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Note

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Copper-Mediated N-Arylations of Hydantoins

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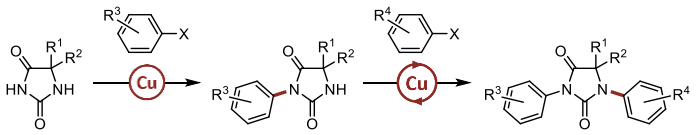
ABSTRACT. A set of two broadly applicable procedures for the N-arylation of hydantoins is reported. The first one relies on the use of stoichiometric copper(I) oxide under ligandless and base-free conditions and enables a clean regioselective arylation at the N^3 nitrogen atom while the second one is based on the use of catalytic copper(I) iodide and *trans-N,N'*-dimethylcyclohexane-1,2-diamine and promotes arylation at the N^1 nitrogen atom. Importantly, the combination of these two procedures affords a straightforward entry to diarylated hydantoins.



Since their discovery by Adolf von Baeyer in 1861,[1] imidazolidine-2,4-diones, more commonly known as hydantoins, have become a major scaffold with applications in many

areas of science.[2] Indeed, in addition to their occurrence in some natural products[3] and to their use in organic synthesis,[4] coordination chemistry,[5] polymer science,[6] or for the design of molecular switches,[7] they had a deep impact in medicinal chemistry and agrochemistry.[2] The most famous and representative hydantoin drugs[2] include Sanofi-Aventis' anti-androgen Nilutamide **1**, Pfizer's anticonvulsant Fosphenytoin **2** or Shionogi's antibacterial Nitrofurantoin **3** (Figure 1). Various clinical candidates based on the hydantoin skeleton have in addition been recently reported, Bristol-Myers Squibb's anti-psoriasis BMS-587101 **4** or Galapagos' anti-cachexia GLGP-0492 **5** being representative examples. Hydantoin derivatives such as thiohydantoins have in addition also revealed to be important in healthcare, as highlighted with Medivation/Astellas' anticancer drug Enzalutamide **6**.[8]

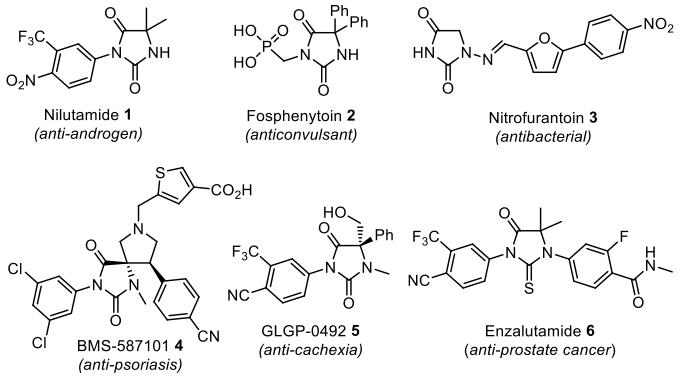


Figure 1. Representative (thio)hydantoin drugs and clinical candidates.

During the past decade, the interest for hydantoins has not declined, which resulted in more than 3.000 publications and patents. This has stimulated many efforts for the development of synthetic routes to hydantoins: in addition to be efficient, reliable and short, they moreover need to be highly modular in a diversity-oriented approach. Classical synthetic pathways to hydantoins such as the Read,[9] Bucherer-Bergs[10] or Blitz[11] reactions indeed all suffer from

limitations and a variety of alternative processes have been reported over the years.[2] However, among all classes of hydantoins, N-arylated ones, that are of particular interest in medicinal chemistry, are not trivial to access using classical methods, notably in terms of the starting materials required. An interesting strategy that would, in addition to involve a limited number of steps from readily available starting materials, be especially relevant for structural diversification, would be based on direct N-arylations of the bare hydantoin scaffold. For some reasons, this attractive approach to *N*-aryl-hydantoins has been mostly restricted to nucleophilic aromatic substitutions and barely investigated:[12-14] we report in this manuscript a set of efficient procedures for the selective arylation of hydantoins at the two nitrogen atoms.

Copper-mediated N^3-arylation of hydantoins. Indeed, based on our combined interests in copper-catalysis[15,16] and process chemistry,[17] we became interested at developing general processes for the arylation of hydantoins at the two nucleophilic nitrogen atoms. We initiated our studies by carefully investigating the scope of the copper-mediated arylation at N^3, a reaction that is best performed under ligandless conditions in the presence of stoichiometric copper(I) oxide,[12b-d] most certainly due to the starting hydantoins acting as supporting ligands that can in addition result in the formation of catalytically inactive copper complexes in the presence of catalytic amounts of copper(I) only. Results from these studies are shown in Figure 2.

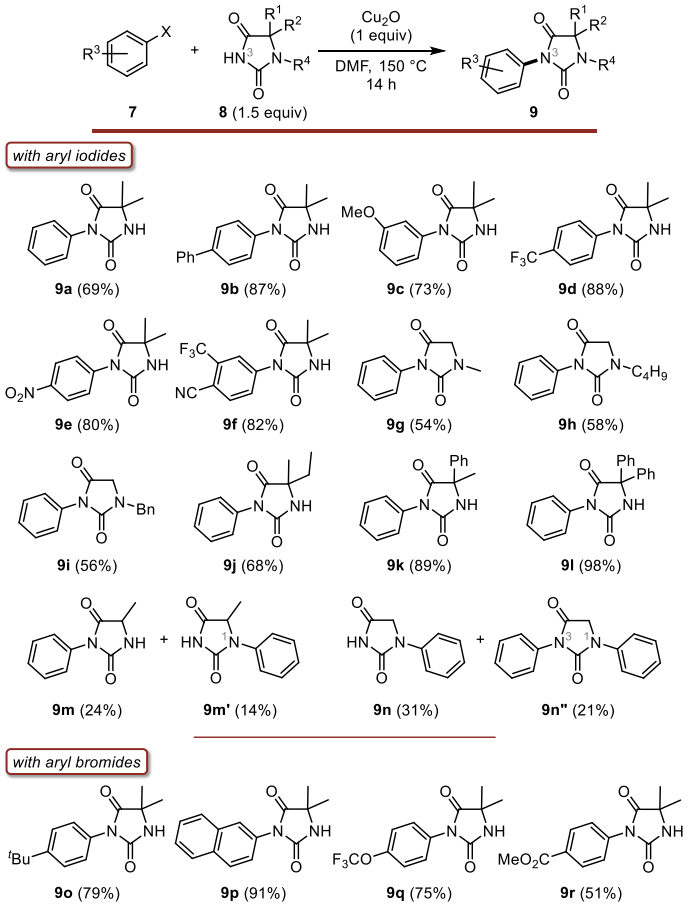


Figure 2. Scope of the copper-mediated N^3-arylation of hydantoins.

