CHAPTER 2
SYNTHESIS OF IMIDAZOLIDINE-2-(THI)ONES VIA SELECTIVE OXIDATION OR THIONATION PROTOCOLS

Summary
This Chapter describes a study of the synthetic scope of imidazolidine-2-(thi)ones via selective C2 oxidation or C2 selective thionation protocols of 1H-imidazolinium salts, which were synthesized via alkylation of an Orru-3CR product.
C2-functionalized 2-imidazolidines and 2-imidazolines - Multicomponent Synthesis and Synthetic Potential
2.1 Introduction

In chapter 1, among biological activity and their role as precursors for homogeneous catalysis, synthetic sequences towards imidazolidine-2-ones and imidazolidine-2-thiones were discussed. Generally, these routes involve multiple synthetic steps, lacking the power for facile scaffold decoration. Nonetheless, based on the complexity generating Orru-3CR, we have recently reported some preliminary results on oxidation\(^1\) and thionation\(^2\) protocols of 2-imidazolinium halides that allows introduction of diversity on five positions of these target scaffolds.\(^1\), \(^3\), \(^4\) However, no study of the scope of the transformations was performed since the focus was on specific targets. Therefore, we now set out to determine the scope of these transformations. A retrosynthetic analysis for this scope-study is depicted in scheme 1.

![Scheme 1](image1)

**Scheme 1** Synthetic strategy

Imidazolidine-2-ones (A) and imidazolidine-2-thiones (B) can be synthesized by either selective C-2 oxidation or C-2 thionation of 2-imidazolinium iodides, which in turn can be synthesized by alkylation of an Orru-3CR product (Scheme 1). This approach allows introduction of diversity of six positions of the target scaffolds.

![Scheme 2](image2)

**Scheme 2** The Orru-3CR

In the Orru-3CR, amines (1), aldehydes or ketones (2) and α-acidic isocyanides (3) are reacted to give the 2-imidazolines, of which product formation is supposed to proceed through a Mannich-type addition of the α-carbanion of an α-acidic isocyanide to the in situ formed (protonated) imine and subsequent cyclization (Scheme 2).\(^2\), \(^3\), \(^4\) This versatile MCR tolerates the use of a large variety of inputs, although utilization of ketones requires addition of AgOAc (2%) as catalyst.
The Finkelstein reaction is a halogen for iodide exchange reaction for primary or secondary halides. Typically, Finkelstein reactions are performed in acetone, using NaI or KI, and achieve, especially for primary or secondary halides, a halogen for iodide exchange. Generally, the reaction equilibrium is shifted through the precipitation of NaX due to its poor solubility in acetone compared to NaI (Scheme 3). The reaction has been reported to perform exceptionally well with allyl, benzyl and α-carbonyl halides. In the recent decade, based on the same principle, the definition of the reaction has been expanded to also include the conversion of alcohols to alkyl iodides via OTs and OMs intermediates. Nevertheless, to prevent polymerization, usage of substrates bearing additional nucleophilic functionalities should be avoided.

### Results

#### Orru-3CR

From a collection of six amines, five aldehydes/ketones and three isocyanides, applying optimized conditions, a diverse set of 2-imidazolines (4a-g) was prepared in reasonable to excellent isolated yields (39 – 100%, Figure 1). Given the reduced reactivity of ketones in this MCR, AgOAc (2 mol%) was added as catalyst for the reaction with acetone (2a) as the carbonyl component. Under these conditions, 2-imidazolines 4a and 4b were isolated in reasonable yield. The moderate yield of 4d can be explained by the relative low α-acidity of methyl 2-isocyanoacetate. AgOAc catalysis was also used in the synthesis of 4g, affording the desired product in quantitative yield in this case.
2.2.2 Alkylation

Next, the 2-imidazolinium halides (6a-j) were obtained in generally excellent isolated yield by either direct alkylation of the corresponding halide (5) in CH₂Cl₂, or by using Finkelstein conditions (Scheme 4, Figure 2). The somewhat lower yield of 6g (84%) can be rationalized by the steric hindrance between the mesityl group and the spirofluorenyl moiety, hampering facile alkylation.
2.2.3 Selective C2 Oxidation and C2 Thionation

For the synthesis of the imidazolidine-2-ones (7, Scheme 5) an mCPBA mediated oxidation procedure in CH₂Cl₂ at 0°C was applied, where, for clean reactions, it has proven essential to add the mCPBA to a cooled (0°C) solution of the 2H-2-imidazolinium halides. To obtain the imidazolidine-2-thiones (8, Scheme 5) a modified procedure of Karkhanis et al. was applied. In this modified procedure, 2-imidazolinium halides are reacted with S₈ and KO₂Bu at room temperature.

**Scheme 5** Oxidation and thionation of 2H-2-imidazolinium halides

\[ \text{EWG} \rightarrow \begin{array}{c} \text{N} R_1 \text{N} R_5 \\ \text{N} R_1 \text{N} R_5 \end{array} \rightarrow \begin{array}{c} \text{O} \\ \text{S} \end{array} \]

a: mCPBA, DCM, 0 °C to rt, 18 h
b: KO₂Bu, S₈, rt, 3h
Imidazolidine-2-ones 7a, 7c and 7d were obtained in good to excellent isolated yield (64 – 96%, Figure 3) by selective C2 oxidation, while no product was obtained from oxidation of substrate 6e. This is probably due to oxidation to the corresponding imidazolium halide or oxidative cleavage of the p-methoxybenzyl group. The yield of 7j was unexpectedly low (12%). In this case, we were not able to provide a plausible rationalization of this result. Spirofluorene imidazolidine-2-thiones (8a-d, 8f-h) were obtained by selective C2-thionation in reasonable to excellent yield (60 – 89%, Figure 3). Imidazolidine-2-thione 8e, however, was obtained in only 53% yield. This can be rationalized by taking into account the acidic nature of the backbone protons, where, considering the basic conditions, deprotonation can lead to various competing side reactions, leading to scrambling of products. On the other hand, the other ester-functionalized imidazolidine-2-thiones, 8j and 8i, were obtained in good (76%) and quantitative yield, respectively. In the latter case, 8i was synthesized in 94% yield over three steps starting from 3c.

