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RING CLOSING METATHESIS REACTIONS OF IMIDAZOLE DERIVATIVES[1]

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Abstract – A series of diene substituted imidazole derivatives has been prepared from the corresponding haloimidazoles via halogen-magnesium exchange and electrophile quench. These derivatives were explored as susbstrates in a ring closing metathesis reaction, which was successful if the imidazolium ion was used. In addition, one successful example of a ring closing metathesis reaction of an enyne derivative was performed, with the resulting diene successfully engaging in a Diels-Alder reaction.

INTRODUCTION

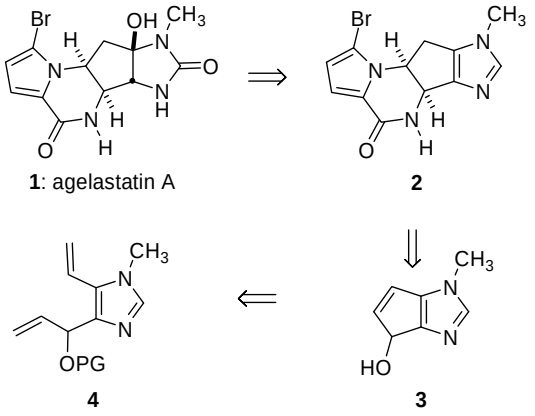


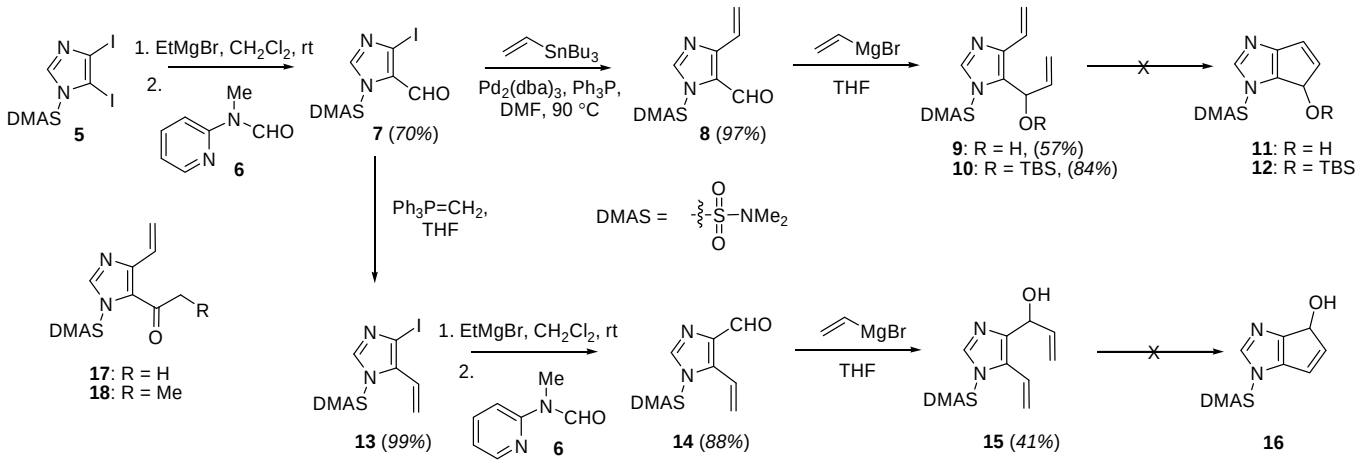
Figure 1: Retrosynthetic analysis of agelstatin A

Our group has been interested for some time in the development of new synthetic methods for the elaboration of a simple imidazoles into more complex derivatives, with the long term goal of applying this chemistry to the total synthesis of a variety of the imidazole-containing natural products.[1] Among these targets, we were interested in developing an approach to the agelastatin family of marine alkaloids, several of which have been shown to possess anti-cancer activity (e.g., agelastatin A (**1**), Figure 1).[2,3] Several strategies and total syntheses of these molecules have been reported,[4-7] including a number involving a ring-closing metathesis (RCM) reaction as a key step.[8-10] One approach we have taken towards a total synthesis of this target is depicted retrosynthetically above (Figure 1) involves the intermediacy of a cyclopentyl imidazole moiety **3**, which we planned on constructing via RCM on the dienyl imidazole.[11] When we initiated this project, no examples existed of the participation of imidazole derivatives in RCM reactions,[12,13] although after our