As illustrated with results from Figure 2, the arylation at N^3 was found to be rather general since upon simple reaction with one equivalent of copper(I) oxide and aryl iodides **7** in DMF at 150 °C for 14 h without an additional base, a range of hydantoins **8** could be readily and selectively arylated at N^3, providing the corresponding *N^3*-aryl-hydantoins **9a**-**n** that could be isolated in good to excellent yields. The reaction was found to proceed smoothly with a range of aryl iodides, regardless of their electronic properties and a variety of hydantoins could be arylated under these conditions. The substitution pattern of the starting hydantoin was however found to have a significant impact on the selectivity of the reaction starting from hydantoins unsubstituted at N^1. Indeed, while 5,5-disubstituted hydantoins were selectivity arylated at N^3 in all cases, removing one of these substituents led to significant competing

arylation at N^1, as demonstrated with the isolation of **9m** and **9m'** in a ca. 2:1 ratio, and the absence of substituents at this position favored the N^1 arylation, *N^1*-phenyl-hydantoin **9n** being now obtained with significant amounts of diarylated product **9n"**. Gratifyingly, the reaction could be successfully extended to the use of aryl bromides, as demonstrated with the arylation to **9o**-**r** isolated in fair to good yields.

Copper-catalyzed N^1-arylation of hydantoins. After briefly studying the scope of the arylation at N^3, we then moved to the more challenging N^1-arylation. To make sure aryl bromides could be used in this transformation, the optimization was performed using 1.2 equiv of aryl bromide **10** and sterically hindered hydantoin **9f**, the resulting N^1-arylated product **11a** being an oxygenated analogue of Enzalutamide **6**. These model substrates were therefore reacted with 20 mol % of copper(I) iodide, 40 mol % of various ligands in the presence of 2 equiv of potassium carbonate in toluene at 110 °C for 64 h: results from these studies are shown in Figure 3. Most ligands commonly used in copper-catalyzed cross-coupling reactions including 2,2,6,6-tetramethyl-3,5-heptanedione $\mathbf{L_1}$, proline $\mathbf{L_2}$, 1,2-dimethylimidazole $\mathbf{L_3}$, 2,2'-bipyridine $\mathbf{L_4}$, and 1,10-phenanthroline $\mathbf{L_5}$ failed to promote the arylation, most certainly because of catalyst deactivation due to multiple coordination of the starting hydantoin, as suggested by its non-total recovery. Excepted for TMEDA, diamine ligands turned out to be more efficient, *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine (Me_2CyDA) being by far the most efficient and promoting the coupling to **11a** in 61% yield, a yield that could be further improved to 70% by using 1.4 equivalents of aryl bromide **10**. As for the reaction time, it could be reduced to 48 h without affecting the yield. Further evaluation of different copper sources (CuBr, CuCl, CuTC, CuOAc, $Cu(CH_3CN)_4PF_6$), bases (K_3PO_4, Cs_2CO_3), solvents (dioxane, acetonitrile, DMF, DMSO) and additives (NaI) did not allow a significant further improvement.

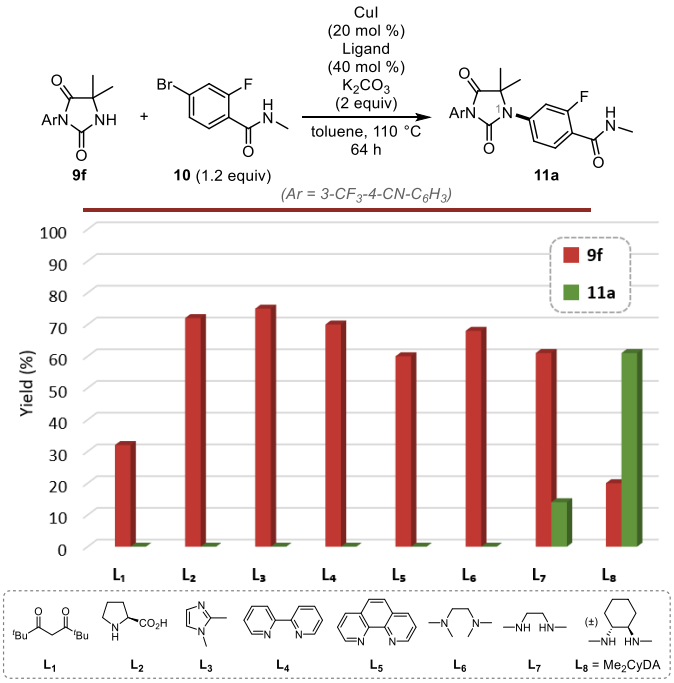


Figure 3. Effect of the ligand on the copper-catalyzed N^1-arylation of hydantoins.

Having these optimized conditions in hand, we next turned our attention to the study of the scope and limitations of the N^1-arylation using representative hydantoins **12** and aryl halides **7** (Figure 4). Gratifyingly, the reaction scope was found to be especially broad, the arylation proceeding smoothly with eletron-rich (**11b**-**d**) and electron-poor (**11e**-**g**) aryl bromides. It could be extended to the introduction of heteroaryl substituents such as a thiophene (**11j**), a pyridine (**11k**) or a benzofuran (**11l**), the main limitation being the absence of reactivity starting with *ortho*-substituted aryl bromides (**11i**). Not surprisingly, aryl iodides performed equally well and similar trends were observed with these reagents. The nature of the substituent(s) at C5 on the starting hydantoin was found to have little effect on the reaction outcome, as demonstrated with the arylation to **11s-v** which all proceeded smoothly. The arylation to **11t** is in addition quite remarkable due to the high steric hindrance close to the reacting center that still did not inhibit the arylation. Finally, it should be noted that various

functional groups such as an ether (**11d**,**p**), an ester (**11e**,**v**), a ketone (**11f**) or a nitro (**11r**) were shown to be compatible with the reaction conditions.

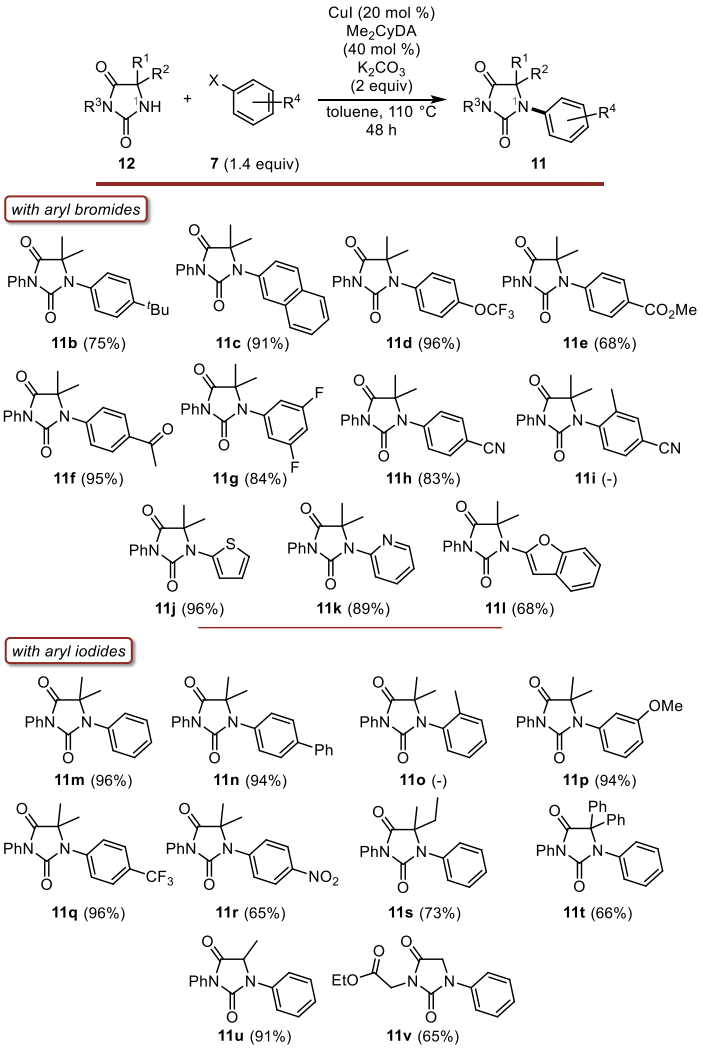


Figure 4. Scope of the copper-catalyzed N^1-arylation of hydantoins.

