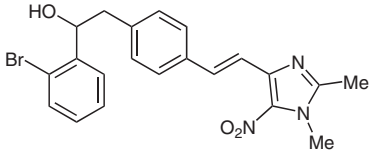
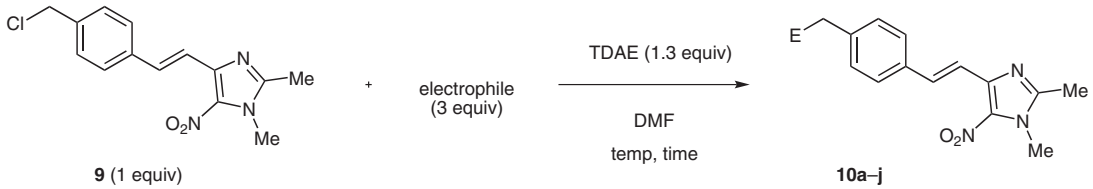
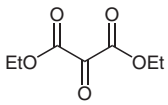
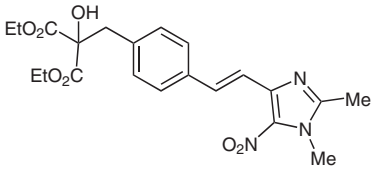
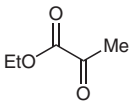
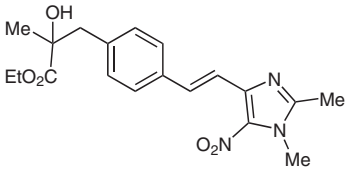
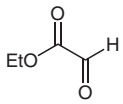
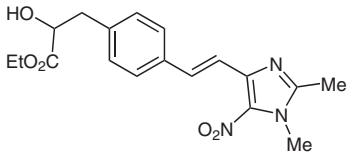
Entry	Electrophile	Temp	Time (h)	Product	Yield (%) of **10**
1		r.t.	1.5	 **10a**	47[a]
2		r.t.	1.5		54
3		r.t.	12	 **10b**	49
4		r.t.	12	 **10c**	52
5		r.t.	1.5	 **10d**	21
6		r.t.	12		33
7		70 °C	4		38
8		r.t.	12	 **10e**	52
9		70 °C	4		34
10		r.t.	2	 **10f**	36
11		r.t.	24		42
12		r.t.	12	 **10g**	33[b]

Table 2 Addition of Chloromethyl **9** with Various Electrophiles Using TDAE Strategy (continued)



Entry	Electrophile	Temp	Time (h)	Product	Yield (%) of **10**
13		r.t.	1	 **10h**	55
14		r.t.	3	 **10i**	31
15		70 °C	4		71
16		r.t.	3	 **10j**	37

[a] Using 1 equiv of TDAE.
[b] In THF, no trace of product **10g** was observed by LC-MS analysis.

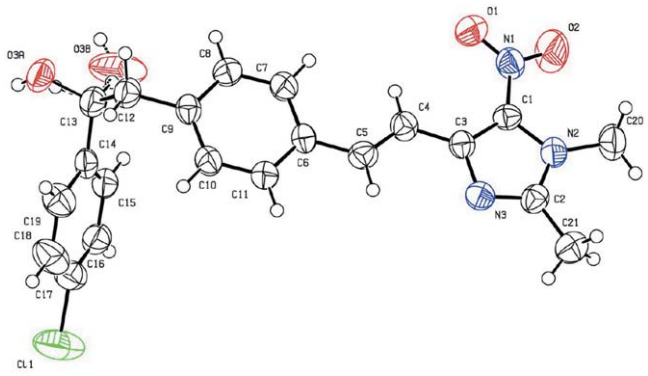


Figure 1 X-ray crystal structure of compound **10d**; major enantiomer (*S*)-**10d** ca. 80% in the crystal

In conclusion, we have prepared the previously unreported 4-[4-(chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole (**9**) using a Stille cross-coupling reaction after establishing the best experimental reaction conditions. This new chloromethylated substrate was reacted toward various electrophiles in the presence of TDAE, affording moderate to good yields of original 4-(4-substituted)styryl-1,2-dimethyl-5-nitro-1*H*-imidazole derivatives that are of biological interest, notably as anti-infectious agents. It is noteworthy that intermediate **9** could also be an appropriate substrate for long-distance-$S_{RN}1$ reactions,[30] and further research is in progress and will be reported in due time.