[1] This manuscript is dedicated to Ekkehard Winterfeldt on the occasion of his 75th birthday.

preliminary report,[14] several additional publications on this topic appeared in the literature.[15-17] The precursors required for evaluation in the RCM reaction could be obtained via sequential metallation and electrophilic trapping based on chemistry developed by Knochel and others.[18,19]

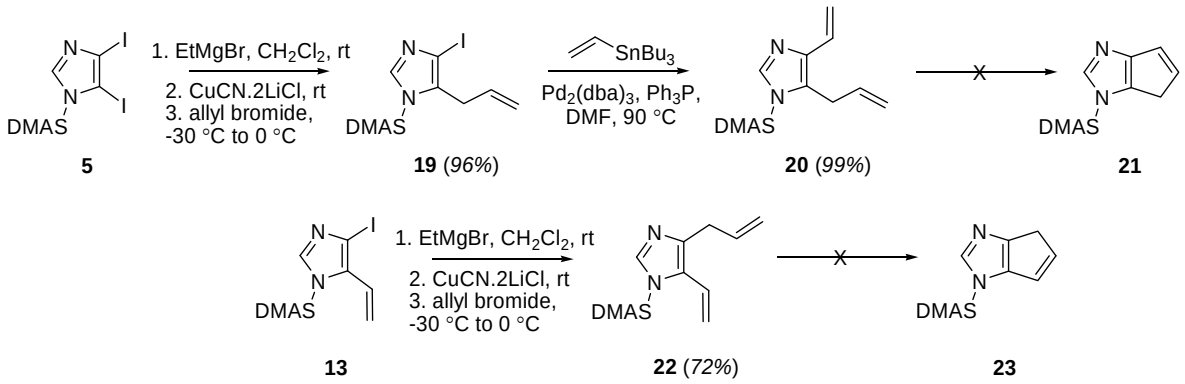
RESULTS AND DISCUSSION



Scheme 1

Our studies commenced with the preparation of the necessary RCM substrate from the diiodoimidazole derivative **5** (Scheme 1).[19] Compound **5** undergoes iodine-magnesium exchange on treatment with EtMgBr which on treatment with *N*-methyl-*N*-formyl pyridine **6** led to the formation of aldehyde **7**.[19,20] Aldehyde **7** was subjected to a Stille reaction with vinyl tributylstannane providing **8**,[21] which in turn can be condensed with vinylmagnesium bromide forming **9**. Unfortunately, when this substrate was subjected to RCM with either the first or second generation Grubbs' catalysts under a variety of conditions, and catalyst loadings (up to 50 mol%) no metathesis was observed. Small amounts of ketones **17** and **18**, resulting from fragmentation or rearrangement of the allylic alcohol were observed,[22,23] but no ring-closing metathesis was observed. In order to circumvent this issue, the hydroxyl moiety was protected as the silyl ether **10**, but unfortunately, this substrate also failed to undergo productive metathesis. Our initial interpretation of this result was that steric interactions between the silyl protecting group and the DMAS-moiety prevented the attainment of a productive conformation, and therefore we investigated the isomeric substrate which may not suffer from such limitations. Preparation of the isomeric substrate was accomplished from **7** by Wittig olefination, metallation (I→MgX) and trapping with **6** provided the aldehyde **14**. Reaction of **14** of vinylmagnesium bromide provided the corresponding allylic alcohol **15**, which unfortunately failed to undergo RCM on treatment with the Grubbs' first generation catalyst either alone or with additives. It is well-known with amino-containing substrates that rates of metathesis can be slow due to the coordination of the amine to

ruthenium, however, this can be circumvented by protonation of the amino moiety prior to metathesis.[24] Unfortunately, conversion of any of the substrates (**9**-**10** and **15**) to the imidazolium salt by pre-treatment with *p*-TsOH before addition of either of the first two generations of metathesis catalysts did not lead to any improvement.[24] We also prepared the corresponding substrates which lacked the hydroxyl group **20** and **22**, and subjected these to the metathesis reaction, but again these experiments were unsuccessful (Scheme 2).

