Efficient C2 functionalisation of 2*H*-2-imidazolines

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Alkylation and oxidation of 2*H*-2-imidazolines, followed by regioselective deprotection, thionation and microwave-assisted Liebeskind–Srogl reaction, efficiently led to 2-aryl-2-imidazolines as new analogues of p53-hdm2 interaction inhibitors (Nutlins).

Introduction

The 2-imidazoline scaffold is found in many biologically active small molecules that target numerous pharmaceutically relevant binding sites and receptors.[1] Although substitution patterns are diverse, most biologically active 2-imidazolines are substituted at C2. For example, the Nutlins, which are highly functionalised 2-imidazolines that shown both *in vitro* and *in vivo* antitumor activity, all contain a C2 aryl moiety that is believed to be essential.[2] The Nutlins are strong inhibitors of hdm2, a protein that negatively modulates the transcriptional activity and stability of the p53 tumor suppressor protein.[3] C2-Substituted imidazolines can be prepared by the condensation of a diamine with an imidate, but variation of the substituents is not straightforward.[4] Alternatively, a trimethylsilyl chloride mediated multicomponent reaction (MCR) between oxazolones, aldehydes and amines can be employed.[5] However, this leads to the formation of C2-functionalised 2-imidazolines with *trans*-oriented C4/C5 phenyl groups. Although some reports exist of methods that give *cis*-oriented C4/C5 phenyl groups,[5] these seem less efficient for the synthesis of Nutlin analogues, which require *cis*-oriented C4/C5 phenyl groups.

Recently, we reported a versatile MCR involving amines, aldehydes and isocyanoacetates to access 2*H*-2-imidazolines.[6] All substituents can be varied easily by the choice of readily available reagents. Furthermore, the reaction generally favours formation of the diastereomer with *cis*-oriented aryl functionalities at C4/C5. Consequently, our method could be exploited to synthesise new, Nutlin-type, p53-hdm2 interaction inhibitors. The approach renders analogues containing an additional carboxylate that may serve to enhance water solubility. However, the 2*H*-2-imidazolines that result from our MCR should be arylated at C2. Here, we present an efficient synthetic strategy to achieve this.

Results and discussion

Four relevant 2*H*-imidazolines (Scheme 1, **4–7**) were selected as starting materials for our synthetic study. The two *cis*-oriented *p*-chlorophenyl (PCP) groups in the backbone of analogues **4** and **5** are also found in Nutlins, where they seem crucial for the interaction with the Trp23 and Leu26 pockets of hdm2.[2] The imidazolines **6** and **7**, containing a 5-indolyl substituent, are also highly relevant, since, according to NMR studies of Nutlins bound to hdm2,[4] these may improve binding to the Trp23 domain of hdm2. Thus, application of the MCR using isocyanoacetate **1**[7] in combination with two different aldehydes (**2**) and amines (**3**) provides the corresponding 2*H*-2-imidazolines **4–7** in high yields.

Direct C2 functionalisation of **4–7** proved not to be straightforward, and a procedure for selective C2 arylation had to be developed. Recently, Liebeskind and Srogl reported the Pd(0)-catalyzed, Cu(I)-mediated coupling of thioether-type species with boronic acids under neutral conditions.[8] The high thiophilicity of the soft Cu(I) carboxylate cofactor facilitates selective C–C coupling with isothioureas even in the presence of a Suzuki-active bromide.[9] This elegant procedure has been used to directly arylate dihydropyrimidine-2-thiones under microwave irradiation.[10] We envisioned the mild and easy sulfoxidation of 2*H*-2-imidazolinium salts through the reaction of *in situ*-generated N-heterocyclic carbenes with elemental sulfur as an appropriate method to

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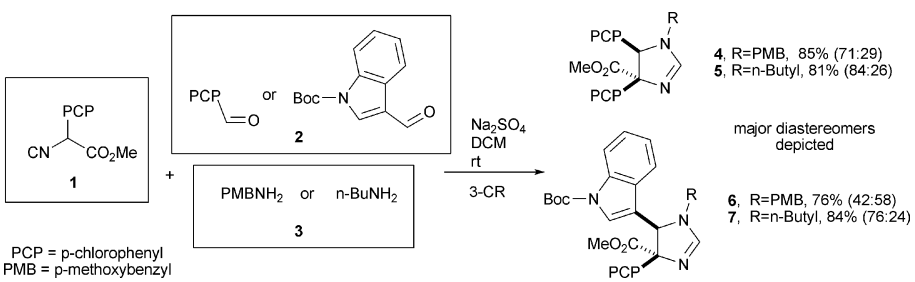
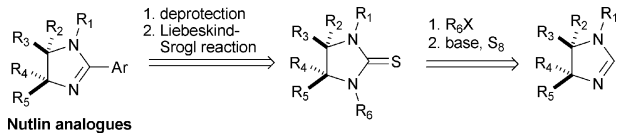


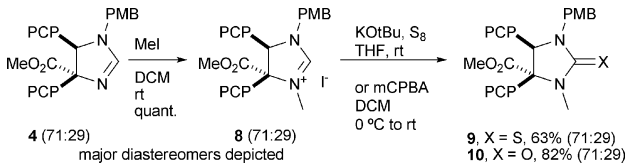
Scheme 1 2*H*-2-Imidazolines **4–7** obtained from a 3-component reaction (3-CR).



Scheme 2 Possible route for C2 functionalisation of 2*H*-2-imidazolines.

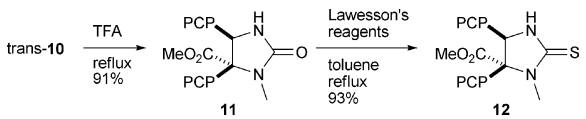
synthesise precursors for Liebeskind–Srogl reactions (Scheme 2).[11] Strategic choice of R^1 and R^3 groups should allow selective deprotection of N1 or N3, leading to Nutlin analogues.

Methylation and sulfoxidation of imidazoline **4** affords the cyclic thiourea **9** in good yield (Scheme 3). Chromatographic separation of the diastereomers was achieved but cleavage of the *p*-methoxybenzyl (PMB) group could not be realised. Both oxidative and acidic conditions cause decomposition, probably because of the sensitive thiocarbonyl group. Therefore, an alternative route was considered. Imidazolidin-2-thiones can be prepared by the thionation of imidazolidin-2-ones using Lawesson's reagent.[12] For this, oxidation of 2*H*-2-imidazolines was required. Although (low-yielding) oxidations of benzimidazoles with *m*CPBA are known,[13] this procedure proved unsuitable for the direct oxidation of imidazolines. In contrast, *m*CPBA-mediated oxidation of imidazolinium salt **8** affords cyclic urea **10** as a mixture of diastereomers, in a combined yield of 82% (Scheme 3). For a clean reaction it proved important to add the *m*CPBA to a cooled solution of **8**. The diastereomers of **10** are conveniently separated by chromatography.



Scheme 3 Oxidation and thionation of C2.