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler bench and are uncorrected. Elemental analysis and HRMS were carried out at the Spectropole, Faculté des Sciences et Techniques de Saint-Jérôme, Marseille, France. NMR spectra were recorded on a Bruker ARX 200 spectrometer at the Faculté de Pharmacie de Marseille (200 MHz ^{1}H NMR: reference $CHCl_3$ δ = 7.26, DMSO-d_6 δ = 2.50 and 50 MHz ^{13}C: reference $CDCl_3$ δ = 76.9, DMSO-d_6 δ = 39.5). Solvents were dried by conventional methods. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm × 10 cm aluminum plates coated with silica gel 60F-254 (Merck) in an appropriate eluent. Visualization was made with UV light (234 nm). HRMS spectra were recorded on QStar Elite (Applied Biosystems SCIEX) spectrometer with a PEG matrix. The experimental exact mass is given for the ion that has the maximum isotopic abundance. Purity of synthesized compounds was checked with LC-MS analyses performed at the Faculty of Pharmacy of Marseille with a Thermo Scientific Accela High Speed LC System® coupled with a single quadrupole mass spectrometer Thermo MSQ Plus®. The RP-HPLC column used was a Thermo

Hypersil Gold® 50 × 2.1 mm (C18 bonded) with particle size: 1.9 μm diameter. The volume of sample injected on the column was 1 μL. The chromatographic analysis, total duration of 8 min, was made with following solvent gradient: $t = 0$ min, H_2O–MeOH 50:50; $0 < t < 4$ min, linear increase in the proportion of H_2O to a ratio H_2O–MeOH 95:5; $4 < t < 6$ min, H_2O–MeOH 95:5; $6 < t < 7$ min, linear decrease in the proportion of H_2O to return to a ratio H_2O–MeOH 50:50; $6 < t < 7$ min, H_2O–MeOH 50:50. The H_2O used was buffered with 5 mM NH_4OAc. Microwave reactions were performed using a Biotage Initiator Microwave oven using 10–20-mL sealed vials; temperatures were measured with an IR sensor and reaction times given as hold times. The preparation of compounds **2**,[19] **3**,[19] **4**,[20] and **6**[18] was achieved as described in the literature.

Crystal-Structure Analysis

The X-ray diffraction measurements were carried out on a Bruker-Nonius KappaCCD diffractometer at 293 K. Structures were solved using SIR92 and refinements calculations based on F^2 were performed using SHELXL-97. The compounds **8** and **10d** were crystallized by slow evaporation of an MeCN solution to provide desired single crystals.

(*E*)-{4-[2-(Tributylstannyl)vinyl]phenyl}methanol (5′)[23]

A 50-mL round-bottomed single-neck flask equipped with a condenser, an argon gas inlet, and a magnetic stir bar was charged with (4-ethynylphenyl)methanol (**3**, 661 mg, 5.0 mmol), Bu_3SnH (1.35 mL, 5.0 mmol), AIBN (25 mg), and toluene (10 mL). The flask was heated to 80 °C overnight. The mixture was then cooled to r.t., and all volatiles were removed under reduced pressure to give a crude product that was purified by column chromatography (PE–EtOAc, 7:3) to give **5′** as a colorless oil; yield: 290 mg (14%).