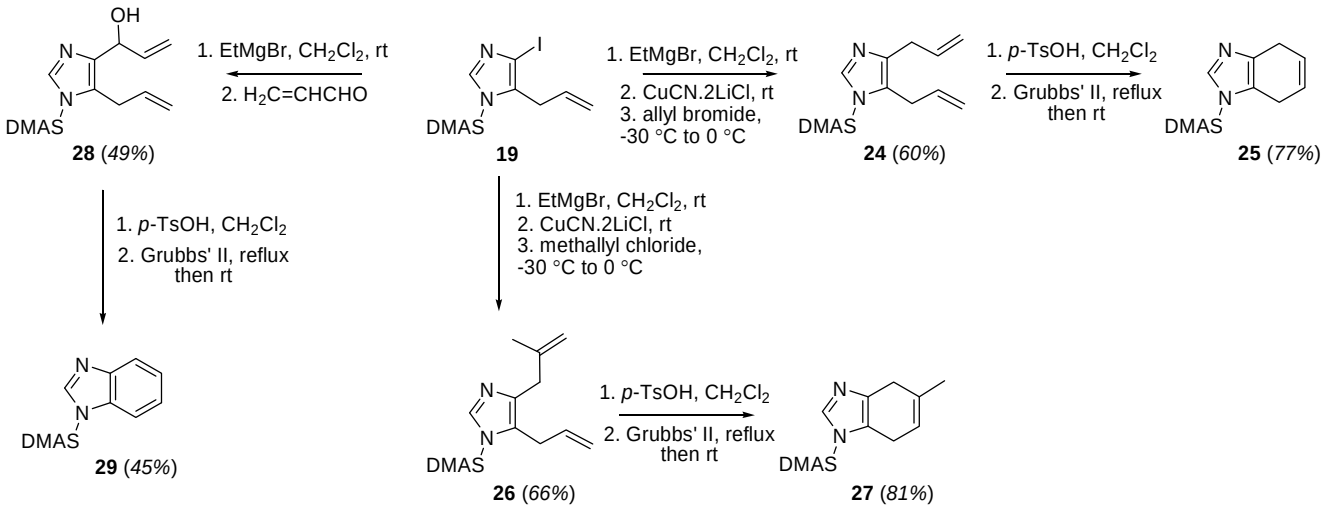


Scheme 2

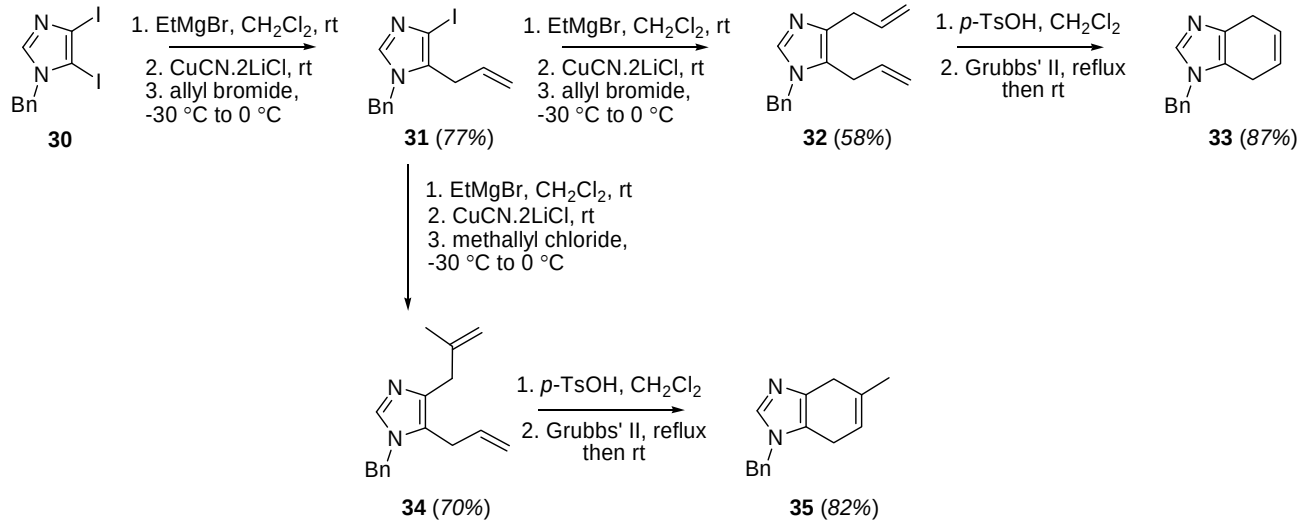
The fact that we saw some reaction, albeit not through the required metathesis manifold, suggested that it might be possible to effect RCM provided that the appropriate substrates could be identified. It occurred to us that there were electronic constraints that were preventing this cyclization from occurring, therefore, with this in mind, we decided to investigate the corresponding 4,5-diallyl substrate **24** in which neither olefin was conjugated with the imidazole. This substrate can be readily constructed from **19** by metallation and treatment with allyl bromide in good yield. When **24** was treated with Grubbs' I catalyst no metathesis was observed, however, when it was reacted with Grubbs' II catalyst a reaction occurred leading to the formation of the expected product **25** in 21% yield. We were highly encouraged by this result and sought to optimize the reaction, this was readily achieved by conversion of the imidazolium salt by pre-treatment of **24** with *p*-TsOH and then introduction of the metathesis catalyst.[24] Under these conditions the RCM reaction proceeded in an excellent 77% yield. Similarly, the related methyl substituted substrate **26**, which was prepared in an analogous fashion to **24**, undergoes productive metathesis in 81% yield after protonation. In an attempt to prepare more functionalized derivatives, allylic alcohol was synthesized and subjected to the RCM reaction. Rather than the expected dihydrobenzimidazole derivative, the dehydrated derivative **29** was obtained in moderate yield.[25-27]

Given that successful metathesis was observed with substrates containing an electron-withdrawing *N*-protecting group, we wondered whether a more electron-donating substituent would be tolerated, and

therefore the corresponding *N*-benzyl derivatives were constructed in an analogous fashion to **24** and **26** from **5** and evaluated. Gratifyingly, after protonation with *p*-TsOH, both the diallyl **32**, and the related methallyl **34** substrate underwent RCM smoothly providing the anticipated dihydrobenzimidazoles **33** and **35** in good yield.