Treatment of *trans*-**10** with TFA (to cleave off the PMB-group) and subsequent thionation provides the Liebeskind–Srogl precursor **12** with a C5 ester function in very high yields (Scheme 4).[14]

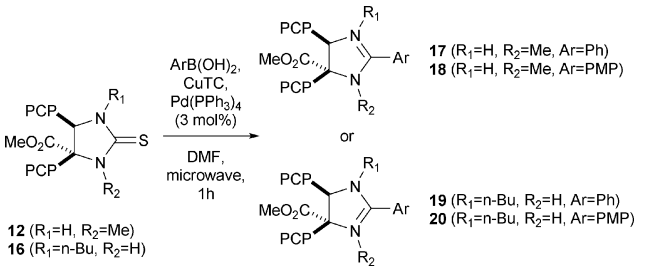


Scheme 4 Synthesis of Liebeskind–Srogl precursor **12**.

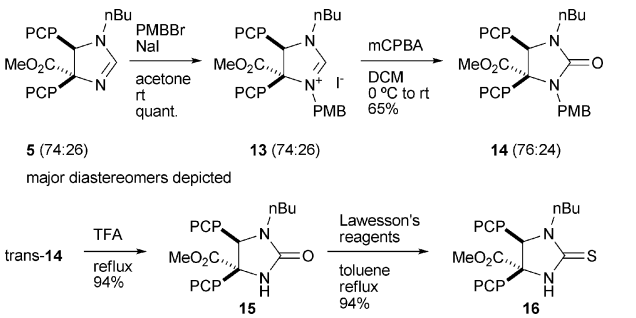
With the above-described methodology available, we now turned to the synthesis of Liebeskind–Srogl precursors containing the ester functionality at C4. Clean formation of imidazolinium salt **13** from **5** can be achieved using PMBBr and NaI under Finkelstein conditions (Scheme 5). Oxidation then gives cyclic urea **14** in reasonable yield, and the diastereomers could be separated chromatographically. Deprotection and subsequent thionation of *trans*-**14** both went smoothly, affording efficiently the desired Liebeskind–Srogl precursor **16**.[14]

With **12** and **16** in hand, we could now perform the Liebeskind–Srogl reactions (Table 1). Reactions were run in sealed vessels with controlled single-mode microwave heating. Initially, coupling reactions between boronic acids and **12** or **16** were performed under

Table 1 Liebeskind–Srogl arylation of **12** and **16**



Product	*T*/°C	Isolated yield (%)
17	100	14
17	130	51
18	100	24
18	130	41
19	100	34
19	130	65
20	100	6
20	130	55



Scheme 5 Synthesis of Liebeskind–Srogl precursor **16**.

conditions reported by Kappe *et al.* ($PhB(OH)_2$, $Pd(PPh_3)_4$, Cu(I) thiophene-2-carboxylate, THF, microwave, 100 °C, 30 min).[10] These conditions, however, gave only traces of C2-arylated products. Conditions were further refined with respect to the solvent, and the reactions proceeded much better in DMF instead of THF. Also, the reaction temperature appears crucial and is important for achieving good conversions to the desired cross-coupling products. Although not fully optimized yet, running the reaction at 130 °C for 1 h ultimately led to efficient Liebeskind–Srogl cross-coupling of **12** and **16** with two different boronic acids, and the corresponding 2-aryl-2-imidazolines **17–20** were isolated in good yields.

Conclusion

In conclusion, a versatile route toward C2-functionalized 2-imidazolines containing Nutlin-like backbones has been developed. Besides the 3-component reaction to access 2*H*-2-imidazolines, key steps involve the oxidation at C2 and the Liebeskind–Srogl coupling of cyclic thioureas with boronic acids. The analogues **17–20** have been prepared in good overall yields (23% to 35%) starting from commercially available aldehydes and amines. The high overall yields and the flexibility make this procedure amenable to library synthesis of potential p53-hdm2 interaction inhibitors.

Experimental

General

All reactions were carried out under atmospheric conditions, unless stated otherwise. Standard syringe techniques were applied for transfer of air-sensitive reagents and dry solvents. Melting points were measured using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained from $CHCl_3$ films on NaCl tablets (unless noted otherwise), using a Matteson Instuments 6030 Galaxy Series FT-IR spectrophotometer, and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 (400.13 MHz and 100.61 MHz respectively) or a Bruker Avance 250 (250.13 MHz and 62.90 MHz respectively) with chemical shifts (δ) reported in ppm downfield from tetramethylsilane. MS and HRMS spectral data were recorded on a Finnigan Mat 900 spectrometer or in the Laboratory of Organic Chemistry of the Wageningen University (NL) on a Finnigan MAT95 spectrometer. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and Baker 7024-02 silica gel (40 μ, 60 Å). Thin layer chromatography was performed using silica plates from Merck (Kieselgel 60 F_{254} on aluminium with fluorescence indicator. Compounds on TLC were visualised by UV-detection unless stated otherwise. THF was dried and distilled from sodium benzophenone ketyl prior to use. DCM was dried and distilled from CaH_2 prior to use. Toluene was distilled from sodium prior to use. DMF was dried and distilled from phenylzinc iodide prior to use. Other commercially available reagents were used as purchased.

Microwave experiments

Microwave-assisted reactions were performed in a Discover (CEM Corporation) single-mode microwave instrument producing controlled irradiation at 2450 MHz, using standard sealed microwave glass vials. Reaction temperatures were monitored with an IR sensor on the outside wall of the reaction vials. Reaction times refer to hold times at the indicated temperatures, not to total irradiation times.

1-(4-Chlorophenyl)-2-methoxy-2-oxoethanaminium chloride. *p*-Chlorophenylglycine (8.62 g, 46.5 mmol) was dissolved in MeOH (110 mL). The solution was cooled to 0 °C and thionyl chloride (6.8 mL, 93 mmol) was added dropwise. The reaction mixture was heated under reflux for 3 h. Cooling to rt followed by concentration *in vacuo* afforded the title compound as a white solid (10.98 g, quant.) ^1H NMR (250 MHz, D_2O) δ (ppm) 7.54 (d, $J = 8.6$ Hz, 2H), 7.49 (d, $J = 8.6$ Hz, 2H), 5.30 (s, 1H), 3.82 (s, 3H).

Methyl 2-amino-2-(4-chlorophenyl)acetate. 1-(4-Chlorophenyl)-2-methoxy-2-oxoethanaminium chloride (3.33 g, 14.1 mmol) was suspended in EtOAc (100 mL). Saturated $NaHCO_3$ (aq.) (80 mL) was added and the suspension was stirred until the organic layer was clear and slightly orange. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine and dried with Na_2SO_4. Filtration and concentration *in vacuo* afforded the title compound as a yellow–orange solid (2.79 g, 99%) ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.36 (s, 4H), 4.67 (s, 1H), 3.73 (s, 3H), 2.60 (br s, 2H).

Methyl 2-(4-chlorophenyl)-2-formamidoacetate. Methyl 2-amino-2-(4-chlorophenyl)acetate (2.79 g, 14.0 mmol) was dissolved in ethyl formate (80 mL), and a small crystal of *p*TSA was added. The reaction mixture was refluxed overnight, cooled to rt and the solvent was evaporated. The product was dissolved in DCM, washed with water, dried with Na_2SO_4, and concentrated *in vacuo* to afford the title compound as a yellow solid (3.15 g, 99%) ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 7.31 (s, 4H), 6.86 (br s, 1H), 5.62 (d, $J = 7.2$ Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 176.6 (C), 170.6 (C), 160.5 (CH), 134.6 (C), 129.2 (2 × CH), 129.0 (2 × CH), 54.4 (CH_3), 53.2 (CH); HRMS (EI, 70 eV) calculated for $C_{10}H_{10}ClNO_3$ (M^+) 227.0349, found 227.0346.