^{1}H NMR (200 MHz, $CDCl_3$), 7.42 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 6.88 (s, 2 H, CH=CH), 4.66 (s, 2 H), 1.66–0.75 (m, 27 H, $SnBu_3$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 145.7, 140.2, 138.4, 129.9, 127.3, 126.3, 65.2, 29.2, 27.4, 13.8, 9.7.

(*E*)-Tributyl(4-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}styryl)stannane (5)

A 100-mL round-bottomed single-neck flask equipped with a condenser, an argon gas inlet, and a magnetic stir bar was charged with 2-[(4-ethynylbenzyl)oxy]tetrahydro-2*H*-pyran (**4**, 4.0 g, 18.5 mmol), Bu_3SnH (4.98 mL, 18.5 mmol), AIBN (121 mg), and toluene (45 mL). The flask was heated to 80 °C overnight under argon. The mixture was then cooled to r.t., and all volatiles were removed under reduced pressure to give a crude product that was purified by column chromatography (PE then PE–EtOAc,9:1) to give **5** as a colorless oil; yield: 6.1 g (65%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 6.88 (s, 2 H, CH=CH), 4.88–4.66 (m, 2 H), 4.51 (d, J = 12.2 Hz, 1 H), 4.02–3.86 (m, 1 H), 3.63–3.49 (m, 1 H), 1.96–1.22 (m, 19 H), 1.03–0.88 (m, 14 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 145.8, 138.3, 137.7, 129.6, 128.2, 126.1, 97.7, 68.6, 62.2, 30.7, 29.2, 27.4, 25.6, 19.5, 13.8, 9.7.

(*E*)-1,2-Dimethyl-5-nitro-4-(4-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}styryl)-1*H*-imidazole (7)

To a PEG-400 (15 mL) soln of 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**6**, 1.34 g, 6.08 mmol, 1 equiv) and styrylstannane **5** (4.01 g, 7.9 mmol, 1.3 equiv) was added $PdCl_2(PPh_3)_2$ (171 mg, 0.24 mmol, 4 mol%) and CuI (46 mg, 0.24 mmol, 4 mol%) in a microwave vial. The mixture was degassed with argon for 15 min and the vial was sealed with a septum. Then, the mixture was heated in a microwave oven at 150 °C for 1 h. After cooling, the mixture was quenched with sat. aq $NaHCO_3$. The mixture was extracted with EtOAc and the organic layer was washed with 5% KF solution and brine. The organic layer was dried (Na_2SO_4) and the volatiles were removed under vacuum. The crude was column chromatographed (silica gel, CH_2Cl_2–acetone, 10:0 then 9:1) provided **7** as a yellow solid; yield: 1.98 g (91%); mp 135 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (s, 2 H, CH=CH), 7.60 (d, J = 7.3 Hz, 2 H), 7.38 (d, J = 7.3 Hz, 2 H), 4.91–4.64 (m, 2 H), 4.52 (d, J = 12.4 Hz, 1 H), 3.98–3.89 (m, 4 H), 3.66–3.41 (m, 1 H), 2.49 (s, 3 H), 1.95–1.38 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.4, 142.6, 139.5, 136.5, 135.8, 128.3, 127.7, 117.9, 97.9, 68.6, 62.3, 34.2, 30.7, 25.6, 19.5, 14.4; CNO_2 not visible under these conditions.

LC-MS (ESI+): t_R = 3.55 min; m/z = 358.24 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{24}N_3O_4$: 358.1761; found: 358.1762.

(*E*)-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}methanol (8)[26]

To a soln of THP-protected alcohol **7** (1.98 g, 5.54 mmol) in MeOH (80 mL) was added a catalytic amount of PTSA (a spatula tip) under an argon atmosphere. The mixture was stirred overnight at r.t. The volatiles were removed under vacuum and the resulting mixture was triturated (minimal amount of Et_2O and a drop of CH_2Cl_2). Filtration of the suspension led to **8** as a yellow solid; yield: 1.48 g (98%); mp 177 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (s, 2 H, CH=CH), 7.60 (d, J = 8.1 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 4.71 (s, 2 H), 3.90 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.4, 142.5, 141.9, 136.4, 135.9, 127.9, 127.5, 118.0, 65.2, 34.2, 14.4; CNO_2 not visible under these conditions.