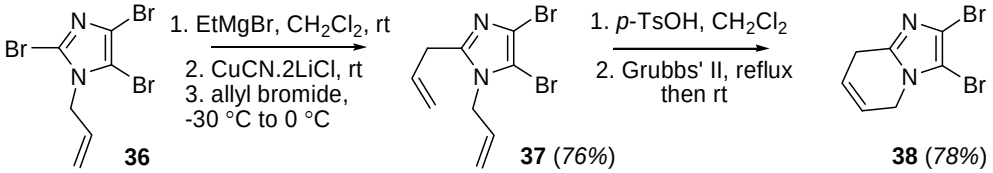


Scheme 3



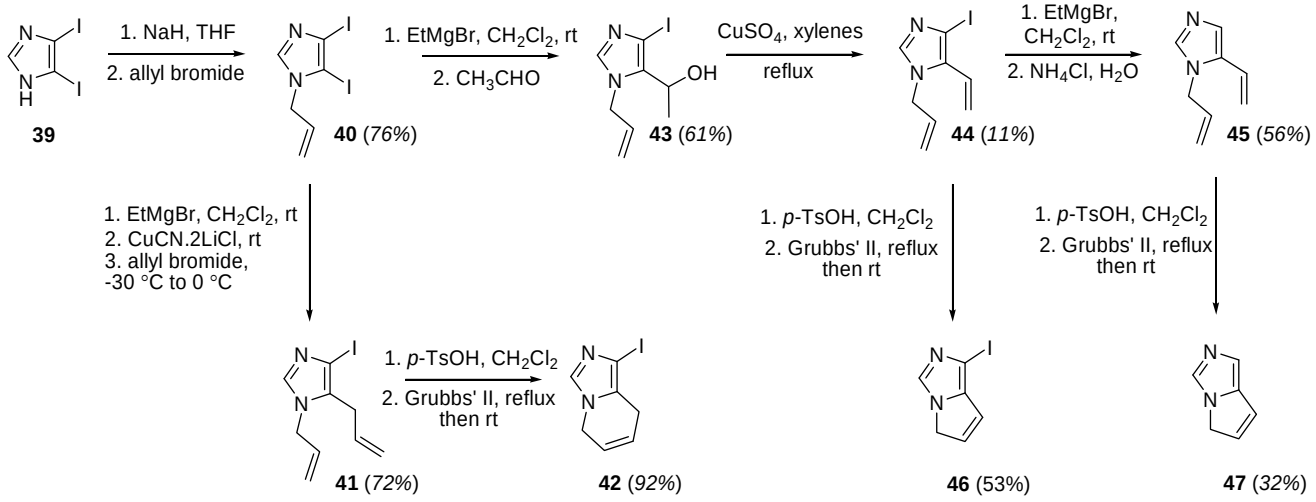
Scheme 4

The success of these experiments with **32** and **34** provided the impetus to investigate substrates which possessed *N*-allyl substitutuents which can be readily prepared from the appropriate haloimidazoles. The known *N*-allyl tribromoimidazole[27] **36** was metallated and then coupled with allyl bromide to give the RCM substrate **37**. Smooth metathesis occurred on exposure to *p*-TsOH and then Grubbs' II catalyst provided **38**.



Scheme 5

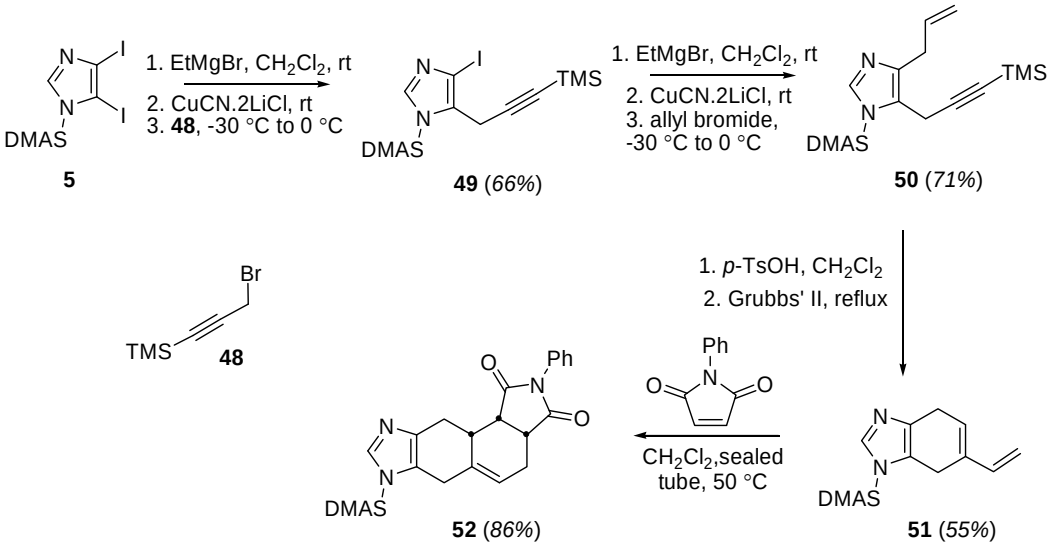
We have also investigated isomeric substrates in which the one of the olefins is at the imidazole 5-position. The first substrate **40** was obtained by allylation of 4,5-diiodoimidazole **39**,[28] which was then converted into the diallyl substrate **41** by metallation and coupling with allyl bromide. Subjection of **41** to RCM led to the efficient formation of the imidazopyridine derivative **42** in 92% yield. Given the success of this cyclization, we decided to investigate the cyclization of the allyl vinyl substrate **44**. These derivatives were a little more difficult to prepare, however, these were obtained in very low yield by metallation and trapping with acetaldehyde providing **43**, and then subjecting the alcohol to elimination. Interestingly, this substrate, when treated with *p*-TsOH, and then Grubbs' II catalyst led to a productive RCM reaction, forming 46, which is in contrast to the related 4,5-substrates. Initially, we had suspected that electronic effects might be responsible for the observed failure, but the successful cyclization of **44** suggested that the root of this problem was more complex. It was also found if the iodo moiety was removed by metallation and quenching with water, and then this substrate **45** was subjected to RCM that cyclization occurred, although providing the product **47** in lower yield.[29]