Methyl 2-(4-chlorophenyl)-2-isocyanoacetate 1. This reaction was carried out under an inert atmosphere of dry nitrogen. Methyl 2-(4-chlorophenyl)-2-formamidoacetate (910 mg, 4.0 mmol) was dissolved in DCM (10 mL) and cooled to −30 °C. Triphosgene (504 mg, 1.7 mmol) and *N*-methylmorpholine (1.57 mL, 14.3 mmol) were added slowly. The solution turned darker orange, and after 30 minutes at −30 °C the temperature was raised to −5 °C and kept at this temperature for an additional 3 hours, during which time the solution slowly turned darker. The reaction mixture was quenched in 20 mL of ice-water. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layers were combined, washed with brine and dried with Na_2SO_4. Concentration *in vacuo* followed by flash column chromatography (cyclohexane–ethyl acetate = 4 : 1), afforded **1** as an orange oil (640 mg, 77%). ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.42 (br s, 4H), 5.35 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 165.6 (C), 162.2 (C), 135.8 (C), 130.2 (C), 129.4 (2 × CH), 128.0 (2 × CH), 59.6 (C), 53.9 (CH_3); IR (neat) 2954 (m), 2148 (s), 1753 (s), 1493 (s), 1435 (m), 1250 (m), 1211 (m), 1092 (s), 1014 (s); HRMS (EI, 70 eV) calculated for $C_{10}H_8ClNO_2$ (M^+) 209.0244, found 209.0248.

General Procedure I for the synthesis of 2-imidazolines

Reactions were carried out under an inert atmosphere of dry nitrogen at a concentration of 1 M of aldehyde **2**, 1 M of amine **3**, and 0.5 M of isocyanide **1** in dry DCM or MeOH. Na_2SO_4 and the aldehyde were added, at rt, to a stirred solution of the amine. After the mixture was stirred for 2 h, the isocyanide was added and the reaction mixture was stirred at rt for an additional 18 h. The reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (*c*-hexane–EtOAc–Et_3N = 2 : 1 : 0.01, gradient, unless stated otherwise).

Methyl 4,5-bis(4-chlorophenyl)-1-(4-methoxybenzyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate 4. According to General Procedure I, reaction between *p*-methoxybenzylamine (2.74 g, 20 mmol), *p*-chlorobenzaldehyde (2.80 g, 20.0 mmol) and isocyanoacetate **1** (2.07 g, 9.9 mmol) in DCM, followed by column chromatography (EtOAc–Et_3N = 1 : 0.01), afforded **4** (3.96 g, 85%) as a 71 : 29 mixture of diastereomers as a yellow solid. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.47 (d, $J = 43.0$ Hz, 1H), 7.36–7.21 (m, 3H + 4H), 7.10–6.98 (m, 4H + 4H), 6.89–6.76 (m, 5H + 5H), 5.28 (s, 1H), 4.64 (s, 1H), 4.36–4.31 (m, 1H + 1H), 3.82 (s, 3H), 3.74 (s,

3H), 3.83–3.74 (m, 4H + 1H), 3.28 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 173.5 (C), 170.6 (C), 159.4 (C), 156.7 (CH), 155.9 (CH), 141.6 (C), 135.9 (C), 134.9 (C), 134.4 (C), 133.7 (2 × C), 133.6 (2 × C), 133.2 (C), 120.0 (2 × CH), 129.4 (2 × CH), 129.3 (2 × CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.08 (2 × CH), 128.06 (2 × CH), 127.8 (2 × CH), 127.1 (C), 126.9 (C), 114.1 (2 × CH), 114.2 (2 × CH), 84.7 (C), 83.8 (C), 72.4 (CH_3), 68.5 (CH_3), 55.1 (CH_3 + CH_3), 53.1 (CH), 52.1 (CH), 48.6 (CH_2), 48.1 (CH_2); IR (neat) 1730 (s), 1602 (s); HRMS (EI, 70 eV) calculated for $C_{25}H_{22}Cl_2N_2O_3$ (M^+) 468.1007, found 468.1002.

Methyl 1-butyl-4,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate 5. According to General Procedure I, reaction between *n*-butylamine (730 mg, 10.0 mmol), *p*-chlorobenzaldehyde (1.40 g, 10.0 mmol) and isocyanoacetate **1** (990 mg, 4.74 mmol) in DCM, followed by column chromatography (EtOAc–Et_3N = 1 : 0.01), afforded **5** (1.61 g, 84%) as a 74 : 26 mixture of diastereomers as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.69 (d, J = 8.7 Hz, 2H), 7.39–7.34 (m, 4H), 7.30–7.26 (m, 3H + 1H), 7.05–7.01 (m, 2H + 2H), 6.90–6.86 (m, 2H + 2H), 5.51 (s, 1H), 4.81 (s, 1H), 3.77 (s, 3H), 3.28 (s, 3H), 3.20–3.08 (m, 1H + 1H), 2.89–2.78 (m, 1H + 1H), 1.54–1.13 (m, 4H + 4H), 0.92–0.79 (m, 3H + 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 173.8 (C), 170.6 (C), 156.8 (CH), 156.1 (CH), 141.9 (C), 136.1 (C), 135.2 (C), 134.4 (C), 134.0 (C), 133.6 (C), 133.5 (C), 133.1 (C), 129.8 (2 × CH), 129.2 (2 × CH), 128.8 (2 × CH), 128.4 (2 × CH), 128.17 (2 × CH), 128.15 (2 × CH), 128.08 (2 × CH), 127.8 (2 × CH), 84.65 (C), 83.9 (C), 73.5 (CH_3), 68.7 (CH_3), 53.1 (CH), 52.1 (CH), 44.8 (CH_2), 44.5 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 19.8 (CH_2), 19.7 (CH_2), 13.6 (CH_3), 13.5 (CH_3); IR (neat) 1729 (s), 1599 (s); HRMS (EI, 70 eV) calculated for $C_{21}H_{22}Cl_2N_2O_2$ (M^+) 404.1058, found 404.1046.