Interestingly, the N^3-aryl-hydantoins **9** resulting from the first arylation were also shown to be excellent substrates for the copper-catalyzed N^1-arylation, as highlighted in Figure 5. Our two procedures therefore enable clean, selective and efficient iterative arylations to N^1,N^3-diaryl-hydantoins **11a**,**w**-**ad**, attractive scaffolds in medicinal chemistry, and facilitate diversification by a simple modulation of the two aryl groups introduced.

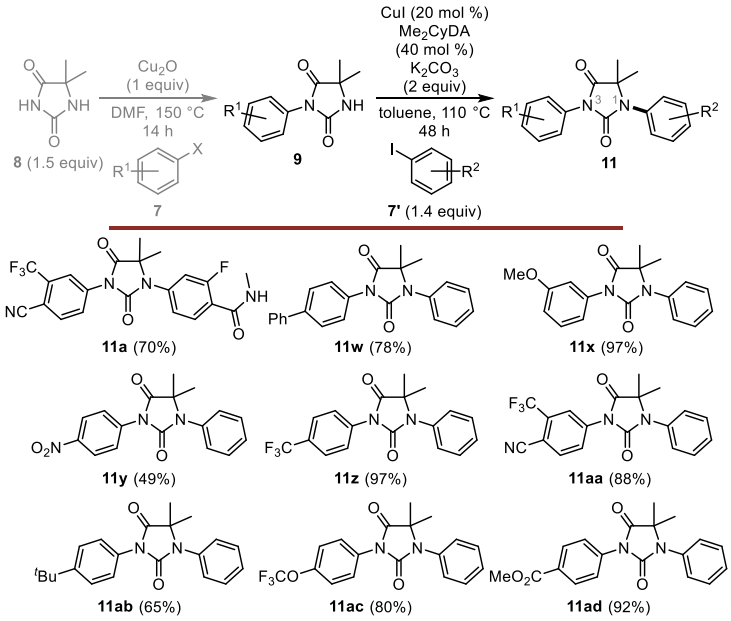
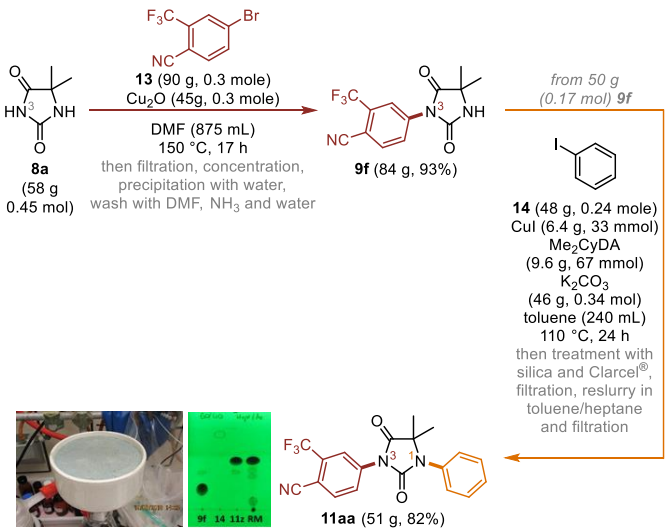


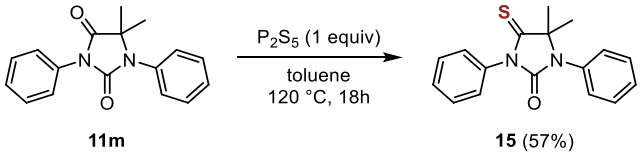
Figure 5. Iterative arylations to N^1,N^3-diaryl-hydantoins.

Copper-mediated iterative arylations of hydantoins on multigram scales. In a final effort to demonstrate the synthetic potential of our procedures, a scale up of the iterative arylations was finally explored. As highlighted in Scheme 1, this turned out to be especially efficient, the first copper-mediated ligandless and base-free arylation of **8a** with **13** providing the desired N^3-arylated product **9f** in 93% on a 84 g scale, using simple purification by precipitation and successive washes with DMF, aqueous ammonia and water. The second arylation at N^1 was undertaken on a 50 g scale using iodobenzene **14** as the arylating agent and gave, after treatment with a mixture of silica and Carcel®, filtration, reslurry in a mixture of toluene and heptane and filtration, the desired doubly arylated hydantoin **11aa** with 82% yield, therefore demonstrating the robustness of the sequence.



Scheme 1. Multigram scale iterative arylations.

C[4]-selective thionation of Diarylhydantoins. We finally turned our attention to the extension of these procedures to the arylations of thiohydantoins: despite extensive trials, we could not find conditions enabling these arylations, which might be due to competing complexation of copper by these substrates which are excellent ligands for copper. Considering in addition that thiohydantoins are known to coordinate to copper by the sulfur atom,[18] their arylation might proceed at sulfur rather than nitrogen. To circumvent this problem, the regioselective thionation of *N*[1],*N*[3]-diphenylhydantoin **11m** with various reagents was examined: of all reagents evaluated, phosphorus pentasulfide P_2S_5 was found the most efficient and enabled a clean and C4-selective thionation to **15** (Scheme 2).[19]



Scheme 2. C4-selective thionation of a *N*[1],*N*[3]-diarylhydantoin.

Conclusions

In conclusion, we have developed and studied a set of two efficient and broadly applicable procedures for the N-arylation of hydantoins at the two nitrogen atoms. The first one relies on the use of stoichiometric amounts of copper(I) oxide under ligandless and base-free conditions and enables a clean and regioselective arylation at the N^3 nitrogen atom while the second one is based on the use of catalytic amounts of copper(I) iodide and *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine and promotes arylation at the N^1 nitrogen atom. The scope of these two procedures have been shown to be quite broad and they are both tolerant to a range of functional groups. Moreover, they rely on simple copper salts and ligands and their robustness on multigram scale has been demonstrated. Importantly, the combination of these two procedures affords a straightforward and general entry to diarylated hydantoins, important scaffolds in medicinal chemistry.

Experimental Section

General Information. All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials unless otherwise stated.

All reagents and solvents were reagent grade. *N,N*-dimethylformamide (99.8%, Extra Dry over Molecular Sieve, AcroSeal®) and toluene (99.5%, Extra Dry over Molecular Sieve, AcroSeal®) were purchased from ACROS Organics and used as supplied.

Copper(I) iodide (99,999% purity) was purchased from Aldrich and used as supplied. Finely powdered anhydrous cesium carbonate was used for copper-mediated coupling reactions. All other reagents were used as supplied.

Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel 60F254 plates. Flash chromatography was performed with silica gel 60 (particle size 35-70 μm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on Bruker 300 or Jeol 400 and 600 MHz spectrometers. Internal reference of δ_H 7.26 was used for $CDCl_3$, δ_H 2.05 was used for acetone-*d*$_6$ and δ_H 2.50 was used for DMSO-*d*$_6$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} = 0), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sext. = sextuplet, m = multiplet, br. = broad, app. = apparent), coupling constant (J/Hz) and integration. Carbon-13 NMR spectra were recorded at 100 or 150 MHz using $CDCl_3$ (δ_C 77.16), acetone-*d*$_6$ (δ_C 29.84) or DMSO-*d*$_6$ (δ_C 39.52) as internal reference. Fluorine-19 NMR spectra were recorded at 376 MHz using CF_3CH_2OH (δ_F -77.59) as internal reference.

Melting points were recorded on a Stuart Scientific Analogue SMP11. Infrared spectra were recorded on a Bruker Alpha (ATR). High-resolution mass-spectra were recorded using a Agilent QTOF 6520 spectrometer.

N^3-Arylation of Hydantoins

General Procedure. A 15 mL pressure tube was charged with the hydantoin (3.0 mmol) and copper oxide (I) (286 mg, 2.0 mmol); the aryl halide (2.0 mmol) was added at this stage if solid.

The tube was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon (three times) before adding the aryl halide (added at this stage if liquid) (2.0 mmol) and anhydrous DMF (5mL). The rubber septum was then replaced by a Teflon-coated screw cap before heating the heterogeneous reaction mixture at 150 °C for 14 hours. The suspension was cooled to room temperature, filtered through a pad of Celite® (washed with EtOAc) and the filtrate was concentrated to *ca.* one tenth of its volume under reduced pressure, poured into a mixture of ice and water (10 mL) and stirred for 30 minutes before adding a 28% aqueous ammonia solution (3 mL). The resulting suspension was stirred for 30 minutes and the precipitate collected by filtration then dried under high vacuum to give the desired arylated hydantoin which was, whenever required, further purified by flash column chromatography over silica gel.

5,5-Dimethyl-3-phenylhydantoin 9a. Yield: 69% (280 mg, 1.37 mmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40. This compound has been previously reported.[20]

3-(1,1'-Biphenyl-4-yl)-5,5-dimethylhydantoin 9b. Yield: 87% (404 mg, 1.44 mmol). White solid, Mp: 185 °C; ^{1}H NMR (600 MHz, acetone-d_6): δ 7.74 (d, J = 8.6 Hz, 2H), 7.72-7.68 (m, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.53-7.43 (m, 3H), 7.38 (t, J = 7.4 Hz, 1H), 1.52 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, acetone-d_6): δ 177.1, 155.2, 141.1, 141.0, 133.0, 129.8, 128.4, 127.8, 127.8, 127.6, 58.9, 25.4; IR (neat): ν_{max} 1713, 1428, 1303, 1144, 837, 768 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1285, found 281.1290.

5,5-Dimethyl-3-(3-methoxyphenyl)-hydantoin 9c. Yield: 73% (344 mg, 1.47 mmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 60/40; Beige solid, Mp: 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (app. t, J = 8.2 Hz, 1H), 7.12-7.01 (m, 1H), 6.99 (d, J = 7.9 Hz,

1H), 6.96-6.90 (m, 2H), 3.81 (br. s, 3H), 1.49 (br. s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 160.1, 155.8, 132.7, 129.8, 118.6, 114.2, 112.1, 58.7, 55.5, 25.1; IR (neat): ν_{max} 2976, 1716, 1418, 1151, 1043, 782, 702 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{15}N_2O_3$ $[M+H]^+$ 235.1077, found 235.1080.

5,5-Dimethyl-3-(4-trifluoromethylphenyl)hydantoin 9d. Yield: 88% (479 mg, 1.76 mmol). Off white solid, Mp: 179 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 7.79 (dd, J = 21.3 and 8.6 Hz, 4H), 7.59 (br. s, 1H), 1.52 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d_6): δ 176.8, 154.6, 137.4, 129.4 (q, J_{C-F} = 32.5 Hz), 127.3, 126.4 (q, J_{C-F} = 3.9 Hz), 123.8, 59.0, 25.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.4 (s); IR (neat): ν_{max} 2361, 1732, 1719, 1410, 1324, 1172, 1110, 1066, 836, 709 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{12}F_3N_2O_2$ $[M+H]^+$ 273.0845, found 273.0849.

5,5-Dimethyl-3-(4-nitrophenyl)hydantoin 9e. Yield: 80% (397 mg, 1.59 mmol). Beige solid, Mp: 168 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.35 (d, J = 9.2 Hz, 2H), 7.86 (d, J = 9.2 Hz, 2H), 7.68 (br. s, 1H), 1.54 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d_6): δ 176.7, 154.3, 147.0, 139.6, 127.1, 124.6, 59.0, 25.3; IR (neat): ν_{max} 2360, 1721, 1522, 1401, 1342, 1135, 841, 726 cm^{-1}; ESIHRMS *m/z* calcd for $C_{11}H_{11}N_3O_4$ $[M+H]^+$ 250.0822, found 250.0829.

5,5-Dimethyl-3-(3-trifluoromethyl-4-cyano-phenyl)hydantoin 9f. Yield: 82% (6.8 g, 22.9 mmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10. This compound has been previously reported.[21]

1-Methyl-3-phenylhydantoin 9g. Yield: 54% (207 mg, 1.09 mmol). Off white solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 50/50. This compound has been previously reported.[22]

1-Butyl-3-phenylhydantoin 9h. Yield: 58% (270 mg, 1.16 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30; Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.33 (m, 5H), 4.02 (s, 2H), 3.48 (t, J = 7.3 Hz, 2H), 1.69-1.53 (m, 2H), 1.40 (sext., J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 169.1, 155.6, 132.0, 129.2, 128.2, 126.2, 49.7, 42.8, 29.9, 20.0, 13.8; IR (neat): ν_{max} 2960, 1713, 1503, 1456, 1420, 1244, 1193, 1136, 760, 692 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{16}N_2O_2Na$ $[M+Na]^+$ 255.1104, found 255.1109.

1-Benzyl-3-phenylhydantoin 9i. Yield: 56% (297 mg, 1.11 mmol). Pale yellow solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30. This compound has been previously reported.[23]

5-Ethyl-5-methyl-3-phenylhydantoin 9j. Yield: 68% (298 mg, 1.36 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 70/30; White solid, Mp: 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.44 (m, 2H), 7.42-7.34 (m, 3H), 6.97 (br. s, 1H), 1.93 (A of ABX_3 syst., J = 14.7 and 7.4 Hz, 1H), 1.71 (B of ABX_3 syst., J = 14.7 and 7.4 Hz, 1H), 1.47 (s, 3H), 0.94 (X of ABX_3 syst., J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.1, 156.4, 131.7, 129.2, 128.3, 126.3, 62.4, 31.2, 23.7, 7.9; IR (neat): ν_{max} 2934, 2368, 1714, 1504, 1412, 1134, 846, 709 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{15}N_2O_2$ $[M+H]^+$ 219.1128, found 219.1143.