Scheme 6

We have constructed and evaluated one enyne containing substrate **50** in the RCM reaction through a largely similar sequence of chemistry. The diiodoimidazole was converted first into the propargyl derivative **49** by sequential treatment with EtMgBr, CuCN.2LiCl and then the propargyl bromide.

Repetition of this sequence, but using allyl bromide provided the RCM substrate **50**. Gratifyingly, it was found that treatment of **50** with Grubbs' II catalyst, after pretreatment with *p*-TsOH, provided the desired diene **51** in 55% yield. As anticipated this diene engaged in a smooth Diels-Alder reaction on treatment with N-phenylmaleimide, providing the corresponding cycloadduct **52** in good yield.



Scheme 7

In summary, we have found that appropriately substituted imidazoles do undergo RCM in moderate to excellent yield provided that the substrate is converted to the imidazolium salt prior to introduction of the Grubbs' second generation catalyst. While this approach was ultimately unsuccessful for application towards the total synthesis of the agelastatin family of marine natural products, it provides a convenient method for the preparation of fused bicyclic imidazoles. One example of enyne RCM is reported, providing substrates that have potential utility in the Diels-Alder reaction, an area that we are actively investigating.

EXPERIMENTAL

All chemicals were purchased from commercial vendors and were used as received unless stated otherwise. All reactions were conducted under an atmosphere of dry nitrogen in oven-dried glassware. Solvents were dried using a Pure-Solv 400 solvent purification system (Innovative Technology, Inc.), except for DMF, which was dried over CaH_2 and then distilled. The ^1H NMR spectra were acquired at 500 MHz in $CDCl_3$, unless indicated otherwise, using residual $CHCl_3$ as reference. ^{13}C NMR spectra were obtained at 125 MHz in $CDCl_3$, unless otherwise indicated, using solvent as internal standard. Low resolution mass spectra were obtained in-house by electron impact (MS-EI), high resolution mass spectra were obtained at the University of Florida by electrospray ionization (HRMS-ESI).