***tert*-Butyl 3-(4-(4-chlorophenyl)-1-(4-methoxybenzyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)-1*H*-indole-1-carboxylate 6.** According to General Procedure I, reaction between *p*-methoxybenzylamine (384 mg, 2.8 mmol), *N*-Boc-indolecarboxaldehyde (690 mg, 2.8 mmol) and isocyanoacetate **1** (419 mg, 2.0 mmol) in DCM, followed by column chromatography, afforded **6** (364 mg, 76%) as a 58 : 42 mixture of diastereomers as an orange–pink solid. ^{1}H NMR (400 MHz, DMSO-d_6, 360 K): δ (ppm) 8.09 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.61–7.56 (m, 3H + 3H), 7.54 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.38–7.32 (m, 2H + 2H), 7.25–7.20 (m, 1H + 1H), 7.09–7.01 (m, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.97 (br s, 1H + 1H), 6.91 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 5.58 (s, 1H), 4.99 (s, 1H), 4.46 (d, J = 15.1 Hz, 1H), 4.39 (d, J = 14.9 Hz, 1H), 3.86–3.82 (m, 1H + 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.07 (s, 3H), 1.67 (s, 9H), 1.59 (s, 9H); ^{13}C NMR (100.6 MHz, DMSO-d_6, 360 K) δ (ppm) 172.5 (C), 170.2 (C), 158.4 (C), 158.3 (C), 156.8 (CH), 156.1 (CH), 148.5 (C), 148.2 (C), 142.2 (C + C), 137.3 (C + C), 134.8 (C + C), 131.7 (C), 131.2 (C), 128.72 (4 × CH), 128.67 (4 × CH), 128.3 (CH), 128.1 (C + C), 128.1 (2 × CH), 127.4 (2 × CH), 126.4 (CH), 125.4 (CH), 124.0 (CH), 123.6 (CH), 122.0 (CH), 121.8 (CH), 119.6 (CH), 119.4 (C), 115.8 (C), 114.3 (CH), 114.0 (CH), 113.54 (2 × CH), 113.46 (2 × CH), 83.8 (C + C), 83.4 (C + C), 65.1 (CH), 61.4 (CH), 54.8 (CH_3), 54.7 (CH_3), 52.0 (CH_3), 50.8 (CH_3), 47.5 (CH_2), 47.3 (CH_2), 27.4 (3 × CH_3), 27.3 (3 × CH_3); IR (KBr) 1733 (s), 1599 (s), 1512 (s), 1452 (s), 1370 (s), 1248 (s), 1153 (s), 1089 (s); HRMS (EI, 70 eV) calculated for $C_{32}H_{32}ClN_3O_5$ (M^+) 573.2030, found 573.2036.

***tert*-Butyl 3-(1-butyl-4-(4-chlorophenyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazol-5-yl)-1*H*-indole-1-carboxylate 7.** According to General Procedure I, reaction between *n*-butylamine (1.10 g, 15.0 mmol), *N*-Boc-indolecarboxaldehyde (3.68 g, 15.0 mmol) and isocyanoacetate **1** (2.89 g, 13.8 mmol) in MeOH, followed by column chromatography, afforded **7** (5.9 g, 84%) as a 76 : 24 mixture of diastereomers as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 328 K) δ (ppm) 8.14 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.62 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.35–6.99 (m, 6H + 5H), 6.88 (d, J = 8.3 Hz, 2H + 2H), 5.83 (s, 1H), 5.04 (s, 1H), 3.74 (s, 3H), 3.16 (s, 3H), 3.13–3.04 (m, 1H + 1H), 2.90–2.84 (m, 1H + 1H), 1.69 (s, 9H), 1.63 (s, 9H), 1.52–1.45 (m, 2H), 1.37–1.12 (m, 2H + 4H), 0.85 (t, J = 7.3 Hz, 3H), 0.77 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 174.0 (C), 156.4 (CH), 156.1 (CH), 149.4 (C), 149.3 (C), 136.9 (2 × C), 133.6 (C), 128.1 (3 × CH + 5 × CH), 127.3 (2 × CH), 125.5 (CH), 124.1 (CH + CH), 122.7 (CH + CH), 120.1 (CH), 115.6 (C), 115.3 (CH), 114.9 (CH), 84.3 (C), 83.9 (C), 67.9 (CH), 62.6 (CH), 53.2 (CH_3), 52.1 (CH_3), 44.8 (CH_2), 44.3 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 28.2 (3 × CH_3), 28.1 (3 × CH_3), 19.8 (CH_2), 19.7 (CH_2), 13.6 (CH_3), 13.5 (CH_3); the aliphatic CH signals could only be found with gs-HSQC measurements at 328 K; the quaternary carbons of the minor diastereomer of **7** could not be detected; IR (KBr) 2957 (s), 1734 (s), 1599 (s), 1570 (m), 1452 (s), 1370 (s), 1257 (s), 1155 (s), 1089 (s); HRMS (EI, 70 eV) calculated for $C_{28}H_{32}ClN_3O_4$ (M^+) 509.2081, found 509.2082.

4,5-Bis(4-chlorophenyl)-1-(4-methoxybenzyl)-4-(methoxycarbonyl)-3-methyl-4,5-dihydro-1*H*-imidazolium iodide 8. Methyl iodide (447 mg, 3.15 mmol) was added to a solution of imidazoline **4** (1.408 g, 3 mmol) in DCM (20 mL). The reaction mixture was stirred at rt for 18 h and concentrated *in vacuo* to afford **8** (1.83 g, quant.) as a 68 : 32 mixture of diastereomers as a pale yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 10.65 (s, 1H), 10.52 (s, 1H), 7.48–7.29 (m, 4H + 2H), 7.20–7.17 (m, 4H + 6H), 7.01–6.91 (m, 2H + 2H), 6.91–6.83 (m, 2H + 2H), 5.73 (s, 1H), 5.45 (d, J = 14.1 Hz, 1H), 5.31 (d, J = 14.4 Hz, 1H), 5.14 (s, 1H), 4.23–4.13 (m, 1H + 1H), 3.96 (s, 3H), 3.80 (s, 3H + 3H), 3.56 (s, 3H), 3.34 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 168.9 (C), 165.8 (C), 160.5 (C), 160.2 (C), 160.1 (CH), 158.4 (CH), 136.9 (2 × C), 135.8 (C), 135.6 (C), 132.9 (C), 131.3 (2 × CH), 131.0 (4 × CH), 130.5 (2 × CH), 130.0 (2 × CH), 129.9 (C), 129.8 (2 × CH), 129.3 (2 × CH), 129.1 (2 × CH), 128.9 (2 × CH), 128.88 (2 × CH), 128.84 (C), 123.4 (2 × C), 123.1 (C), 114.7 (2 × CH), 114.6 (2 × CH), 80.6 (C), 80.2 (C), 74.1 (CH_3), 70.2 (CH_3), 55.4 (2 × CH_3), 54.6 (CH), 53.2 (CH), 50.5 (CH_2), 50.4 (CH_2), 34.9 (CH_3), 33.3 (CH_3); IR (neat) 1745 (s), 1642 (s), 1611 (s).

Methyl 4,5-bis(4-chlorophenyl)-1-(4-methoxybenzyl)-3-methyl-2-thioxoimidazolidine-4-carboxylate 9. This reaction was carried out under an inert atmosphere of dry argon. A Schlenk tube was charged with imidazolinium iodide **8** (608 mg, 1.0 mmol), KO^{t}Bu (118 mg, 1.05 mmol) and S_8 (256 mg, 1.0 mmol). THF (30 mL) was added and the reaction mixture was stirred at rt for 2 h. Then, water was added and the mixture was extracted with EtOAc (3×). The organic layers were dried with Na_2SO_4 and concentrated

in vacuo. Purification using flash column chromatography (toluene visualisation on TLC with UV and with iodine) afforded **9a** (229 mg, 45%) and **9b** (92 mg, 18%) as white solids.