Figure 3  Imidazolidine-2-(thi)ones
2.3 Conclusions

We have presented a short and resource-efficient three-step synthetic strategy towards imidazolidine-2-ones (7) and imidazolidine-2-thiones (8) by either selective C-2 oxidation or C-2 thionation protocols of 2-imidazolinium halides. This methodology allows facile installation of six points of diversity in the target scaffolds by the complexity generating Orru-3CR. The target heterocycles were obtained in up to 70% and 94% overall yields over 3 steps respectively. With these results in hand, follow-up chemistry towards the synthesis of a range of biologically active compounds and novel analogues is currently under investigation.

2.4 Acknowledgements

M. C. Smoluch and F. J. J. de Kanter are kindly acknowledged for HRMS and NMR measurements, respectively.

2.5 Experimental Section

Materials and Instrumentation

All reactions were carried out under inert atmospheric conditions, unless stated otherwise. Infrared (IR) spectra were obtained from neat samples or from CHCl₃ films on NaCl tablets using a Matteson Instruments 6030 Galaxy Series FT-IR spectrophotometer and wavelengths (ν) are reported in cm⁻¹. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 (400.13 and 100.61 MHz, respectively), a Bruker Avance 250 (250.13 and 62.90 MHz, respectively) with chemical shifts (δ) reported in ppm, internally referenced to residual solvent resonances of CDCl₃ (¹H δ: = 7.26 ppm; ¹³C{¹H} δ: = 77.00 ppm), and coupling constants (J) are reported in Hz. Peak assignment was also done with the aid of gs-COSY, gs-HMQC, and gs-HMBC measurements. HRMS spectra data were recorded on a Finnigan Mat 900 spectrometer (EI) or a micrOTOF-Q instrument in positive ion mode (ESI). 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 F254) on aluminum with fluorescence indicator. Compounds on TLC were visualized by UV-detection unless stated otherwise. DCM was dried and freshly distilled from CaH₂ prior to use. THF and Et₂O were dried and distilled from sodium benzophenone ketyl prior to use. Cyclohexane was distilled prior to use as eluent for chromatography. 2-(trimethylsilyl)ethanamine was synthesized according to literature procedure and stored in Et₂O under inert atmosphere.
at 4°C. 2-imidazolines 4b, 4e, 4f, and imidazolinium halides 6e-g were synthesized according to literature procedures, whereas all other commercially available reagents were used as purchased without further purification.

**General Procedure I for the Synthesis of 2-imidazolines:** To a stirred mixture of Na₂SO₄ and the amine component (1.0 M) in freshly distilled DCM or MeOH, the aldehyde component (1.0 M) was added and stirred at room temperature for 3 h. Then, the isocyanide component (0.5 M) was added and the resulting reaction mixture was stirred for an additional 18 h, followed by filtration and concentration in vacuo. The crude product was purified by silica gel flash column chromatography (EtOAc : c-Hex : NEt₃ = 1.0 : 4.0 : 0.01 → gradient, unless stated otherwise).

**General Procedure II for the Synthesis of 2-imidazolines:** To a stirred mixture of Na₂SO₄, the amine component (1.0 M) and AgOAc (0.02 eq) in freshly distilled DCM or MeOH, the aldehyde component (1.0 M) was added and stirred at room temperature for 3 h. Then, the isocyanide component (0.5 M) was added and the resulting reaction mixture was stirred for an additional 18 h, followed by filtration and concentration in vacuo. The crude product was purified by silica gel flash column chromatography (EtOAc : c-Hex : NEt₃ = 1.0 : 4.0 : 0.01 → gradient, unless stated otherwise).

**2-imidazoline 4a:** 100 ml of a solution of an unknown concentration of 2-(trimethylsilyl)ethanamine in ether was concentrated to approximately 10 ml. After the solution was put under inert atmosphere an excess of Na₂SO₄ and acetone (250 μl, 3.4 mmol, 1.5 eq) were successively added and at rt. The resulting mixture was stirred for 3 hours. Then, 9-isocyano-9H-fluorene (321.7 mg, 1.7 mmol, 1.5 eq) and AgOAc (18.8 mg, 0.11 mmol, 0.05 eq) were added and the resulting reaction mixture was stirred for 18 hours at rt. Then the reaction mixture was successively filtered, concentrated in vacuo and subjected to silica gel flash column chromatography to afford 2-imidazoline 4a as a white foam (354.3 mg, 1.02 mmol, 60%). Analysis:

- **1H NMR (250 MHz CDCl₃)** δ: 7.64 – 7.60 (m, 2H), 7.53 – 7.48 (m, 2H), 7.35 – 7.20 (m, 2H), 3.14 – 3.06 (m, 2H), 2.902 (s, 3H), 1.09 – 1.01 (m, 2H), 1.069 (s, 6H);
- **13C NMR (63 MHz CDCl₃)** δ: 157.2 (CH), 128.2 (CH), 126.2 (CH), 126.1 (CH), 119.6 (CH), 124.1 (CH), 120.1 (CH), 37.9 (CH₂), 22.7 (CH₃), 19.0 (2x CH₂), -1.8 (3x CH₃); IR (thin film): 3074, 3060, 3060, 2953, 2925, 2853, 1728, 1485, 1482, 1379, 1322, 1211, 907, 734; HRMS (EI, 70 eV) calculated for C₂₂H₂₈N₂Si 348.55662, found 348.20108.