1-Dimethylsulfamoyl-4-iodo-1*H*-imidazole-5-carboxaldehyde (7): A 3.0 M solution of EtMgBr in Et_2O (2.2 mL, 6.6 mmol) was added to a solution of the diiodo compound **5**[19] (2.50 g, 5.85 mmol) in dry CH_2Cl_2 (25 mL). The resulting solution was stirred at rt for 30 min and then *N*-methyl-*N*-2-pyridylformamide (**6**) (0.77 mL, 6.44 mmol) was added. After stirring at rt for a further 2 h the mixture was diluted with CH_2Cl_2 and poured into half saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried by anhydrous $MgSO_4$ and triturated with Et_2O, the Et_2O was filtered off and the remaining solid was separated by flash chromatography (EtOAc/hexane, 1:1) to furnish **7** (1.35 g, 70%) as a yellow solid: mp 109.0-109.5 °C; ^{1}H NMR: δ = 3.01 (s, 6H), 8.09 (s, 1H), 9.80 (s, 1H); ^{13}C NMR: δ = 38.7, 102.0, 129.1, 145.1, 178.9; IR (KBr, cm^{-1}): 3116, 2898, 1744, 1671, 1390, 1171; EIMS (*m/z*): 65, 108 (100%), 222, 250, 301, 329 (M^+), 330 ($M^+ + 1$); Anal. Calcd for $C_6H_8IN_3O_3S$: C, 21.90; H, 2.45; N, 12.77. Found: C, 22.05; H, 2.45; N, 12.34.

1-Dimethylsulfamoyl-4-vinyl-1*H*-imidazole-5-carboxaldehyde (8): The aldehyde **7** (1.00 g, 3.04 mmol) was combined with $Pd_2(dba)_3$ (87.5 mg, 0.096 mmol) and PPh_3 (100 mg, 0.38 mmol) and vinyl tributyltin (1.7 mL, 6.1 mmol) in DMF (16 mL) under Ar protection. The mixture was heated at 85-90 °C for 19 h and cooled to rt and then filtered through Celite. The filtrate was diluted with EtOAc, washed with H_2O several times. The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford oily product **8** (672 mg, 97%) which polymerizes on extended standing at rt, therefore it was used directly for the next step. ^{1}H NMR: δ = 2.94 (s, 6H), 5.65 (dd, 1H, *J* = 1.8, 11.0 Hz), 6.39 (dd, 1H, *J* = 1.8, 17.2 Hz), 7.22 (dd, 1H, *J* = 11.0, 17.2 Hz), 8.00 (s, 1H), 10.17 (s, 1H); ^{13}C NMR: δ = 38.3, 123.0, 125.3, 126.4, 142.3, 150.1, 179.6; IR ($CHCl_3$, cm^{-1}): 2924, 1676, 1514, 1391, 1169; EIMS (*m/z*): 65 (100%), 97, 108, 123, 187, 204, 229 (M^+), 230 ($M^+ + 1$); Anal. Calcd for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 41.96; H, 5.10; N, 18.07.

1-(1-Dimethylsulfamoyl-4-vinyl-1*H*-imidazol-5-yl)prop-2-en-1-ol (9): The aldehyde **8** (108 mg, 0.470 mmol) was dissolved in dry THF (3 mL). The mixture was cooled to 0 °C and vinylmagnesium bromide (0.71 mL, 0.71 mmol, 1.0 M in THF) was added dropwise. The whole mixture was allowed to warm to rt and stirred for 2 h. Saturated aqueous NH_4Cl solution was added to the mixture and it was extracted with EtOAc. The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 2:3) to furnish **9** (68 mg, 56%) as colorless solid: mp 101.5-102.0 °C. ^{1}H NMR: δ = 2.91 (s, 6H), 5.27 (dd, 1H, *J* = 1.8, 11.0 Hz), 5.28 (d, 1H, *J* = 10.6 Hz), 5.37 (d, 1H, *J* = 17.2 Hz), 5.71 (m, 1H), 6.00 (dd, 1H, *J* = 1.8, 17.2 Hz), 6.11 (ddd, 1H, *J* = 4.8, 10.6, 17.2 Hz), 6.82 (dd, 1H, *J* = 11.0, 17.2 Hz), 7.84 (s, 1H); ^{13}C NMR: δ = 38.2, 65.3, 116.1,

116.3, 126.8, 127.8, 137.7, 138.5, 140.1; IR (KBr, cm^{-1}): 3222, 2930, 1866, 1704, 1645, 1541, 1384; EIMS (*m/z*): 65 (100%), 108, 133, 161, 244, 258 (M^+); Anal. Calcd for $C_{10}H_{15}N_3O_3S$: C, 46.68; H, 5.88; N, 16.33. Found: C, 46.82; H, 6.23; N, 16.06.