9a (most polar isomer): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.12–7.03 (m, 6H), 6.82 (d, $J = 8.6$ Hz, 2H), 6.85–6.66 (m, 4H), 5.74 (d, $J = 14.7$ Hz, 1H), 5.29 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.76 (d, $J = 14.7$ Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.5 (C), 159.2 (2 × C), 134.6 (C), 134.5 (C), 132.0 (C), 131.3 (C), 129.8 (4 × CH), 128.6 (2 × CH), 128.51 (2 × CH), 128.45 (2 × CH), 127.5 (C), 113.9 (2 × CH), 77.8 (C), 68.1 (CH_3), 55.2 (CH_3), 53.3 (CH), 49.1 (CH_2), 34.2 (CH_3); IR (neat) 1751 (s), 1610 (m); HRMS (EI, 70 eV) calculated for $C_{26}H_{24}Cl_2N_2O_3S$ (M^+) 514.0885, found 514.0902.

9b (least polar isomer): Mp 120–121 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.36 (d, $J = 8.5$ Hz, 2H), 2.50 (d, $J = 8.7$ Hz, 2H), 7.11–7.04 (m, 6H), 6.81 (d, $J = 8.6$ Hz, 2H), 5.79 (d, $J = 14.6$ Hz, 1H), 4.73 (s, 1H), 3.80 (s, 3H), 3.62 (d, $J = 14.6$ Hz, 1H), 3.28 (s, 3H), 3.08 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 183.0 (C), 168.1 (C), 159.5 (C), 136.3 (C), 135.4 (C), 135.0 (C), 133.3 (C), 130.2 (4 × CH), 129.1 (2 × CH), 128.1 (4 × CH), 127.2 (C), 114.0 (2 × CH), 77.5 (C), 70.8 (CH_3), 55.3 (CH_3), 52.2 (CH), 48.7 (CH_2), 33.1 (CH_3); IR (neat) 1737 (s), 1612 (m); HRMS (EI, 70 eV) calculated for $C_{26}H_{24}Cl_2N_2O_3S$ (M^+) 514.0885, found 514.0899.

Methyl 4,5-bis(4-chlorophenyl)-1-(4-methoxybenzyl)-3-methyl-2-oxoimidazolidine-4-carboxylate 10. To a cooled (0 °C) solution of imidazolinium iodide **8** (611 mg, 1.0 mmol) in DCM (20 mL), 85% *m*CPBA (610 mg, 3.0 mmol) was added. The yellow solution abruptly turned red. The reaction mixture was stirred at rt for 18 h, washed twice with saturated Na_2CO_3 (aq.), dried with Na_2SO_4 and concentrated *in vacuo*. Purification using flash column chromatography (*c*-hexane–EtOAc = 4 : 1) afforded *trans*-**10** (289 mg, 58%) and *cis*-**10** (120 mg, 24%) as white solids.

trans-**10** (most polar isomer): Mp 88–90 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.09–6.95 (m, 6H), 6.81–6.68 (m, 6H), 5.03 (s, 1H), 4.96 (d, J = 14.8 Hz, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.52 (d, J = 14.8 Hz, 1H), 2.94 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 171.2 (C), 160.2 (C), 159.2 (C), 134.3 (C), 134.1 (C), 132.7 (C), 132.1 (C), 130.0 (4 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (C), 113.9 (2 × CH), 73.8 (C), 64.3 (CH_3), 55.3 (CH_3), 53.0 (CH), 45.5 (CH_2), 29.6 (CH_3); IR (neat) 1738 (s), 1710 (s), 1611 (m); HRMS (EI, 70 eV) calculated for $C_{26}H_{24}Cl_2N_2O_4$ (M^+) 498.1113, found 498.1096.

cis-**10** (least polar isomer): Mp 143–145 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.29–6.90 (m, 10H), 6.73 (d, $J = 8.7$ Hz, 2H), 4.95 (d, $J = 14.6$ Hz, 1H), 4.39 (s, 1H), 3.72 (s, 3H), 3.40 (d, $J = 14.6$ Hz, 1H), 3.26 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 168.9 (C), 159.5 (C), 159.3 (C), 136.4 (C), 135.0 (C), 134.6 (C), 133.7 (C), 130.1 (2 × CH), 129.6 (2 × CH), 128.8 (4 × CH), 128.4 (2 × CH), 127.7 (C), 114.0 (2 × CH), 73.7 (C), 67.2 (CH_3), 55.3 (CH_3), 52.0 (CH), 45.2 (CH_2), 28.6 (CH_3); IR (neat) 1741 (s), 1711 (s), 1611 (m); HRMS (EI, 70 eV) calculated for $C_{26}H_{24}Cl_2N_2O_4$ (M^+) 498.1113, found 498.1107.

General Procedure II for the Cleavage of PMB groups

A 0.25–0.30 M solution of imidazolidinone was refluxed for 1 h. After cooling to rt followed by evaporation of TFA, the crude product was dissolved in EtOAc, washed with saturated $NaHCO_3$ (aq.) solution and brine, dried with Na_2SO_4 and concentrated *in vacuo*. Purification was performed using flash column chromatography (*c*-hexane–EtOAc = 1 : 1, gradient).

***trans*-Methyl 4,5-bis(4-chlorophenyl)-3-methyl-2-oxoimidazolidine-4-carboxylate 11.** According to General Procedure II, deprotection of imidazolidinone *trans*-**10** (455 mg, 0.88 mmol), followed by column chromatography, afforded **11** (304 mg, 91%) as a white solid. Mp 214–216 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.29–7.06 (m, 4H), 6.93 (d, $J = 8.3$ Hz, 2H), 6.72 (d, $J = 8.4$ Hz, 2H), 5.56 (s, 1H), 5.50 (br s, 1H), 3.92 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 171.4 (C), 161.1 (C), 135.8 (C), 135.2 (C), 134.4 (C), 134.0 (C), 129.0 (2 × CH), 128.4 (4 × CH), 128.2 (2 × CH), 75.7 (C), 61.5 (CH_3), 53.1 (CH), 29.1 (CH_3); IR (KBr) 1734 (s), 1716 (s); HRMS (EI, 70 eV) calculated for $C_{18}H_{16}Cl_2N_2O_3$ (M^+) 378.0538, found 378.0526.

***cis*-Methyl 4,5-bis(4-chlorophenyl)-3-methyl-2-oxoimidazolidine-4-carboxylate.** According to General Procedure II, deprotection of imidazolidinone *cis*-**10** (516 mg, 1.0 mmol), followed by column chromatography, afforded the title compound (396 mg, 99%) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.45 (d, $J = 8.8$ Hz, 2H), 7.35 (d, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 5.19 (s, 1H), 4.86 (s, 1H), 3.33 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 168.6 (C), 160.8 (C), 136.1 (C), 135.8 (C), 135.1 (C), 135.0 (C), 129.1 (2 × CH), 128.8 (2 × CH), 128.75 (2 × CH), 128.72 (2 × CH), 76.0 (C), 65.1 (CH), 52.1 (CH_3), 28.2 (CH_3); IR (KBr) 1747 (s), 1720 (s), 1494 (m), 1435 (m); HRMS (EI, 70 eV) calculated for $C_{18}H_{16}Cl_2N_2O_3$ (M^+) 378.0538, found 378.0531.