**2-imidazoline 4c:** According general procedure I, the reaction between benzylamine (214.31 mg, 218.7 μl, 2.0 mmol), 5-methylfuran-2-carbaldehyde (220.2 mg, 200 μl, 2.0 mmol), 9-isocyano-9H-fluorene (382.5 mg, 2.0 mmol) to afford 2-imidazoline 4c as white foam (636.6 mg, 1.63 mmol, 81%). Analysis:

- **1H NMR (400 MHz CDCl₃)** δ: 7.58 – 7.56 (m, 2H), 7.53 – 7.50 (m, 1H), 7.41 – 7.37 (m, 2H), 7.35 – 7.27 (m, 4H), 7.25 – 7.20 (m, 4H), 7.10 – 7.05 (m, 1H), 5.74 (d, J = 3.2, 2H), 5.67 – 5.66 (m, 1H), 4.739 (s, 1H), 4.63 (d, J = 14.8, 1H), 4.14 (d, J = 14.8, 1H), 2.08 (s, 5H);**
- **13C NMR (63 MHz CDCl₃)** δ: 158.1 (CH), 140.3 (c), 136.2 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 126.1 (CH), 123.5 (CH), 119.5 (CH), 119.2 (CH), 109.8 (CH), 105.9 (CH), 66.1 (C), 50.3 (CH), 13.5 (CH₃);** IR (thin film): 3074, 2035, 2825, 1450, 1421, 1374, 1282, 1275, 1159, 1079, 1021, 914, 790, 731, 702; HRMS (EI, 70 eV) calculated for C₂⁷H₂₃N₂O (M + H⁺) 391.1810, found 391.1815.
2-imidazoline 4d: According general procedure I, n-buty Amine (213.0 mg, 202.8 μl, 2.01 mmol), benzaldehyde (146.8 mg, 190.6 μl, 2.0 mmol), methyl 2-isocyanoacetate (190.74 mg, 182.0 μl, 2.0 mmol) to afford 2-imidazoline 4d as white foam (206.0 mg, 0.79 mmol, 39%).

(Single diastereoisomer) Analysis: \( \text{H} \) NMR (250 MHz CDCl\(_3\)) \( \delta \): 7.26 – 7.07 (m, 6H), 6.95 – 6.86 (m, 1H), 7.41 (d, \( J = 5.5 \), 1H), 4.40 – 4.37 (m, 1H), 3.64 (s, 3H), 3.07 – 2.93 (m, 1H), 2.87 – 2.80 (m, 1H), 1.38 – 1.24 (m, 2H), 1.23 – 1.11 (m, 2H), 0.72 (t, \( J = 4.6 \), 3H);

\( \text{C} \) NMR (63 MHz CDCl\(_3\)) \( \delta \): 172.4 (C), 157.0 (CH), 140.3 (C), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 78.1 (CH), 65.9 (CH), 52.5 (CH3), 45.0 (CH2), 30.1 (CH2), 19.9 (CH2), 13.6 (CH3); IR (thin film): 3055, 2962, 2932, 2874, 1628, 1373, 1265, 1207, 733; HRMS (EI, 70 eV) calculated for C\(_{15}\)H\(_{21}\)N\(_2\)O\(_2\) (M + H\(^{+}\)) 259.1441, found 259.1435.

2-imidazoline 4g: According general procedure II, \( \rho \)-Toluidine (214 mg, 2.01 mmol), 5-methylfurfural (200 μl, 2.00 mmol), AgOAc (7 mg, 0.04 mmol) and isocyanide 3c (350 mg, 2.00 mmol) to afford 4g as white crystals as a 3:1 mixture of diastereomers (1.87 mmol, 94%). Mp. 145-147 °C.

\( \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.80 (s, 1H); 7,25 (m, 2H); 7.16 (m, 3H); 7.03 (t, \( J = 8.0 \) Hz, 2H); 6.91 (d, \( J = 8,0 \) Hz, 2H); 6.16 (s, 1H); 5.88 (d, \( J = 4,0 \) Hz, 1H); 5.49 (d, \( J = 4,0 \) Hz, 1H); 3.76 (s, 3 H); 2.25 (s, 3H); 1.86 (s, 3H).

\( \text{C} \) NMR (125 MHz): \( \delta \): 173.4 (C); 152.2 (C); 151.1 (CH); 142.7 (C); 137.7 (C); 136.3 (C); 132.5 (C ); 129.9 (2 CH); 128.3 (CH); 127.3 (2 CH); 126.6 (2 CH); 116.8 (2 CH); 111.0 (CH); 105.6 (CH); 84.4 (C); 63.1 (CH); 53.3 (CH3); 20.6 (CH3) 13.2 (CH3). HRMS: calculated for C\(_{23}\)H\(_{23}\)N\(_2\)O\(_3\) (M + H\(^{+}\)) 375.1703, found 375.1703. Mp: 146-147 °C.

General Procedure III for the Synthesis of 2-imidazolinium halides: Reactions were carried out at a concentration of 0.15 – 0.25 M of imidazoline in dry DCM, unless noted otherwise. The halide was added to a stirred solution of the imidazoline, and the reaction mixture was stirred at rt for 18 h. Then, the reaction mixture was concentrated in vacuo. The crude product was washed with pentane or Et\(_2\)O.

General Procedure IV for the Synthesis of 2-imidazolinium halides: Reactions were carried out at a concentration of 1.0 M of imidazoline in acetone. The halide (1.0 eq) was added to a stirred solution of the 2-imidazoline and KI (1.0 eq). The reaction mixture was stirred at rt for 18 h and concentrated in vacuo. Then the reaction mixture was taken up in DMC and subsequently filtrated over celite and concentrated in vacuo.

2-imidazolinium iodide 6a: According general procedure III, the reaction between 2-imidazoline 4a (100.0 mg, 0.24 mmol), MeI (18.9 μl, 0.24 mmol) to afford 2-imidazolinium 6a as a pale yellow foam (130.0 mg, 0.24 mmol, 100%). Analysis: \( \text{H} \) NMR (250 MHz CDCl\(_3\)) \( \delta \): 10.11 (s, 1H), 7.72 – 7.69 (m, 2H), 7.56 – 7.45 (m, 4H), 7.40 – 7.30 (m, 2H), 3.59 – 3.52 (m, 2H), 2.90 (s, 3H), 1.39-1.34 (m, 2H), 1.23 (s, 6H), 0.15 (s, 9H);

\( \text{C} \) NMR (63 MHz CDCl\(_3\)) \( \delta \): 158.1 (CH), 141.1 (C),138.3 (C), 131.0 (CH), 129.1 (CH), 128.1 (CH2), 128.3 (CH), 127.3 (2 CH); 126.6 (2 CH); 116.8 (2 CH); 111.0 (CH); 105.6 (CH); 84.4 (C); 63.1 (CH); 53.3 (CH); 20.6 (CH3) 13.2 (CH3). HRMS: calculated for C\(_{23}\)H\(_{31}\)N\(_2\)Si (M - I\(^{-}\)) 363.2251, found 363.2255.