3,5-Diphenyl-5-methylhydantoin 9k. Yield: 89% (1.6 g, 5.86 mmol). White solid. This compound has been previously reported.[24]

3,5,5-Triphenylhydantoin 9l. Yield: 98% (642 mg, 1.95 mmol). White solid. This compound has been previously reported.[25]

5-Methyl-3-phenylhydantoin 9m. Yield: 24% (92 mg, 483 µmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40. This compound has been previously reported.[26]

5-Methyl-1-phenylhydantoin 9m'. Yield: 14% (53 mg, 279 µmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40. This compound has been previously reported.[27]

1-Phenylhydantoin 9n. Yield: 31% (110 mg, 625 µmol). White solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40. This compound has been previously reported.[28]

1,3-Diphenylhydantoin 9n''. Yield: 21% (52 mg, 206 µmol). Off white solid. Solvent system for flash column chromatography: petroleum ether/EtOAc: 60/40. This compound has been previously reported.[29]

3-(4-*tert*-Butylphenyl)-5,5-dimethylhydantoin 9o. Yield: 79% (412 mg, 1.58 mmol). White solid, Mp: 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 6.09 (br. s, 1H), 1.54 (s, 6H), 1.33 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 155.7, 151.4, 129.0, 126.2 (br.), 125.8 (br.), 58.7, 34.8, 31.5 (br.), 25.4 (br.); IR (neat): ν_{max} 2970, 1715, 1520, 1422, 1145, 831 cm^{-1}; ESIHRMS *m/z* calcd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$ 261.1598, found 261.1594.

5,5-Dimethyl-3-(naphthalen-2-yl)hydantoin 9p. Yield: 91% (461 mg, 1.81 mmol). White solid, Mp: 212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.92 (m, 2H), 7.90-7.85 (m, 2H), 7.55-7.49 (m, 3H), 6.26 (br. s, 1H), 1.57 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 155.7, 133.3, 132.8, 129.1 (2C), 128.3, 127.9, 126.9, 126.7, 125.3, 123.9, 58.9, 25.5; IR (neat): ν_{max} 1722,

1426, 1151, 811, 749 cm^{-1}; ESIHRMS *m/z* calcd for $C_{15}H_{15}N_2O_2$ $[M+H]^+$ 255.1128, found 255.1138.

5,5-Dimethyl-3-(4-trifluoromethoxyphenyl)hydantoin 9q. Yield: 75% (431 mg, 1.50 mmol). Off white solid, Mp: 146 °C; ^1H NMR (600 MHz, acetone-d_6): δ 7.62 (d, J = 9.0 Hz, 2H), 7.52 (br. s, 1H), 7.44 (d, J = 8.5 Hz, 2H), 1.51 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ 176.9, 154.9, 148.5, 132.7, 128.8, 122.1, 121.4 (q, J_{C-F} = 255.5 Hz), 59.0, 25.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.2 (s); IR (neat): ν_{max} 2937, 2361, 1719, 1513, 1407, 1255, 1186, 1135, 839 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{12}F_3N_2O_3$ $[M+H]^+$ 289.0795, found 289.0799.

5,5-Dimethyl-3-(4-methoxycarbonylphenyl)hydantoin 9r. This compound was prepared according to the general procedure with an additional extraction (EtOAc) of the filtrate. Yield: 51% (267 mg, 1.02 mmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 60/40; White solid, Mp: 141 °C; ^1H NMR (300 MHz, acetone-d_6): δ 8.09 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.56 (br. s, 1H), 3.90 (s, 3H), 1.52 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ 176.8, 166.6, 154.7, 137.9, 130.4, 129.7, 126.7, 58.9, 52.5, 25.3; IR (neat): ν_{max} 1729, 1715, 1412, 1276, 1143, 773, 726, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{15}N_2O_4$ $[M+H]^+$ 263.1026, found 263.1030.

N^1-Arylation of Hydantoins

General Procedure. A 15 mL pressure tube was charged with the arylated hydantoin (1.0 mmol), copper iodide (38 mg, 0.2 mmol) and potassium carbonate (276 mg, 2.0 mmol); the aryl halide (1.4 mmol) was added at this stage if solid. The tube was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon (three times) before adding the aryl halide (added at this stage if liquid) (1.4 mmol), anhydrous toluene (1.5 mL) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.4 mmol). The rubber septum was then

replaced by a Teflon-coated screw cap before heating the reaction mixture at 110 °C for 48 hours. The suspension was cooled to room temperature, filtered over a plug of silica gel/Celite® (washed with EtOAc) and concentrated. The crude residue was finally purified by flash chromatography over silica gel.

5,5-Dimethyl-1-(4-methylcarbamoylphenyl)-3-(3-trifluoromethyl-4-cyano-phenyl)hydantoin 11a. Yield: 70% (2.9 g, 6.38 mmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 50/50. This compound has been previously reported.[30]

1-(4-*tert*-Butylphenyl)-5,5-dimethyl-3-phenylhydantoin 11b. Yield: 75% (251 mg, 746 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; Off white solid, Mp: 141 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53-7.49 (m, 2H), 7.49-7.45 (m, 4H), 7.39-7.35 (app. tt, J = 7.3 and 1.4 Hz, 1H), 7.25-7.22 (d, J = 8.6 Hz, 2H), 1.55 (s, 6H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 175.4, 154.1, 151.7, 132.0, 131.2, 129.1, 128.6, 128.1, 126.6, 126.2, 63.5, 34.8, 31.4, 24.2; IR (neat): ν_{max} 2968, 1715, 1396, 1204, 1138, 766 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$ 337.1911, found 337.1913.

5,5-Dimethyl-1-(naphthalen-2-yl)-3-phenylhydantoin 11c. Yield: 91% (300 mg, 908 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20; Beige solid, Mp: 163 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (d, J = 8.7 Hz, 1 H), 7.92-7.85 (m, 2H), 7.84 (d, J = 2.0 Hz, 1H), 7.58-7.54 (m, 4H), 7.52-7.48 (m, 2H), 7.43 (dd, J = 8.7 and 2.1 Hz, 1H), 7.39 (tt, J = 7.4 and 1.3 Hz, 1H), 1.62 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 175.3, 154.2, 133.6, 133.0, 131.9, 131.6, 129.6, 129.1, 128.2, 128.1, 127.9, 127.9, 127.0, 126.9, 126.6, 126.3, 63.8, 24.4; IR (neat): ν_{max} 2981, 1716, 1504, 1401, 1201, 1143, 779 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$ 331.1441, found 331.1440.

5,5-Dimethyl-3-phenyl-1-(4-trifluoromethoxyphenyl)hydantoin 11d. Yield: 96% (349 mg, 958 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 95/5; Pale yellow solid, Mp: 96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.44 (m, 4H), 7.40-7.34 (m, 3H), 7.32-7.27 (m, 2H), 1.53 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.8, 153.8, 148.8, 132.6, 131.7, 130.3, 129.0, 128.2, 126.1, 121.9, 120.4 (q, J = 258.0 Hz), 63.5, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3 (s); IR (neat): ν_{max} 1715, 1506, 1411, 1266, 1200, 1156, 770 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{16}F_3N_2O_3$ $[M+H]^+$ 365.1108, found 365.1109.