General Procedure III for the thionation of imidazolidinones

Reactions were performed under an inert atmosphere of dry nitrogen at a concentration of 0.020 M of imidazolidinone in dry toluene. A reaction vessel was charged with imidazolidinone (1 equiv.) and Lawesson's reagent (1 equiv.). Toluene was added and the suspension was heated to reflux temperature. The resulting solution was refluxed for 18 h, cooled to room temperature and concentrated *in vacuo*. The crude product was loaded on to a pre-packed silica column. Impurities were eluted with toluene and then the product was eluted with toluene–EtOAc = 4 : 1, gradient. Visualisation on TLC was performed with UV and with iodine.

***trans*-Methyl 4,5-bis(4-chlorophenyl)-3-methyl-2-thioxoimidazolidine-4-carboxylate 12.** According to General Procedure III, thionation of imidazolidinone **11** (1.00 g, 2.64 mmol), followed by column chromatography, afforded **12** (2.46 g, 93%) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.06–6.99 (m, 4H), 6.84 (d, $J = 8.3$ Hz, 2H), 6.60–6.55 (m, 3H), 5.63 (s, 1H), 3.86 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 184.4 (C), 170.3 (C), 134.9 (C), 134.5 (C), 133.9 (C), 130.7 (C), 128.8 (2 × CH), 128.6 (2 × CH), 128.4 (4 × CH), 80.0 (C), 65.0 (CH), 53.5 (CH_3), 33.5 (CH_3); IR (KBr) 3174 (br), 1737 (s), 1596 (w), 1491 (s), 1393 (m), 1256 (s); HRMS (EI, 70 eV) calculated for $C_{18}H_{16}Cl_2N_2O_2S$ (M^+) 394.0310, found 394.0303.

***cis*-Methyl 4,5-bis(4-chlorophenyl)-3-methyl-2-thioxoimidazolidine-4-carboxylate.** According to General Procedure III, thionation of cis-methyl 4,5-bis(4-chlorophenyl)-3-methyl-2-oxoimidazolidine-4-carboxylate (374 mg, 0.98 mmol), followed by column chromatography, afforded the title compound (336 mg,

87%) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.40 (d, $J = 8.9$ Hz, 2H), 7.34 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 8.3$ Hz, 2H), 7.09 (d, $J = 8.3$ Hz, 2H), 8.95 (s, 1H), 5.04 (s, 1H), 3.28 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 183.9 (C), 167.4 (C), 135.7 (C), 135.32 (C), 135.28 (C), 134.8 (C), 129.3 (2 × CH), 128.80 (2 × CH), 128.75 (2 × CH), 128.5 (2 × CH), 80.1 (C), 68.8 (CH), 52.4 (CH_3), 32.3 (CH_3); IR (KBr) 3162 (br), 1737 (s), 1596 (w), 1491 (s), 1393 (m), 1256 (s); HRMS (EI, 70 eV) calculated for $C_{18}H_{16}Cl_2N_2O_2S$ (M^+) 394.0310, found 394.0299.

1-Butyl-4,5-bis(4-chlorophenyl)-3-(4-methoxybenzyl)-4-(methoxycarbonyl)-4,5-dihydro-1*H*-imidazolium iodide 13. *p*-Methoxybenzyl bromide (1.46 g, 7.28 mmol) was added to a solution of imidazoline **5** (2.95 g, 7.28 mmol) and NaI (1.09 g, 7.28 mmol) in acetone (90 mL). The reaction mixture was stirred at rt for 18 h, filtered and concentrated *in vacuo* to afford **13** (4.75 g, quant.) as a 74 : 26 mixture of diastereomers as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.40 (s, 1H), 9.27 (s, 1H), 7.68 (d, $J =$ 8.6 Hz, 2H), 7.51 (d, $J = 8.7$ Hz, 2H), 7.47–7.42 (m, 2H + 2H), 7.22 (d, $J = 8.6$ Hz, 2H), 7.16–7.07 (m, 6H + 2H), 6.96 (d, $J = 8.5$ Hz, 2H), 6.91–6.86 (m, 4H), 6.16 (s, 1H), 5.59 (s, 1H), 5.21 (d, $J =$ 14.5 Hz, 1H), 4.66 (d, $J = 14.5$ Hz, 1H), 4.52 (d, $J = 13.6$ Hz, 1H), 4.35 (d, $J = 13.7$ Hz, 1H), 3.89 (s, 3H), 3.89–3.82 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.79–2.65 (m, 1H), 3.38–3.35 (m, 1H), 3.36 (s, 3H), 3.26–3.19 (m, 1H), 1.71–1.57 (m, 2H + 2H), 1.32–1.21 (m, 2H + 2H), 0.90–0.84 (m, 3H + 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.0 (C), 166.0 (C), 160.1 (C), 158.6 (2 × CH), 156.2 (C), 136.9 (C), 136.8 (C), 135.9 (C), 135.8 (C), 133.2 (C), 132.2 (C), 131.7 (2 × CH), 130.3 (2 × CH), 130.1 (2 × CH), 129.93 (C), 129.89 (2 × CH), 129.7 (2 × CH), 129.5 (2 × CH), 129.4 (2 × CH), 129.20 (2 × CH), 129.17 (2 × CH), 129.1 (2 × CH), 128.6 (C), 125.7 (C), 124.0 (C), 114.8 (2 × CH), 114.6 (2 × CH), 80.7 (C), 80.6 (C), 76.9 (CH), 71.4 (CH), 55.4 (CH_3), 55.3 (CH_3), 54.4 (CH_3), 53.0 (CH_3), 50.6 (CH_2), 50.3 (CH_2), 47.6 (CH_2), 47.3 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 19.6 (CH_2), 19.5 (CH_2), 13.5 (CH_3), 13.4 (CH_3); IR (KBr) 1641 (s), 1513 (m), 1250 (s).

Methyl 1-butyl-4,5-bis(4-chlorophenyl)-3-(4-methoxybenzyl)-2-oxoimidazolidine-4-carboxylate 14. To a cooled (0 °C) solution of imidazolinium iodide **13** (265 mg, 0.41 mmol) in DCM (8 mL), 85% *m*CPBA (247 mg, 1.22 mmol) was added. The yellow solution abruptly turned dark orange. The reaction mixture was stirred at rt for 18 h, while a colour change from dark orange to light pink to dark red was observed. Then, the reaction mixture was washed twice with saturated Na_2CO_3 (aq.), dried with Na_2SO_4 and concentrated *in vacuo*. Purification using flash column chromatography (pentane–EtOAc = 7 : 1, visualisation on TLC with CerMOP [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.1 g L^{-1}), $Ce(SO_4)_2\cdot 4H_2O$ (4 g L^{-1}) in H_2SO_4 (10%)]) afforded *trans*-**14** (109 mg, 49%) and *cis*-**14** (36 mg, 16%) as white solids.