2H-imidazolidinium iodide 6b: According general procedure III the reaction between 2-imidazoline 4b (338.4 mg, 1.00 mmol) and MeI (66.0 μl, 1.00 mmol) to afford imidazolinium 6b as a pale yellow foam (480,1 mg, 1.00 mmol, 100%). Analysis: \( \text{H} \) NMR (250 MHz CDCl\(_3\)) \( \delta \): 9.98 (s, 1H), 7.77 – 7.62 (m, 2H), 7.60 – 7.50 (m, 2H), 7.50 – 7.38 (m, 4H), 7.37 – 7.26 (m, 4H), 4.87 (s, 2H), 2.84 (s, 3H), 1.09 (s, 6H); \( \text{C} \) NMR (63 MHz CDCl\(_3\)) \( \delta \): 159.1 (CH), 158.4 (CH), 154.8 (C), 141.0 (C), 140. -7 (C), 138.2 (C), 137.7 (C), 133.9 (C), 131.0 (CH), 129.4 (CH), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.9
(CH), 128.8 (CH), 126.5 (CH), 126.1 (CH), 121.0 (CH), 119.8 (CH), 72.2 (CH₂), 69.3 (CH), 48.6 (C), 47.0 (C), 29.7 (C), 24.2 (2x CH₃); IR (thin film): 3072, 3033, 2932, 2902, 2342, 1633, 1577, 1540, 1448, 1363, 1285, 1210, 1153, 1101, 916, 754, 754, 724, 703; HRMS (EI, 70 eV) calculated for C₃₂H₂₄N₂ (M - H) 353.1777, found 353.1688.

2-imidazolinium iodide 6c: According to general procedure IV, the reaction between 2-imidazoline 4b (1.072 g, 2.80 mmol), KI (0.526 mg, 2.80 mmol) and chloro(methoxy)methane (254.0 mg, 142 μl, 2.80 mmol) to afford 2-imidazolinium iodide 6c as a yellow foam (1.427 g, 2.80 mmol, 100%). Analysis: H NMR (250 MHz CDCl₃): δ: 10.15 (s, 1 H), 7.75 – 7.55 (m, 5H), 7.50 – 7.35 (m, 5H), 7.30 – 7.20 (m, 3H), 4.95 (s, 2H), 4.63 (s, 2H), 3.10 (3H); ¹³C NMR (63 MHz CDCl₃): δ: 159.1 (CH), 140.7 (C), 138.6 (C), 133.4 (C), 130.8 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 128.4 (CH), 127.7 (CH), 126.9 (CH), 126.6 (CH), 126.0 (CH), 120.8 (CH), 119.8 (C), 81.5 (C), 78.0 (CH₂), 73.4 (C), 57.5 (CH), 48.9 (CH), 23.7 (CH₃); IR (thin film): 3468, 3433, 3005, 2551, 2824, 1620, 1451, 1354, 1265, 1192, 1103, 1049, 918, 745, 710; HRMS (EI, 70 eV) calculated for C₆₃H₄₇N₂ 338.1777, found 338.2598 (M - H₃).

2-imidazolinium iodide 6d: According to general procedure IV, the reaction between 2-imidazoline 4c (600.0 mg, 1.53 mmol), KI (253.9 mg, 1.53 mmol) and chloro(methoxy)methane (122.4 mg, 116 μl, 1.53 mmol) to afford 2-imidazolinium iodide 6d as a yellow foam (791.7 mg, 1.41 mmol, 92%). Analysis: H NMR (250 MHz CDCl₃): δ: 10.76 (s, 1H), 7.50 – 7.02 (m, 14H), 6.01 (m, 1H), 5.67 (m, 1H), 5.32 (d, J = 14.3), 5.30 (s, 1H), 4.55 (s, 3H), 4.50 – 4.51 (m, 1H), 4.48 (d, J = 14.3), 3.06 (s, 3H), 2.02 (s, 2H); ¹³C NMR (63 MHz CDCl₃): δ: 160.0 (CH), 154.5 (C), 143.8 (C), 141.4 (C), 141.1 (C), 139.5 (C), 136.9 (C), 132.0 (C), 130.9 (CH), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.2 (CH), 128.9 (CH), 127.7 (CH), 126.5 (CH), 123.2 (CH), 20.5 (CH), 114.3 (CH), 107.1 (CH), 77.7 (CH₂), 67.9 (CH₂), 57.2 (CH₂), 51.5 (CH₃); IR (thin film): 3032, 2924, 2924, 2855, 1624, 1451, 1366, 1261, 1192, 1111, 1018, 918, 733, 706; HRMS (EI, 70 eV) calculated for C₃₃H₂₈N₂O₂ (M - H) 435.2067, found 435.2076.

2-imidazolinium iodide 6e: According to general procedure IV, the reaction between 2-imidazoline 4d (200.0 mg, 0.77 mmol) and 4-methoxybenzylbromide (154.8 mg, 111 μl, 0.77 mmol) to afford 2-imidazolinium iodide 6e as a yellow foam (356.7 mg, 0.70 mmol, 91%). Analysis: H NMR (250 MHz CDCl₃): δ: 10.18 (s, 1H), 7.39 – 7.36 (m, 2H), 2.29 – 2.26 (m, 3H), 7.19 – 7.19 (m, 3H), 6.79 – 6.73 (m, 2H), 5.30 (d, J = 14.3, 1H), 5.21 (d, J = 7.3, 1H), 4.59 (d, J = 14.3, 1H), 4.14 (d, J = 7.3, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.70 – 3.60 (m, 1H), 3.06 – 3.00 (m, 1H), 1.56 – 1.50 (m, 2H), 1.19 – 1.13 (m, 2H), 0.76 (s, J = 7.4, 3H); ¹³C NMR (63 MHz CDCl₃): δ: 168.9 (C), 160.2 (C), 156.8 (CH), 135.1 (C), 130.9 (CH), 130.02 (CH), 129.6 (CH), 127.1 (CH), 124.2 (C), 114.7 (CH), 113.8 (CH), 71.4 (CH₂), 67.7, 67, 5 (2x CH₂), 55, 36 (CH), 46.2 (CH₂), 19.5 (2x CH₃), 19.4 (CH₃); IR (thin film): 3337, 2959, 2932, 2870, 1720, 1601, 1459, 1349, 1346, 1250, 1192, 1111, 1030, 945, 837, 737, 702; HRMS (EI, 70 eV) calculated for C₃₃H₂₈N₂O₂ (M - H) 381.2173, found 381.2174.