LC-MS (ESI+): t_R = 1.17 min; m/z = 274.30 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_3$: 274.1186; found: 274.1185.

(*E*)-4-[4-(Chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole (9)

To a 100-mL dry round-bottomed single-neck flask equipped with a condenser was introduced alcohol **8** (1.52 g, 5.55 mmol) and freshly distilled $SOCl_2$ (15 mL) under an argon atmosphere. The yellow mixture was vigorously stirred overnight at r.t. The excess $SOCl_2$ was distilled off. The crude product was triturated (PE–CH_2Cl_2 and a drop of MeOH), filtered, and thoroughly washed with PE leading to chloride **9** as a yellow solid; yield: 1.55 g (96%); mp 199 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.62 (s, 2 H, CH=CH), 7.46 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 4.48 (s, 2 H), 3.77 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.3, 141.6, 138.3, 136.5, 136.3, 129.1, 127.9, 118.0, 46.0, 34.2, 14.2; CNO_2 not visible under these conditions.

LC-MS (ESI+): t_R = 3.60 min; m/z = 292.06 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_3O_2Cl$: 292.0847; found: 292.0848.

(*E*)-4-(4-Substituted)styryl-1,2-dimethyl-5-nitro-1*H*-imidazoles 10a–j; General Procedure

A Schlenk tube equipped with a septum was charged with (*E*)-4-[4-(chloromethyl)styryl]-1,2-dimethyl-5-nitro-1*H*-imidazole (**9**, 120 mg, 0.41 mmol,1 equiv) and electrophile (1.23 mmol, 3 equiv). The tube was purged and filled with argon gas, and then anhydrous DMF (6 mL) was added. The solution was stirred at –20 °C and TDAE (125 μ L, 0.53 mmol, 1.3 equiv) was added dropwise via a syringe and the mixture was kept at this temperature for 1 h under vigorous stirring. The solution was then warmed to the required temperature and for the required time (see Table 2); TLC analysis showed the total consumption of **9**. The mixture was quenched with H_2O (5 mL) and EtOAc (15 mL) was added. The organic layer was washed with

H_2O (3 × 15 mL), dried (Na_2SO_4), and finally concentrated under vacuum. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2–acetone, 10:0 then 9:1) gave the corresponding compound **10**.

(*E*)-*N*-(2-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-1-phenylethyl)-4-methylbenzenesulfonamide (10a)
Yellow solid; yield: 114 mg (54%); mp 232 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.30 (d, *J* = 7.2 Hz, 1 H, NH), 7.61 (s, 2 H_{alkene}), 7.39 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.19–7.15 (m, 5 H), 7.13–7.00 (m, 4 H), 4.43 (d, *J* = 7.4 Hz, 1 H), 3.81 (s, 3 H), 2.83 (d, *J* = 7.5 Hz, 2 H), 2.44 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 150.3, 142.2, 141.7, 141.3, 139.0, 138.5, 135.5, 134.5, 134.0, 129.8, 129.0, 128.0, 126.9, 126.8, 126.6, 126.1, 117.2, 59.1, 43.1, 33.8, 20.9, 13.8.

LC-MS (ESI+): t_R = 4.06 min; *m*/*z* = 517.17 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{29}N_4O_4S$: 517.1904; found: 517.1903.