trans-**14** (most polar isomer): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.42–7.27 (m, 8H), 7.17–7.06 (m, 8H), 6.88–6.62 (m, 2H + 4H), 6.60 (d, $J = 8.7$ Hz, 2H), 5.58 (s, 1H), 4.96 (d, $J = 15.9$ Hz, 1H), 4.81 (s, 1H), 4.35 (d, $J = 15.1$ Hz, 1H), 4.18–4.11 (m, 1H + 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.73–3.60 (m, 1H + 1H), 3.38 (s, 3H), 3.23 (s, 3H), 2.75–2.64 (m, 1H + 1H), 1.54–1.22 (m, 4H + 4H), 0.99–0.85 (m, 3H + 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.5 (C), 168.9 (C), 160.7 (C), 160.3 (C), 158.5 (2 × C), 137.3 (C), 134.9 (C), 134.6 (C), 134.3 (C), 134.1 (C), 133.8 (C), 132.7 (C), 132.6 (C), 130.9 (C), 130.3 (C), 129.7 (2 × CH), 128.9 (2 × CH), 128.7 (4 × CH + 4 × CH), 128.2 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH + 2 × CH), 113.7 (2 × CH), 113.4 (2 × CH), 74.0 (C), 73.8 (C), 69.1 (CH), 64.7 (CH), 55.24 (CH_3), 55.20 55.2 (CH_3), 52.7 55.2 (CH_3), 51.8 55.2 (CH_3), 46.8 (CH_2), 46.0 (CH_2), 42.0 (CH_2), 41.8 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 20.0 (CH_2), 19.9 (CH_2), 13.74 (CH_3), 13.67 (CH_3); IR (KBr) 1707 (s), 1513 (s), 1244 (s); HRMS (EI, 70 eV) calculated for $C_{29}H_{30}Cl_2N_2O_4$ (M^+) 540.1583, found 540.1587.

cis-**14** (least polar isomer): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.42–7.27 (m, 8H), 7.17–7.06 (m, 8H), 6.88–6.62 (m, 2H + 4H), 6.60 (d, $J = 8.7$ Hz, 2H), 5.58 (s, 1H), 4.96 (d, $J = 15.9$ Hz, 1H), 4.81 (s, 1H), 4.35 (d, $J = 15.1$ Hz, 1H), 4.18–4.11 (m, 1H + 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.73–3.60 (m, 1H + 1H), 3.38 (s, 3H), 3.23 (s, 3H), 2.75–2.64 (m, 1H + 1H), 1.54–1.22 (m, 4H + 4H), 0.99–0.85 (m, 3H + 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 170.5 (C), 168.9 (C), 160.7 (C), 160.3 (C), 158.5 (2 × C), 137.3 (C), 134.9 (C), 134.6 (C), 134.3 (C), 134.1 (C), 133.8 (C), 132.7 (C), 132.6 (C), 130.9 (C), 130.3 (C), 129.7 (2 × CH), 128.9 (2 × CH), 128.7 (4 × CH + 4 × CH), 128.2 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH + 2 × CH), 113.7 (2 × CH), 113.4 (2 × CH), 74.0 (C), 73.8 (C), 69.1 (CH), 64.7 (CH), 55.24 (CH_3), 55.20 55.2 (CH_3), 52.7 55.2 (CH_3), 51.8 55.2 (CH_3), 46.8 (CH_2), 46.0 (CH_2), 42.0 (CH_2), 41.8 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 20.0 (CH_2), 19.9 (CH_2), 13.74 (CH_3), 13.67 (CH_3); IR (KBr) 1707 (s), 1513 (s), 1244 (s); HRMS (EI, 70 eV) calculated for $C_{29}H_{30}Cl_2N_2O_4$ (M^+) 540.1583, found 540.1587.

Methyl 1-butyl-4,5-bis(4-chlorophenyl)-2-oxoimidazolidine-4-carboxylate 15. According to General Procedure II, deprotection of imidazolidinone *trans*-**14** (2.15 g, 3.97 mmol), followed by column chromatography, afforded **15** (1.57 g, 94%) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.66 (d, $J = 8.8$ Hz, 2H), 7.43–7.38 (m, 4H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.13–7.09 (m, 6H), 6.91 (d, $J = 8.5$ Hz, 2H), 5.90 (s, 1H), 5.50 (s, 1H), 5.47 (s, 1H), 4.77 (s, 1H), 3.82 (s, 3H), 3.65–3.51 (m, 1H + 1H), 3.35 (s, 3H), 2.60–2.48 (m, 1H + 1H), 1.47–1.35 (m, 2H), 1.33–1.13 (m, 2H + 2H), 1.10–1.07 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H), 0.77 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 172.5 (C), 169.3 (C), 160.0 (C), 159.4 (C), 139.3 (C), 135.0 (C), 134.7 (C), 134.5 (C), 134.3 (C), 134.2 (C), 133.5 (C), 133.1 (C), 128.9 (2 × CH), 128.9 (2 × CH), 128.49 (2 × CH), 128.46 (2 × CH), 127.3 (4 × CH), 127.2 (4 × CH), 70.3 (CH), 69.4 (C), 68.9 (C), 65.7 (CH), 53.5 (CH_3), 52.6 (CH_3), 41.0 (CH_2), 40.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 19.7 (CH_2), 19.6 (CH_2), 13.6 (CH_3), 13.5 (CH_3); IR (KBr) 3233 (br), 2956 (m), 1701 (s), 1492 (s), 1231 (s), 1092 (s); HRMS (EI, 70 eV) calculated for $C_{21}H_{22}Cl_2N_2O_3$ (M^+) 420.1007, found 420.0989.

Methyl 1-butyl-4,5-bis(4-chlorophenyl)-2-thioxoimidazolidine-4-carboxylate 16. According to General Procedure III, thionation of imidazolidinone **15** (250 mg, 0.59 mmol), followed by column chromatography, afforded **16** as a white solid (245 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, $J = 8.7$ Hz, 2H), 7.43 (d, $J = 8.7$ Hz, 2H), 7.39 (d, $J = 8.6$ Hz, 2H), 7.28–7.20 (m, 2H), 7.15–7.10 (m, 6H), 7.04 (d, $J = 8.7$ Hz, 2H), 6.86 (s, 1H), 6.84 (s, 1H), 5.70 (s, 1H), 4.92 (s, 1H), 4.22–4.14 (m, 1H), 4.09–4.05 (m, 1H), 3.83 (s, 3H), 3.38 (s, 3H), 2.79–2.72 (m, 1H), 2.67–2.63 (m, 1H), 1.57–1.49 (m, 2H), 1.35–1.26 (m, 2H + 2H), 1.09–1.03 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H), 0.77 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 182.9 (C), 181.8 (C), 171.4 (C),

167.9 (C), 136.2 (C), 135.5 (C), 135.2 (C), 134.7 (2 × C), 133.4 (C), 132.6 (C), 131.9 (C), 129.2 (2 × CH), 128.7 (4 × CH), 128.7 (4 × CH), 127.2 (4 × CH), 126.8 (2 × CH), 74.4 (CH), 72.4 (C), 72.2 (C), 69.7 (CH), 53.8 (CH_3), 52.8 (CH_3), 45.0 (CH_2), 44.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 19.7 (CH_2), 19.4 (CH_2), 13.7 (CH_3), 13.5 (CH_3); IR (KBr) 3162 (br), 2952 (s), 1729 (s), 1593 (m), 1491 (s), 1231 (s); HRMS (EI, 70 eV) calculated for $C_{21}H_{22}Cl_2N_2O_2S$ (M^+) 436.0779, found 436.0777.