5,5-Dimethyl-1-(4-methoxycarbonylphenyl)-3-phenylhydantoin 11e. Yield: 68% (231 mg, 682 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20; White solid, Mp: 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.6 Hz, 2H), 7.50-7.43 (m, 6H), 7.42-7.35 (m, 1H), 3.93 (s, 3H), 1.59 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.8, 166.3, 153.8, 138.9, 131.6, 130.9, 129.7, 129.1, 128.4, 127.8, 136.2, 63.9, 52.4, 24.4; IR (neat): ν_{max} 2977, 1708, 1414, 1276, 1201, 1112, 769 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ 339.1339, found 339.1341.

1-(4-Acetylphenyl)-5,5-dimethyl-3-phenylhydantoin 11f. Yield: 95% (305 mg, 947 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 70/30; Yellow solid, Mp: 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.01 (d, J = 8.4 Hz, 2H), 7.51-7.44 (m, 6H), 7.41-7.35 (m, 1H), 2.61 (s, 3H), 1.60 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 197.0, 174.8, 153.7, 139.0, 136.4, 131.6, 129.6, 129.1, 128.4, 127.8, 126.2, 63.9, 26.7, 24.4; IR (neat): ν_{max} 2969, 1710, 1675, 1405, 1363, 1202, 766 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1390, found 323.1399.

1-(3,5-Difluorophenyl)-5,5-dimethyl-3-phenylhydantoin 11g. Yield: 84% (267 mg, 847 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 95/5; Beige solid, Mp:

122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.45 (m, 4H), 7.43-7.36 (m, 1H), 6.96 (app. dd, J = 7.7 and 2.2 Hz, 2H), 6.86 (app. tt, J = 8.8 and 2.3 Hz, 1H), 1.59 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.5, 163.3 (d, J = 249.6 Hz), 163.2 (d, J = 249.5 Hz), 153.6, 136.9 (app. t, J = 12.4 Hz), 131.5, 129.2, 128.5, 126.2, 111.4 (d, J = 27.1 Hz), 111.4 (d, J = 11.7 Hz), 104.0 (app. t, J = 25.2 Hz), 63.9, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.1 (t, $J_{C\text{-}F}$ = 8.1 Hz); IR (neat): ν_{max} 1717, 1412, 1304, 1120, 990, 859, 731 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{15}F_2N_2O_2$ $[M+H]^+$ 317.1096, found 317.1107.

5,5-Dimethyl-1-(4-cyano-phenyl)-3-phenylhydantoin 11h. Yield: 83% (124 mg, 407 µmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 75/25; White solid, Mp: 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.52-7.45 (m, 4H), 7.43-7.38 (m, 1H), 1.63 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.5, 153.7, 139.2, 133.6, 131.4, 129.3, 128.6, 127.9, 126.2, 118.1, 111.7, 64.1, 24.6; IR (neat): ν_{max} 2225, 1780, 1722, 1503, 1406, 1350, 1198, 838, 742 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{15}N_3O_2Na$ $[M+Na]^+$ 328.1056, found 328.1056.

5,5-Dimethyl-3-phenyl-1-(thiophen-2-yl)hydantoin 11j. Yield: 96% (274 mg, 956 µmol). Solvent system for flash column chromatographyz: cyclohexane/EtOAc: 80/20; Beige solid, Mp: 99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.44 (m, 4H), 7.41-7.35 (m, 2H), 7.34-7.30 (m, 1H), 7.20-7.15 (m, 1H), 1.60 (br. s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.0, 153.4, 132.3, 131.7, 129.1, 128.2, 126.2, 125.7, 125.4, 119.6, 63.3, 23.9; IR (neat): ν_{max} 1711, 1412, 1338, 1200, 736, 690 cm^{-1}; ESIHRMS *m/z* calcd for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$ 287.0849, found 287.0860.

5,5-Dimethyl-3-phenyl-1-(pyridin-2-yl)hydantoin 11k. Yield: 89% (250 mg, 887 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; White solid, Mp: 101 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, J = 4.9 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.53-7.45 (m, 4H), 7.43-7.38 (m, 1H), 7.10-7.05 (m, 1H), 1.93 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.5, 153.2, 150.7, 147.4, 138.0, 131.5, 129.2, 128.5, 126.5, 119.9, 116.2, 64.6, 23.9; IR (neat): ν_{max} 1716, 1407, 1360, 1200, 1154, 884, 767 cm^{-1}; ESIHRMS *m/z* calcd for $C_{16}H_{16}N_3O_2$ $[M+H]^+$ 282.1237, found 282.1249.

1-(Benzofuran-2-yl)-5,5-dimethyl-3-phenylhydantoin 11l. Yield: 68% (219 mg, 684 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 95/5; Off white solid, Mp: 99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.2 Hz, 1H), 7.55-7.47 (m, 5H), 7.47-7.39 (m, 1H), 7.35-7.25 (m, 2H), 6.83 (s, 1H), 1.80 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.4, 152.0, 151.6, 145.0, 131.3, 129.2, 128.6, 128.2, 126.3, 124.1, 123.5, 121.0, 111.0, 97.8, 64.0, 24.0; IR (neat): ν_{max} 2360, 1717, 1604, 1405, 1385, 1240, 1151, 740 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{16}N_2O_3Na$ $[M+Na]^+$ 343.1053, found 343.1072.

5,5-Dimethyl-1,3-diphenylhydantoin 11m. Yield: 96% (1.3 g, 4.67 mmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 85/15. This compound has been previously reported.[31]

1-(1,1'-Biphenyl-4-yl)-5,5-dimethyl-3-phenylhydantoin 11n. Yield: 94% (333 mg, 935 µmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10. This compound has been previously reported.[14a]

5,5-Dimethyl-1-(3-methoxyphenyl)-3-phenylhydantoin 11p. Yield: 94% (292 mg, 941 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 85/15; White solid, Mp: 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.44 (m, 4H), 7.40-7.33 (t, J = 8.2 Hz 2H), 6.98-6.89 (m, 2H), 6.87 (t, J = 2.2 Hz, 1H), 3.82 (s, 3H), 1.56 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.2, 160.5, 159.9, 135.2, 131.9, 130.2, 129.1, 128.2, 126.2, 121.0, 114.9, 114.2, 63.6, 55.6,

24.2; IR (neat): ν_{max} 1715, 1599, 1400, 1248, 797, 693 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1390, found 311.1404.

5,5-Dimethyl-3-phenyl-1-(4-trifluoromethylphenyl)hydantoin 11q. Yield: 96% (336 mg, 964 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; Yellow solid, Mp: 100 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75-7.70 (d, *J* = 8.1 Hz, 2H), 7.54-7.45 (m, 6H), 7.42-7.35 (m, 1H), 1.59 (br. s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.7, 153.8, 137.9, 131.6, 130.1 (q, *J* = 32.8 Hz), 129.1, 128.4, 128.3, 126.7 (q, *J* = 3.6 Hz), 126.1, 123.8 (q, *J* = 272.4 Hz), 63.8, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.1 (s); IR (neat): ν_{max} 1715, 1414, 1322, 1122, 1067, 753 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{16}F_3N_2O_2$ $[M+H]^+$ 349.1158, found 349.1167.