(*E*)-*N*-(2-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-1-{4-methoxyphenyl}ethyl)-4-methylbenzenesulfonamide (10b)
Yellow solid; yield: 110 mg (49%); mp 235 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.19 (d, *J* = 8.7 Hz, 1 H, NH), 7.60 (s, 2 H), 7.35 (dd, *J* = 16.4, 7.9 Hz, 4 H), 7.21–6.91 (m, 6 H), 6.71 (d, *J* = 8.3 Hz, 2 H), 4.38 (dd, *J* = 15.7, 7.6 Hz, 1 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 2.83 (d, *J* = 7.2 Hz, 2 H), 2.43 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 158.1, 150.3, 141.6, 141.3, 139.1, 138.6, 135.5, 134.5, 134.0, 133.9, 129.8, 129.0, 127.8, 126.9, 126.1, 117.2, 113.3, 58.6, 55.0, 43.1, 33.8, 20.9, 13.8.

LC-MS (ESI+): t_R = 3.90 min; *m*/*z* = 546.43 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{31}N_4O_5S$: 547.2010; found: 547.2010.

(*E*)-*N*-(2-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-1-{4-fluorophenyl}ethyl)-4-methylbenzenesulfonamide (10c)
Yellow solid; yield: 115 mg (52%); mp 240 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.30 (d, *J* = 8.8 Hz, 1 H), 7.60 (s, 2 H), 7.43–6.91 (m, 12 H), 4.46 (dd, *J* = 16.0, 7.6 Hz, 1 H), 3.79 (s, 3 H), 2.83 (d, *J* = 7.4 Hz, 2 H), 2.43 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 161.1 (d, *J* = 242.6 Hz), 150.3, 141.9, 141.3, 138.8, 138.4, 138.2 (d, *J* = 3.0 Hz), 135.5, 134.5, 134.0, 129.8, 129.0, 128.6 (d, *J* = 8.2 Hz), 126.9, 126.1, 117.3, 114.6 (d, *J* = 21.3 Hz), 58.4, 43.1, 33.8, 20.9, 13.8.

LC-MS (ESI+): t_R = 4.12 min; *m*/*z* = 534.96 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{28}N_4O_4SF$: 535.1810; found: 535.1810.

(*E*)-1-(4-Chlorophenyl)-2-{4-[2-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}ethanol (10d)[26]
Yellow solid; yield: 78 mg (38%); mp 192 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.61 (s, 2 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.33 (s, 4 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 5.42 (d, *J* = 4.6 Hz, OH), 4.78 (dd, *J* = 11.3, 6.1 Hz, 1 H), 3.78 (s, 3 H), 2.89 (d, *J* = 6.4 Hz, 2 H), 2.42 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 150.3, 144.5, 141.3, 140.0, 135.6, 134.4, 133.7, 131.2, 130.2, 127.9, 127.8, 126.8, 117.1, 72.8, 45.2, 33.8, 13.8.

LC-MS (ESI+): t_R = 3.99 min; *m*/*z* = 398.05 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}N_3O_3Cl$: 398.1266; found: 398.1268.

(*E*)-4-(2-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-1-hydroxyethyl)benzonitrile (10e)
Yellow solid; yield: 83 mg (52%); mp 227 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 7.77 (d, *J* = 8.2 Hz, 2 H), 7.62 (s, 2 H), 7.51 (d, *J* = 6.9 Hz, 4 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 5.59 (d, *J* = 4.7 Hz, OH), 4.88 (dd, *J* = 11.3, 6.1 Hz, 1 H), 3.80 (s, 3 H), 2.91 (d, *J* = 6.5 Hz, 2 H), 2.44 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 151.3, 150.3, 141.3, 139.7, 135.5, 134.5, 133.8, 131.9, 130.2, 127.0, 126.9, 119.0, 117.2, 109.5, 72.8, 44.9, 33.8, 13.8.

LC-MS (ESI+): t_R = 2.97 min; *m*/*z* = 389.10 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{21}N_4O_3$: 389.1608; found: 389.1610.