2-imidazolinium iodide 6f: According to general procedure IV, the reaction between 2-imidazoline 4g (100 mg, 0.27 mmol) and benzyl bromide (34 μl, 0.28 mmol) to afford 2-imidazolinium iodide 6f as an off-white brittle salt (0.27 mmol, 100%). H NMR (400 MHz, DMSO): δ: 9.76 (s, 1H), 7.44 – 7.16 (br. m, 14 H); 6.20 (d, J = 3.2 Hz, 1H), 5.65 (d, J = 3.2 Hz, 1H), 5.19 (d, J = 16.0, 1H); 4.75 (d, J = 16.0 br. m., 1H); 3.50 (s, J = 3H); 2.26 (s, 3H); 1.77 (s, 3H).

2-imidazolinium iodide 6g: According to general procedure III, the reaction between 2-imidazoline 4g (100 mg, 0.27 mmol) and Mel (20 μL, 0.32 mmol) to afford 6g as a yellow salt (0.25 mmol, 92%). Indicative signals: H NMR (400 MHz, DMSO) δ: 9.64 (s, 1H), 7.57 – 7.01 (br. m, 9H) 6.20 (d, J = 3.2 Hz, 1H), 5.66 (d, J = 3.2 Hz, 1H); 3.95 (s, 3H); 3.62 (s, 3H); 3.55 (s, 1H); 2.26 (s, 3H); 1.76 (s, 3H).
General procedure V for the Syntheses of Imidazolidine-2-ones: To a solution of the 2-imidazolinium salt (0.05 M) in freshly distilled DCM mCPBA (3.0 eq) was added at 0°C. The reaction mixture was stirred at rt for 18 h and subsequently washed with Na2CO3 (2x), concentrated in vacuo and subjected to silica gel flash column chromatography (EtOAc : c-Hex : NEt3 = 1.0 : 4.0 : 0.01 → gradient, unless stated otherwise).

Imidazolidine-2-one 7a: According to general procedure V, the reaction between 2-imidazolinium iodide 6a (100.0 mg, 0.203 mmol) and mCPBA (123.6 mg, 0.609 mmol) to afford imidazolidine-2-one 7a as a pale yellow foam (49.1 mg, 0.130 mmol, 64 %). Analysis:

1H NMR (250 MHz CDCl3) δ: 7.71 – 7.60 (m, 2H), 7.49 – 7.40 (m, 2H), 7.39 – 7.36 (m, 2H), 7.29 – 7.22 (m, 2H), 3.27 – 3.20 (m, 2H), 2.32 (s, 3H), 1.43 (s, 6H), 1.08 – 1.01 (m, 2H), 0.07 (s, 9H);
13C NMR (63 MHz CDCl3) δ: 161.4 (C), 142.9 (C), 141.1 (C), 129.2 (CH), 127.0 (CH), 126.1 (CH), 120.2 (CH), 78.0 (C), 63.0 (C), 36.2 (CH2), 26.9 (CH3), 23.1 (CH3), 19.1 (CH2), -1.7 (CH3); IR (thin film): 3059, 2951, 1697, 1447, 1423, 1393, 1346, 1246, 1150, 1037, 860, 837, 748, 733; HRMS (EI, 70 eV) calculated for C23H31N2OSi (M + H)+ 379.2200, found 379.2168.

Imidazolidine-2-one 7b: According to general procedure V, the reaction between 2H-imidazolinium iodide 6c (142 mg, 0.278 mmol) and mCPBA (169.5 mg, 0.835 mmol) to afford imidazolidine-2-one 7b as a pale yellow foam (78.7 mg, 0.197 mmol, 71 %).

Analysis:

1H NMR (250 MHz CDCl3) δ: 7.66 – 7.58 (m, 2H), 7.50 – 7.42 (m, 3H), 7.39 – 7.28 (m, 4H), 7.27 – 7.14 (m, 4H), 4.50 (s, 2H), 4.35 (s, 2H), 3.20 (s, 3H), 0.98 (s, 6H);
13C NMR (100 MHz CDCl3) δ: 167.0 (C), 143.1 (C), 140.9 (C), 139.5 (C), 129.3 (CH), 128.4 (CH), 127.2 (CH), 126.9 (CH), 120.0 (CH), 76.5 (C), 74.5 (CH2), 63.8 (C), 55.9 (CH3), 44.3 (CH2), 23.2 (2x CH3); IR (thin film): 3063, 2924, 2855, 1689, 1447, 1396, 1354, 1296, 1273, 1072, 1030, 737; HRMS (EI, 70 eV) calculated for C26H27N2O2 (M + H)+ 399.2073, found 399.20731.

Imidazolidine-2-one 7d: According to general procedure V, the reaction between 2H-imidazolinium iodide 6d (265.0 mg, 0.506 mmol) and mCPBA (247.7 mg, 1.58 mmol) to afford imidazolidine-2-one 7d as a pale yellow foam (221.0 mg, 0.490 mmol, 97%).