5,5-Dimethyl-1-(4-nitrophenyl)-3-phenylhydantoin 11r. Yield: 65% (213 mg, 654 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 70/30; Yellow solid, Mp: 131 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30-8.23 (m, 2H), 7.62-7.57 (m, 2H), 7.50-7.44 (m, 4H), 7.42-7.35 (m, 1H), 1.63 (br. s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 153.5, 146.3, 140.9, 131.3, 129.1, 128.5, 127.3, 126.1, 124.8, 64.0, 24.3; IR (neat): ν_{max} 1716, 1515, 1407, 1334, 1198, 769, 751 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{16}N_3O_4$ $[M+H]^+$ 326.1135, found 326.1133.

5-Ethyl-5-methyl-1,3-diphenylhydantoin 11s. Yield: 73% (107 mg, 365 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; White solid, Mp: 129 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51-7.43 (m, 6H), 7.42-7.33 (m, 4H), 2.02 (A of ABX_3 syst., *J* = 14.6 and 7.4 Hz, 1H), 1.76 (B of ABX_3 syst., *J* = 14.6 and 7.4 Hz, 1H), 1.55 (s, 3H), 1.05 (X of ABX_3 syst., *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.6, 154.7, 134.4, 131.8, 129.6, 129.1, 128.3, 128.2 (2C), 126.3, 67.6, 29.9, 23.7, 8.2; IR (neat): ν_{max} 2934, 1712,

1494, 1412, 1374, 1190, 762, 693 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$ 317.1260, found 317.1275.

1,3,5,5-Tetraphenylhydantoin 11t. Yield: 66% (265 mg, 655 µmol). White solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20. This compound has been previously reported.[32]

1,3-Diphenyl-5-methylhydantoin 11u. Yield: 91% (63 mg, 237 µmol). Off white Solid. Solvent system for flash column chromatography: cyclohexane/EtOAc: 85/15. This compound has been previously reported.[14c]

3-(2-Ethoxy-2-oxoethyl)-1-phenylhydantoin 11v. Yield: 65% (456 mg, 1.74 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc: 80/20; Pale yellow solid, Mp: 155 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.5 Hz, 2H), 7.40 (t, J = 8.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 4.40 (s, 2H), 4.35 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 168.0, 166.9, 153.5, 137.5, 129.5, 124.8, 118.6, 62.2, 50.2, 39.9, 14.3; IR (neat): ν_{max} 2982, 1710, 1445, 1383, 1216, 1017, 747 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{14}N_2O_4Na$ $[M+Na]^+$ 285.0846, found 285.0855.

3-(1,1'-Biphenyl-4-yl)-5,5-dimethyl-1-phenylhydantoin 11w. Yield: 78% (279 mg, 782 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 85/15; White solid, Mp: 115 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73-7.68 (m, 2H), 7.64-7.59 (m, 4H), 7.52-7.41 (m, 5H), 7.40-7.33 (m, 3H), 1.58 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.3, 154.0, 141.2, 140.4, 134.2, 131.0, 129.7, 129.1, 128.9, 128.7, 127.8, 127.7, 127.3, 126.4, 63.6, 24.3; IR (neat): ν_{max} 1715, 1488, 1407, 1379, 1200, 1151, 765, 695 cm^{-1}; ESIHRMS *m/z* calcd for $C_{23}H_{21}N_2O_2$ $[M+H]^+$ 357.1598, found 357.1610.

5,5-Dimethyl-3-(3-methoxyphenyl)-1-phenylhydantoin 11x. Yield: 97% (193 mg, 622 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 70/30; White solid, Mp: 58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.43 (m, 2H), 7.43-7.36 (m, 2H), 7.35-7.31 (m, 2H), 7.13-7.09 (m, 1H), 7.08 (t, J = 2.2 Hz, 1H), 6.92 (ddd, J = 8.4, 2.5 and 0.7 Hz, 1H), 3.81 (s, 3H), 1.54 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.1, 159.9, 153.8, 134.0, 132.8, 129.6, 129.5, 129.0, 128.5, 118.3, 114.3, 111.7, 63.4, 55.4, 24.0; IR (neat): ν_{max} 2935, 1721, 1495, 1401, 1200, 773 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1390, found 311.1404.

5,5-Dimethyl-3-(4-nitrophenyl)-1-phenylhydantoin 11y. Yield: 49% (158 mg, 487 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20; Pale yellow solid, Mp: 213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 9.2 Hz, 2H), 7.85 (d, J = 9.2 Hz, 2H), 7.53-7.43 (m, 3H), 7.34-7.30 (m, 2H), 1.57 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.7, 153.0, 146.5, 137.8, 133.5, 129.9, 129.2 (2C), 126.0, 124.4, 63.7, 24.3; IR (neat): ν_{max} 2936, 2362, 1716, 1517, 1411, 1342, 1201, 846, 763, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{16}N_3O_4$ $[M+H]^+$ 326.1135, found 326.1148.

5,5-Dimethyl-1-phenyl-3-(4-trifluoromethylphenyl)hydantoin 11z. Yield: 97% (338 mg, 970 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; White solid, Mp: 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (app. s, 4H), 7.51-7.40 (m, 3H), 7.35-7.30 (m, 2H), 1.56 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.9, 153.3, 135.2, 133.7, 129.8 (q, J = 35.8 Hz), 129.7, 129.1, 128.9, 126.1 (q, J = 3.7 Hz), 126.0, 123.9 (q, J = 272.3 Hz), 63.6, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.1 (s); IR (neat): ν_{max} 2357, 1716, 1406, 1325, 1127, 1066, 843 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{16}F_3N_2O_2$ $[M+H]^+$ 349.1158, found 349.1169.

3-(4-Cyano-3-trifluoromethylphenyl)-5,5-dimethyl-1-phenylhydantoin 11aa. Yield: 88% (1.1 g, 2.97 mmol). Solvent system for flash column chromatography: petroleum ether/EtOAc:

80/20; White solid, Mp: 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.4 and 2.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.54-7.44 (m, 3H), 7.33-7.28 (m, 2H), 1.58 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.5, 152.6, 136.5, 135.5, 133.8 (q, J_{C-F} = 33.1 Hz), 133.2, 130.0, 129.4, 129.2, 128.3, 123.4 (q, J_{C-F} = 4.8 Hz), 120.7, 115.1, 108.6, 63.8, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.5 (s); IR (neat): ν_{max} 2986, 2232, 1719, 1404, 1313, 1131, 850, 691 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{15}F_3N_3O_2$ $[M+H]^+$ 374.1111, found 374.1127.

3-(4-*tert*-Butylphenyl)-5,5-dimethyl-1-phenylhydantoin 11ab. Yield: 65% (219 mg, 651 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; White solid, Mp: 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.39 (m, 7H), 7.36-7.31 (m, 2H), 1.55 (s, 6H), 1.34 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.4, 154.2, 151.2, 134.2, 129.6, 129.1, 129.0, 128.6, 126.1, 125.7, 63.5, 34.8, 31.4, 24.2; IR (neat): ν_{max} 2966, 1714, 1400, 1199, 1142, 839, 763, 690 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$ 337.1911, found 337.1925.