General Procedure IV for the microwave-assisted Liebeskind–Srogl reactions

A dry microwave vessel was charged with imidazolidine-2-thione (0.25 mmol), aryl boronic acid (0.38 mmol), Cu(I) thiophene-2-carboxylate (144.7 mg, 0.75 mmol) and $Pd(PPh_3)_4$ (8.9 mg, 7.5 μmol). The vessel was flushed with Ar and sealed. Dry DMF was added through the septum and the reaction mixture was irradiated in the microwave at 130 °C for 1 h, unless stated otherwise. After cooling, DMF was removed *in vacuo* at 50 °C. The crude mixture was diluted with saturated $NaHCO_3$ (aq.) and extracted with DCM. The organic layer was washed twice with saturated $NaHCO_3$ (aq.), dried with Na_2SO_4 and concentrated *in vacuo*. Purification was performed with flash column chromatography (*c*-hexane–EtOAc–Et_3N = 5 : 1 : 0.01, gradient).

***trans*-Methyl 4,5-bis(4-chlorophenyl)-1-methyl-2-phenyl-4,5-dihydro-1*H*-imidazole-5-carboxylate 17.** According to General Procedure IV, arylation of imidazolidin-2-thione **12** (100 mg, 0.25 mmol) with phenyl boronic acid (46 mg, 0.38 mmol) followed by column chromatography afforded **17** (56 mg, 51%) as a yellow solid together with starting material **12** (2 mg, 2%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.79–7.68 (m, 2H), 7.57–7.45 (m, 3H), 7.06 (d, J = 8.6 Hz, 2H), 7.03 (s, 4H), 6.79 (d, J = 8.5 Hz, 2H), 5.96 (s, 1H), 3.97 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 173.2 (C), 165.5 (C), 137.4 (C), 133.6 (C), 133.0 (C), 132.5 (C), 130.8 (C), 130.8 (CH), 129.5 (2 × CH), 128.7 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.6 (2 × CH), 81.1 (C), 76.0 (CH), 52.9 (CH_3), 33.0 (CH_3); IR (KBr) 1726 (s), 1589 (m), 1487 (m), 1379 (m), 1231 (m); HRMS (EI, 70 eV) calculated for $C_{24}H_{20}Cl_2N_2O_2$ (M^+) 438.0902, found 438.0883.

***trans*-Methyl 4,5-bis(4-chlorophenyl)-2-(4-methoxyphenyl)-1-methyl-4,5-dihydro-1*H*-imidazole-5-carboxylate 18.** According to General Procedure IV, arylation of imidazolidin-2-thione **12** (100 mg, 0.25 mmol) with *p*-methoxyphenyl boronic acid (58 mg, 0.38 mmol) followed by column chromatography afforded **18** (48 mg, 41%) as a yellow solid, together with starting material **12** (5 mg, 5%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.69 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.01 (br s, 6H), 6.77 (d, J = 8.5 Hz, 2H), 5.92 (br s, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 2.89 (s, 3H); IR (KBr); HRMS (EI, 70 eV) calculated for $C_{25}H_{22}Cl_2N_2O_3$ (M^+) 468.1007, found 468.1002.

Methyl 1-butyl-4,5-bis(4-chlorophenyl)-2-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylate 19. According to General Procedure IV, arylation of imidazolidin-2-thione **16** (109 mg, 0.25 mmol) with phenyl boronic acid (46 mg, 0.38 mmol) followed by column chromatography afforded **19** (78 mg, 65%) as a yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.82 (d, J = 8.7 Hz, 2H), 7.68–7.64 (m, 2H + 2H), 7.50–7.47 (m, 3H + 3H), 7.40–7.33 (m, 2H), 7.09–6.92 (m, 8H + 4H), 5.73 (s, 1H), 4.95 (s, 1H), 3.78 (s, 3H), 3.31–3.21 (m, 1H + 1H), 3.25 (s, 3H), 2.85–2.79 (m, 1H + 1H), 1.37–1.06 (m, 4H + 4H), 0.71 (t, J = 7.2 Hz, 3H), 0.59 (t, J = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 174.5 (C), 171.4 (C), 167.7 (C), 167.1 (C), 143.1 (2 × C), 135.9 (C), 134.5 (C), 133.3 (C), 132.6 (C), 132.4 (C), 131.9 (C), 130.0 (2 × C), 131.0 (CH), 130.8 (C), 130.2 (2 × CH), 129.6 (2 × CH), 129.1 (2 × CH), 128.99 (2 × CH), 128.97 (2 × CH + 2 × CH), 128.9 (2 × CH), 128.8 (2 × CH + 2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 82.8 (C), 82.6 (C), 75.4 (CH), 70.3 (CH), 53.5 (CH_3), 52.6 (CH_3), 45.9 (CH_2), 45.8 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 19.8 (CH_2), 19.4 (CH_2), 13.9 (CH_3), 13.7 (CH_3); IR (KBr) 2928 (s), 1726 (s), 1490 (s), 1241 (s); HRMS (EI, 70 eV) calculated for $C_{25}H_{23}Cl_2N_2$ (M^+ − CO_2Me) 421.1238, found 421.1223; the molecular ion could not be detected.

Methyl 1-butyl-4,5-bis(4-chlorophenyl)-2-(4-methoxyphenyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate 20. According to General Procedure IV, arylation of imidazolidin-2-thione **16** (109 mg, 0.25 mmol) with *p*-methoxyphenyl boronic acid (58 mg, 0.38 mmol) followed by column chromatography afforded **20** (71 mg, 55%) as a yellow solid, together with starting material **16** (14 mg, 13%). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.81 (d, J = 8.5 Hz, 2H), 7.68–7.60 (m, 2H + 2H), 7.39–7.36 (m, 2H), 7.08–6.90 (m, 10H + 6H), 5.70 (s, 1H), 4.90 (s, 1H), 3.87 (s, 3H + 3H), 3.77 (s, 3H), 3.33–3.23 (m, 1H + 1H), 3.23 (s, 3H), 2.88–2.80 (m, 1H + 1H), 1.33–1.01 (m, 4H + 4H), 0.85 (t, J = 6.0 Hz, 3H), 0.72 (t, J = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 174.6 (C), 171.6 (C), 167.5 (C), 166.9 (C), 161.8 (C), 161.7 (C), 143.3 (2 × C), 137.5 (C), 136.2 (C), 134.6 (C), 134.0 (C), 133.7 (C), 133.3 (C), 130.7 (2 × CH), 130.5 (2 × CH), 130.2 (2 × CH + 2 × CH), 129.6 (2 × CH), 129.1 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.1 (2 × CH), 123.1 (C), 123.0 (C), 114.6 (2 × CH), 114.3 (2 × CH), 82.8 (C), 82.5 (C), 75.5 (CH), 70.3 (CH), 55.8 (CH_3 + CH_3), 53.5 (CH_3), 52.5 (CH_3), 46.3 (CH_2), 46.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 20.1 (CH_2), 19.8 (CH_2), 14.0 (CH_3), 13.8 (CH_3); IR (KBr) 2924 (s), 1734 (s), 1611 (s), 1490 (s), 1251 (s); HRMS (EI, 70 eV) calculated for $C_{26}H_{25}Cl_2N_2$ (M^+ − CO_2Me) 451.1344, found 451.1336; the molecular ion could not be detected.

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