Analysis:

1H NMR (400 MHz CDCl3) δ: 7.58 – 7.48 (m, 2H), 7.34 – 7.21 (m, 9H), 7.20 – 7.13 (m, 1H), 7.08 – 7.01 (m, 1H), 5.83 – 5.82 (m, 1H), 5.78 – 5.77 (m, 1H), 5.11 (d, J = 13.4, 1H), 4.57 (s, 1H), 4.37 (d, J = 11.2, 1H), 4.31 (d, J = 11.2, 1H), 3.38 (d, J = 13.4, 1H), 3.12 (s, 3H), 2.08 (s, 3H);
13C NMR (63 MHz CDCl3) δ: 161.6 (C), 152.2 (C), 146.5 (C), 146.3 (C), 141.5 (C), 140.5 (C), 139.6 (C), 136.5 (C), 129.2 (2x CH), 128.6 (2x CH), 128.4 (2x CH), 127.8 (CH), 127.5 (CH), 126.8 (CH), 125.9 (2x CH), 123.0 (2x CH), 119.8 (CH), 119.6 (CH), 73.7 (CH2), 72.1 (C), 61.5 (CH), 55.6 (CH3), 46.5 (CH2), 13.3 (CH3); IR (thin film): 3059, 2032, 2924, 2828, 1701, 1447, 1420, 1384, 1292, 1261, 1161, 1084, 1022, 914, 794, 737; HRMS (EI, 70 eV) calculated for C29H27N2O3 (M + H)+ 451.2016, found 451.2004.

Imidazolidine-2-one 7e: According to general procedure V, the reaction between 2-imidazolinium iodide 6e (100.0 mg, 0.196 mmol) and mCPBA (123.6 mg, 0.590 mmol). No product could be isolated.

Imidazolidine-2-one 7j: According to general procedure V the reaction of imidazoline halide 6j (52 mg, 0.1 mmol), mCPBA (52 mg, 0.3 mmol) to afford 7j (5 mg, 0.012 mmol, 12%).

1H NMR (500 MHz, CDCl3): δ: 7.39 (d, J = 7.2 Hz, 2H); 7.21 (d, J = 7.2 Hz, 2H); 7.08 - 7.03 (m, 5H); 5.95 (s, 1H); 5.84 (d, J = 3.2 Hz, 1H); 5.53 (d, J = 4.2 Hz, 2H); 3.88 (s, 3H); 2.99 (s, 3H); 2.26 (s, 3H); 1.87 (s, 3H).
13C NMR (125 MHz, CDCl3): δ: 171.8 (C); 157.5 (C); 152.3 (C); 146.2 (C); 136.2 (C); 133.1 (C); 133.0 (C); 129.2 (CH); 128.9 (CH); 128.2 (CH); 127.0 (CH); 120.3 (CH); 110.7 (CH); 105.8 (CH); 73.4 (C); 61.7 (CH); 53.0 (CH3); 30.2 (CH3); 21.1 (CH3); 13.1 (CH3). HRMS: Calculated for C24H25N2O4 (M + H)+: 405.1809 (M + H)+, found: 405.1809.
General procedure VI for the Synthesis of Imidazolidine-2-thiones: Reactions were carried out under an inert atmosphere of dry argon at a 0.04 M concentration of imidazoline salt in freshly distilled THF. The reaction vessel was charged with 2H-imidazoline halide, KOtBu (1.0 eq) and S8 (1.0 eq), flushed two times with argon. THF was added and the reaction mixture was stirred at rt for 2 h after which water was added. The mixture was subsequently extracted with Et2O (2x), EtOAc (2x), DCM (2x). The combined organic layers were subsequently dried with Na2SO4, filtered, concentrated in vacuo and subjected to silica gel flash column chromatography EtOAc : Toluene (0.0 : 1.0 → gradient, visualization on TLC with UV and iodine).

**Imidazolidine-2-thione 8a:** According to general procedure VI, the reaction between 2H-imidazolinium iodide 6a (141.3 mg, 0.288 mmol), KOtBu (69.8 mg, 0.288 mmol) and S8 (73.3 mg, 0.288 mmol) to afford imidazolidine-2-thione 8a as a yellow foam (71.8 mg, 0.224 mmol, 78 %). Analysis: 1H NMR (250 MHz CDCl3) δ: 7.72 – 7.41 (m, 2H), 7.41 – 7.34 (m, 4H), 7.32 – 7.22 (m, 2H), 3.70 – 3.62 (m, 2H), 2.64 (s, 3H), 1.26 – 1.12 (m, 2H), 1.11 (s, 3H); 13C NMR (63 MHz CDCl3) δ: 180.2, 141.9 (C), 140.9 (C), 129.5 (2x CH), 127.3 (2x CH), 126.1 (2x CH), 120.3 (2x CH), 98.0 (C), 66.87 (C), 40.1 (CH2), 31.0 (CH3), 22.8 (2xCH3), 17.8 (CH2), -1.7 (3x CH3); IR (thin film): 3072, 3038, 2998, 2974, 2369, 2343, 1458, 14483, 1408, 1364, 1283, 1246, 1150, 1013, 858, 840, 768, 754, 735; HRMS (EI, 70 eV) calculated for C23H30N2SSi 394.64820, found 394.218909.

**Imidazolidine-2-thione 8b:** According to general procedure VI, the reaction between 2H-imidazolinium iodide 6b (275.5 mg, 0.573 mmol), KOtBu (145.0 mg, 0.573 mmol) and S8 (152.2 mg, 0.573 mmol) to afford imidazolidine-2-thione 8b as a pale yellow foam (154.2 mg, 0.401 mmol, 70 %). Analysis: 1H NMR (250 MHz CDCl3) δ: 7.66 – 7.55 (m, 4H), 7.42 – 7.18 (m, 9 H), 5.01 (s, 2H), 2.72 (s, 3H), 1.03 (s, 6H); 13C NMR (63 MHz CDCl3) δ: 141.1 (C), 138.2 (C), 133.8 (C), 131.0 (CH), 129.5 (CH), 129.4 (CH), 129.2 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 126.7 (CH), 126.4 (CH), 126.2 (CH), 121.0 (CH), 119.7 (CH), 72.2 (CH2), 48.4 (C), 46.9 (C), 31.5 (CH3), 24.1 (2x CH3); IR (thin film): 3060, 3033, 2974, 2931, 2854, 2190, 1633, 1585, 1449, 1362, 1298.22, 1210, 1153, 1013, 858, 768, 754, 735; HRMS (EI, 70 eV) calculated for C25H24N2S (M+ ) 344.1660, found 344.1662.