(*E*)-2-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-1-(4-nitrophenyl)ethanol (10f)
Yellow solid; yield: 70 mg (42%); mp 238 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 8.17 (d, *J* = 8.7 Hz, 2 H), 7.64–7.48 (m, 6 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 5.67 (d, *J* = 4.7 Hz, OH), 4.95 (dd, *J* = 11.7, 6.4 Hz, 1 H), 3.80 (s, 3 H), 2.94 (d, *J* = 6.2 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 153.5, 150.3, 146.4, 141.3, 139.5, 135.5, 134.5, 133.9, 130.2, 127.2, 126.9, 123.1, 117.2, 72.6, 44.9, 33.8, 13.8.

LC-MS (ESI+): t_R = 3.39 min; *m*/*z* = 409.01 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}N_4O_5$: 409.1506; found: 409.1503.

(*E*)-1-(2-Bromophenyl)-2-{4-[2-(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}ethanol (10g)
Yellow solid; yield: 60 mg (33%); mp 198 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.72 (s, 2 H), 7.61 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.40–7.24 (m, 4 H), 7.14 (td, *J* = 7.7, 1.6 Hz, 1 H), 5.25 (dd, *J* = 9.3, 3.0 Hz, 1 H), 3.86 (s, 3 H), 3.17 (dd, *J* = 13.8, 3.0 Hz, 1 H), 2.76 (dd, *J* = 13.8, 9.3 Hz, 1 H), 2.43 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.3, 143.1, 142.4, 142.4, 139.7, 136.9, 134.9, 132.7, 130.1, 129.0, 127.9, 127.8, 127.5, 121.8, 117.3, 73.9, 44.2, 34.2, 14.2.

LC-MS (ESI+): t_R = 4.11 min; *m*/*z* = 441.93 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{21}N_3O_3Br$: 442.0761; found: 442.0760.

Diethyl (*E*)-2-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]benzyl}-2-hydroxymalonate (10h)
Yellow solid; yield: 97 mg (55%); mp 153 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 1.4 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 3.87 (s, 3 H), 3.34 (s, 2 H), 2.47 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.0, 149.4, 142.5, 136.5, 135.8, 135.4, 130.9, 127.4, 117.8, 79.3, 62.8, 40.4, 34.1, 14.3, 14.1; CNO_2 not visible under these conditions.

LC-MS (ESI+): t_R = 3.35 min; *m*/*z* = 432.06 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_7$: 432.1765; found: 432.1764.

Ethyl (*E*)-3-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-2-hydroxy-2-methylpropanoate (10i)
Yellow solid; yield: 109 mg (71%); mp 142 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71 (s, 2 H), 7.51 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.13 (s, 1 H, OH), 3.00 (dd, *J* = 31.5, 13.5 Hz, 2 H), 2.48 (s, 3 H), 1.49 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.2, 149.4, 142.5, 137.3, 136.6, 135.1, 130.7, 127.4, 117.6, 75.2, 62.1, 46.2, 34.1, 26.1, 14.4, 14.3; CNO_2 not visible under these conditions.

LC-MS (ESI+): t_R = 3.15 min; *m*/*z* = 374.14 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{24}N_3O_5$: 374.1710; found: 374.1710.

Ethyl (*E*)-3-{4-[2-(1,2-Dimethyl-5-nitro-1*H*-imidazol-4-yl)vinyl]phenyl}-2-hydroxypropanoate (10j)
Yellow solid; yield: 55 mg (37%); mp 112 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 1.3 Hz, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 4.43 (s, 1 H, OH), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.13 (dd, *J* = 13.9, 4.5 Hz, 1 H), 3.04–2.85 (m, 2 H), 2.47 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.2, 149.4, 142.6, 137.6, 136.5, 135.1, 130.1, 127.6, 117.7, 71.2, 61.9, 40.5, 34.1, 14.4, 14.3; CNO_2 not visible under these conditions.

LC-MS (ESI+): t_R = 2.73 min; *m*/*z* = 360.24 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}N_3O_5$: 360.1554; found: 360.1555.

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