5,5-Dimethyl-1-phenyl-3-(4-trifluoromethoxyphenyl)hydantoin 11ac. Yield: 80% (292 mg, 802 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 90/10; White solid, Mp: 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 9.0 Hz, 2H), 7.52-7.41 (m, 3H), 7.35-7.29 (m, 4H), 1.55 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 175.1, 153.7, 148.4, 133.9, 130.4, 129.8, 129.1, 128.9, 127.5, 121.6, 120.6 (q, J_{C-F} = 257.7 Hz), 63.7, 24.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3 (s); IR (neat): ν_{max} 2935, 2363, 1714, 1514, 1403, 1254, 1199, 1164, 762 cm^{-1}; ESIHRMS *m/z* calcd for $C_{18}H_{16}F_3N_2O_3$ $[M+H]^+$ 365.1108, found 365.1120.

5,5-Dimethyl-3-(4-methoxycarbonylphenyl)-1-phenylhydantoin 11ad. Yield: 92% (119 mg, 351 µmol). Solvent system for flash column chromatography: cyclohexane/EtOAc: 80/20; White solid, Mp: 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.7 Hz, 2H),

7.67 (d, J = 8.7 Hz, 2H), 7.52-7.41 (m, 3H), 7.34-7.30 (m, 2H), 3.93 (s, 3H), 1.56 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 175.0, 166.5, 153.5, 136.0, 133.9, 130.4, 129.8, 129.4, 129.2, 128.9, 125.6, 63.6, 52.4, 24.3; IR (neat): ν_{max} 2954, 2364, 1714, 1412, 1277, 1199, 1115, 767, 697 cm^{-1}; ESIHRMS *m/z* calcd for $C_{19}H_{19}N_2O_4$ $[M+H]^+$ 339.1339, found 339.1352.

Multigram Scale Procedures

N^3-Arylation of 4,4-dimethylhydantoin 8a. A 2 L four-necked round bottom flask equipped with a condenser, a mechanical stirrer and a temperature probe was charged with 4-iodo-2-trifluoromethylbenzonitrile (90.0 g, 303 mmol), copper(I) oxide (97% grade, 44.7 g, 303 mmol) and *N,N*-dimethylformamide (873 mL). 5,5-Dimethylhydantoin **8a** (58.2 g, 455 mmol) was added and the flask was fitted with a glass stopper. The reaction mixture was stirred at 150 °C for 16 hours. After cooling to room temperature, the red suspension was filtered through a cardboard filter and washed with *N,N*-dimethylformamide (58 mL). The filtrate was concentrated under reduced pressure, dissolved in *N,N*-dimethylformamide (58 mL) and the green suspension was transferred into an addition funnel. A 1 L four-necked round bottom flask equipped with a condenser, a mechanical stirrer, a temperature probe and the latter addition funnel was charged with 233 mL of demineralized water. The green suspension was added over 10 minutes and stirred for 30 minutes before adding a 28% aqueous ammonia solution (111 mL) over 5 minutes. The resulting mixture was stirred for 30 minutes. The precipitate was collected by filtration, washed with water (3x58 mL) and then dried under high vacuum at 40 °C for 72 hours to yield 5,5-dimethyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin **9f** as a white solid (83.6 g, 281 mmol, 93%).

N^1-Arylation of 5,5-dimethyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin 9f. A 1 L four-necked round bottom flask equipped with a condenser, a mechanical stirrer and a

temperature probe was charged with 5,5-dimethyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin **9f** (50.0 g, 168 mmol), copper iodide (6.40 g, 33.6 mmol) potassium carbonate (46.5 g, 336 mmol) and toluene (240 mL). The flask was fitted with a glass stopper and was then flushed with nitrogen at 22 +/- 3 °C before *trans-N,N'*-dimethylcyclohexane-1,2-diamine (9.60 g, 67.3 mmol) was added over *ca.* 2 minutes. The reaction mixture turned blue and a slight exotherm (up to 26 °C) was observed (Picture 1, Supporting Information). Iodobenzene (48.0 g, 235 mmol) was added over 5 minutes (Picture 2, Supporting Information) and the mixture was then heated to reflux (110 °C, Picture 3, Supporting Information) and stirred for 24 hours (the mixture turns green upon heating, Picture 4, Supporting Information). TLC (heptane/ethyl acetate: 60/40) showed complete consumption of the starting material (Picture 5, Supporting Information). The temperature was adjusted to 22 +/- 3 °C and ethyl acetate (340 mL) was added followed by silica (50.0 g) and Clarcel® (50.0 g). The mixture was stirred for 15 min and filtered through a Büchner (Picture 6, Supporting Information). The cake was copiously washed with ethyl acetate (1650 mL). The filtrate was concentrated to low volume at 40 °C under vacuum to yield a brown residue (117 g). Toluene (340 mL) and heptane (200 mL) were added and the resulting suspension was stirred for 1 h at 22 +/- 3 °C and then for 1 hour at 2 +/- 3 °C (Picture 7, Supporting Information). The cake was washed twice with a cold mixture of toluene (30 mL) and heptane (20 mL) (Picture 8, Supporting Information). The wet product (98.7 g) was dried under vacuum at 50 °C for 18 hours to yield 5,5-dimethyl-1-phenyl-3-(3-trifluoromethyl-4-cyanophenyl)hydantoin **11z** as an off-white solid (51.3 g, 137 mmol, 82%).

C4-Selective Thionation of 5,5-Dimethyl-1,3-diphenylhydantoin

5,5-Dimethyl-1,3-diphenyl-4-thiohydantoin 15. In a pressure tube, 5,5-dimethyl-1,3-diphenylhydantoin **11l** (140 mg, 0.50 mmol) was dissolved in toluene (2 mL) before adding phosphorus pentasulfide (111 mg, 0.50 mmol). The pressure tube was flushed with argon and closed with a Teflon-coated screw cap before heating the reaction mixture at 120 °C for 18 hours. The mixture was then cooled to room temperature, quenched with a 1M aqueous solution of hydrochloric acid and extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography over silica gel (cyclohexane/EtOAc: gradient from 90/10 to 80/20) to give the desired 5,5-dimethyl-1,3-diphenyl-4-thiohydantoin, obtained as a white solid and as a single regioisomer (85 mg, 0.29 mmol, 57%). The regioselectivity of the thionation and the structure of this compound have been assigned on the basis of ^{13}C NMR chemical shifts (C2, C4 and C5) as well as by comparison of the ^{13}C NMR chemical shifts reported for enzalutamide.[33] The two regioisomers have been reported in 1983 but had been misassigned.[19] Mp: 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.43 (m, 8H), 7.38-7.35 (m, 2H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 154.2, 134.5, 134.3, 129.6, 129.2 (3C), 128.9, 127.7, 72.3, 28.1 IR (neat): ν_{max} 1751, 1495, 1408, 1371, 1297, 1194, 1169, 1102, 753, 695, 664 cm^{-1}; ESIHRMS *m/z* calcd for $C_{17}H_{16}N_2OSNa$ $[M+Na]^+$ 319.0876, found 319.0884.

Author Contributions. ‡ These authors contributed equally.

Supporting Information Available. Pictures of the different stages of the multigram scale N^1-arylation and copies of NMR spectra (PDF), Primary NMR data files (ZIP). This material is available free of charge on the ACS Publication Website.

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