**Imidazolidine-2-thione 8c:** According to general procedure VI, the reaction between 2H-imidazolinium iodide 6c (1.159 g, 2.79 mmol), KOtBu (573.2 mg, 2.79 mmol) and S8 (601.7 mg, 2.79 mmol) to afford imidazolidine-2-thione 8c as a yellow foam (640 mg, 1.87 mmol, 67 %). Analysis: 1H NMR (250 MHz CDCl3) δ: 7.64 – 7.58 (m, 4H), 7.44 – 7.16 (m, 9H), 5.05 (s, 2H) 4.76 (s, 2H), 3.22 (s, 3H), 1.01 (s, 6H); 13C NMR (63 MHz CDCl3) δ: 184.4 (C), 142.0 (C), 140.7 (C), 138.5 (C), 129.5 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 126.7 (CH), 126.4 (CH), 126.2 (CH), 121.0 (CH), 119.7 (CH), 72.2 (CH2), 48.4 (C), 46.9 (C), 31.5 (CH3), 24.1 (2x CH3); IR (thin film): 3060, 3036, 3019, 2974, 2931, 2854, 2190, 1633, 1585, 1449, 1362, 1298.22, 1210, 1153, 1101, 917, 754, 726, 704; HRMS (EI, 70 eV) calculated for C26H26N2OS (M+ ) 414.56244, found 414.17617.

**Imidazolidine-2-thione 8d:** According to general procedure VI, the reaction between 2H-imidazolinium iodide 6d (100 mg, 0.177 mmol), KOtBu (19.9 mg, 0.177 mmol) and S8 (45.6 mg, 0.177 mmol) to afford imidazolidine-2-thione 8d as a yellow foam (49.4 mg, 0.106 mmol, 60 %). Analysis: 1H NMR (250 MHz CDCl3) δ: 7.58 – 7.53 (m, 2H), 7.39 – 7.24 (m, 6H), 7.20 – 7.13 (m, 2H), 7.12 – 7.02 (m, 1H), 7.10 – 6.94 (m, 2H), 5.91 (d, J = 14.6, 1H), 5.86 (d, J = 2.2, 1H), 5.00 (s, 1H), 4.79 (m, J = 11.0, 1H), 4.73 (m, J = 11.0, 1H), 4.09 (d, J = 14.5, 1H), 3.13 (s, 3H), 1.44 (s, 3H); 13C NMR (63 MHz CDCl3) δ: 152.8 (C), 146.3 (C), 145.6 (C), 140.8 (C), 140.2 (C), 139.4 (C), 136.0 (C), 129.6 (CH), 129.5 (CH), 129.0 (2x CH), 128.5 (2x CH), 128.1 (CH), 127.8 (2x CH), 126.9 (2x CH), 126.4 (CH), 125.5 (CH), 123.1 (CH), 119.9 (CH), 119.8 (CH), 76.6 (CH),
Imidazolidine-2-thione 8e: According to general procedure VI, the reaction between 2-imidazolinium iodide 6e (100 mg, 0.196 mmol), KOtBu (22.1 mg, 0.196 mmol) and S8 (50.5 mg, 0.196 mmol), to afford imidazolidine-2-thione 8e as a yellow foam (43.1 mg, 0.104 mmol, 53 %). Analysis: 1H NMR (250 MHz CDCl3) δ: 7.27 – 7.20 (m, 2H), 7.20 – 7.15 (m, 2H), 7.01 – 6.97 (m, 2H), 6.91 (s, 1H), 5.56 (d, J = 14.9, 1H), 4.79 (d, J = 4.6, 1H), 4.27 (d, J = 4.6, 1H), 3.83 (d, J = 4.6, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 2.86 – 2.74 (m, 1H), 1.48 – 1.37 (m, 2H), 1.30 – 1.15 (m, 2H), 0.81 (d, J = 7.2, 3H); 13C NMR (63 MHz CDCl3) δ: 128.3 (C), 169.9 (C), 159.2 (C), 138.2 (C), 129.9 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 127.9 (C), 126.6 (CH), 125.5 (CH), 114.0 (CH), 65.9 (CH), 64.5 (CH), 55.2 (CH2), 49.5 (CH2), 45.2 (CH2), 28.0 (CH2), 19.8 (CH2), 13.8 (CH3); IR (thin film): 2955, 2928, 2855, 1730, 1612, 1512, 1454, 1435, 1250, 1219, 1177, 1034, 752; HRMS (EI, 70 eV) calculated for C29H27N2O2S (M + H+) 467.17932, found 467.17943.

Imidazolidine-2-thione 8f: According to general procedure VI, the reaction between 2-imidazolinium iodide 6f (93 mg, 0.22 mmol), KOtBu (25 mg, 0.22 mmol) and S8 (57 mg, 0.22 mmol to afford imidazolidine-2-thione 8f as a white foam (64 mg, 0.20 mmol, 89%). 1H NMR (250 MHz CDCl3) δ: 7.71 (d, J = 7.5, 2H), 7.53 – 7.35 (m, 6H), 3.96 (s, 2H), 2.58 (s, 3H), 1.74 (s, 9H); 13C NMR (63 MHz CDCl3) δ: 182.5 (C), 143.4 (2×C), 139.0 (2×C), 128.7 (2×CH), 127.4 (2×CH), 119.3 (2×CH), 70.9 (C), 55.8 (C), 55.5 (CH2), 29.2 (CH3), 27.0 (3×CH3); IR (neat) 1471, 1446, 1418, 1309; HRMS (EI, 70 eV) calculated for C20H22N2S (M+) 322.1504, found 322.1493.

Imidazolidine-2-thione 8g: According to general procedure VI, the reaction between 2-imidazolinium iodide 6g (90 mg, 0.20 mmol), KOtBu (25 mg, 0.22 mmol) and S8 (53 mg, 0.20 mmol) to afford imidazolidine-2-thione 8g as a white foam (66 mg, 0.15 mmol, 76%). 1H NMR (250 MHz CDCl3) δ: 7.55 (d, J = 7.6, 2H), 7.32 – 7.26 (m, 2H), 7.18 (d, J = 7.4, 2H), 7.09 – 7.06 (m, 2H), 6.33 (s, 2H), 4.78 (s, 2H), 3.77 (s, 2H), 2.06 (s, 3H), 1.83 (s, 6H), 1.74 (s, 9H); 13C NMR (63 MHz CDCl3) δ: 184.2 (C), 143.9 (2×C), 139.5 (2×C), 137.5 (2×C), 135.9 (C), 130.4 (C), 128.9 (2×CH), 128.3 (2×CH), 127.6 (2×CH), 123.8 (2×CH), 119.7 (2×CH), 71.9 (C), 57.1 (CH), 57.0 (C), 43.6 (CH3), 28.0 (3×CH3), 20.5 (CH3), 19.7 (2×CH2); IR (KBr) 1450, 1402, 1362, 1308, 1213; HRMS (EI, 70 eV) calculated for C29H32N2S (M+) 440.2286, found 440.2265.

Imidazolidine-2-thione 8h: According to general procedure VI, the reaction between 2-imidazolinium bromide 6h (553 mg, 1.0 mmol), KOtBu (118 mg, 1.05 mmol), and S8 (256 mg, 1.0 mmol to afford imidazolidine-2-thione 8h as a white foam (449 mg, 0.89 mmol, 89%). 1H NMR (250 MHz CDCl3) δ: 7.67 (d, J = 7.5, 1H), 7.59 (d, J = 7.5, 1H), 7.48 – 7.36 (m, 4H), 7.29 – 7.13 (m, 2H), 7.07 – 6.87 (m, 8H), 6.76 (d, J = 7.6, 1H), 6.00 (d, J = 15.3, 1H), 4.98 (d, J = 15.1, 1H), 4.48 (d, J = 15.3, 1H), 3.97 (d, J = 4.6, 1H), 3.86 (s, 3H), 3.70 (d, J = 15.1, 1H), 2.06 – 1.98 (m, 1H), 0.57 (d, J = 7.1, 3H), 0.47 (d, J = 7.0, 3H); 13C NMR (63 MHz CDCl3) δ: 186.6 (C), 159.0 (C), 144.9 (C), 141.5 (C), 141.0 (C), 140.3 (C), 138.6 (C), 129.7 (CH), 129.4 (2×CH), 129.2 (CH), 128.3 (C), 128.0 (2×CH), 127.6 (3×CH), 127.5 (CH), 127.2 (CH), 126.6 (CH), 124.9 (CH), 120.0 (CH), 119.8 (CH), 114.0 (2×CH), 76.5 (C), 70.3 (CH), 55.3 (CH2), 50.4 (CH3), 48.3 (CH3), 28.2 (CH), 19.3 (CH3), 18.5 (CH3); IR (KBr) 161, 1512, 1441, 1248; HRMS (EI, 70 eV) calculated for C33H32N2OS (M+) 504.2235, found 504.2229; Elemental analysis: calculated for C33H32N2OS (%): C 78.53, H 6.39, N 5.55, S 6.35, found C 77.37, H 6.88, N 5.22, S 6.47.
Imidazolidine-2-thione 8i: According to general procedure VI the reaction between 2-imidazolinium iodide 6i (60 mg, 0.1 mmol), KOTBu (15 mg, 0.12 mmol) and S8 (5 mg, 0.12 mmol) to afford 8i (50 mg, 0.1 mmol, 100%). 1H NMR (500 MHz, CDCl3): δ 7.32-7.20 (br. m, 10H); 7.13 (d, J = 8.0 Hz, 2H); 6.91 (d, J = 8.0 Hz, 2H); 5.80 (d, J = 3.2 Hz, 1H); 5.80 (d, J = 16.4 Hz, 1H); 5.00 (d, J = 3.2 Hz, 1H); 4.03 (d, J = 16.4 Hz, 1H); 3.26 (s, 3H); 2.30 (s, 3H); 1.87 (s, 3H). 13C NMR (500 MHz, CDCl3): δ 184.4 (C); 169.5 (C); 152.8 (C); 144.1 (C); 137.7 (C); 137.3 (C); 137.0 (C); 133.9 (C); 129.5 (CH); 128.4 (CH); 128.2 (CH); 128.0 (CH); 127.1 (CH); 127.1 (CH); 126.6 (CH); 126.3 (CH); 112.7 (CH); 105.8 (CH); 66.9 (CH3); 60.4 (C); 51.0 (CH3); 50.3 (CH2); 13.1 (CH3). HRMS (ESI): Calculated for C30H29N2O3S+ (M+H+) 497.1893, found 497.1872.

Imidazolidine-2-thione 8j: According to general procedure IV the reaction between 2-imidazolinium iodide 6j (50 mg, 0.1 mmol), KOTBu (15 mg, 0.12 mmol) and S8 (5 mg, 0.12 mmol) to afford 8j as a 3:1 mixture of diastereomers (32 mg, 0.076 mmol, 76%). Major product: 1H NMR (500 MHz, CDCl3): δ 7.25-7.21 (m, 5H); 7.12 (d, J = 8.0 Hz, 2H); 7.02 (d, J = 8.0 Hz, 2H); 6.01 (s, 1H); 5.85 (d, J = 3.2 Hz, 1H); 5.22 (d, J = 3.2 Hz, 1H); 3.93 (s, 3H); 3.11 (s, 3H); 2.39 (s, 3H); 1.83 (s, 3H). 13C NMR (125 MHz, CDCl3): δ 183.1 (C); 170.7 (C); 152.6 (C); 145.2 (C) 137.2 (C); 137.0 (C); 133.9 (C); 129.5 (CH); 128.4 (CH); 128.2 (CH); 128.0 (CH); 127.1 (CH); 127.1 (CH); 111.9 (CH); 105.9 (CH); 77.8 (C); 67.2 (CH); 53.3 (CH3); 34.3 (CH3); 21.1 (CH3) 13.2 (CH3). HRMS (ESI): Calculated for C24H25N2O3S+ (M+H+) 421.1580 (M+H+) found: 421.1555.

2.6 References