5-[1-(*tert*-Butyldimethylsilyloxy)-2-propenyl]-1-dimethylsulfamoyl-4-vinyl-1*H*-imidazole (10): Alcohol **9** (300 mg, 1.17 mmol) was combined with TBSCl (211 mg, 1.40 mmol) and imidazole (190 mg, 2.80 mmol) in DMF (4 mL) and The mixture was stirred at rt for 3 h and then diluted with 5% aqueous $NaHCO_3$ (3 mL) and extracted with Et_2O four times. The organic layer was combined and dried with anhydrous $MgSO_4$ and condensed by vacuum. The remaining mixture was purified by flash chromatography (EtOAc/hexane, 2:3) to afford **10** (365 mg, 84%) as colorless solid: mp 53.2-54.0 °C; ^1H NMR: δ = -0.05 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 2.87 (s, 6H), 5.13 (d, 1H, *J* = 10.2 Hz), 5.22 (dd, 1H, *J* = 1.8, 10.2 Hz), 5.25 (d, 1H, *J* = 17.2 Hz), 5.72 (d, 1H, *J* = 4.8 Hz), 5.96 (m, 1H), 5.97 (dd, 1H, *J* = 1.8, 17.2 Hz), 6.93 (dd, 1H, *J* = 11.0, 17.2 Hz), 7.82 (s, 1H); ^{13}C NMR: δ = -5.1, -4.9, 18.3, 25.8, 38.1, 66.7, 114.7, 114.9, 127.9, 128.5, 137.6, 138.6, 140.4; IR (KBr, cm^{-1}): 3112, 2932, 2858, 1393, 1256; EIMS (*m/z*): 65, 75, 115, 133 (100%), 153, 240, 314, 356, 372 (M^+); Anal. Calcd for $C_{16}H_{29}N_3O_3SSi$: C, 51.72; H, 7.87; N, 11.31. Found: C, 51.54; H, 7.84; N, 11.17.

1-Dimethylsulfamoyl-4-iodo-5-vinyl-1*H*-imidazole (13): $BrPPh_3CH_3$ (3.12 g, 8.73 mmol) was dissolved in THF (17 mL) under Ar in a 250 mL round bottom flask containing a magnetic stir bar. KHDMS (1.97 g, 9.90 mmol) was dissolved in THF (45 mL) in a second flask and then transferred by cannula into the flask containing the phosphonium salt. The resulting mixture was stirred for 1 h, then aldehyde **7** (1.80 g, 5.47 mmol), dissolved in THF (30 mL), was added to the ylide solution. The mixture was stirred for 1 hour at rt then aqueous NH_4Cl (500 mL) was added to the reaction mixture and the aqueous phase was extracted with EtOAc several times. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to yield product **13** (1.65 g, 92%) as colorless solid: mp 70.0-71.0 °C; ^1H NMR: δ = 2.86 (s, 6H), 5.60 (d, 1H, *J* = 11.7 Hz), 6.10 (d, 1H, *J* = 18.0 Hz), 6.78 (dd, 1H, *J* = 11.7, 18.0 Hz), 7.86 (s, 1H); ^{13}C NMR: δ = 38.4, 86.6, 122.2, 123.1, 130.4, 139.7; IR (KBr, cm^{-1}): 3130, 3012, 1673, 1625, 1455, 1392, 1272, 1145; EIMS (*m/z*): 65, 95, 108, 129, 142, 202, 221, 285, 328 (M^+ + 1, 100%); Anal. Calcd for $C_7H_{10}IN_3O_2S$: C, 25.70; H, 3.08; N, 12.84. Found: C, 25.64; H, 3.12; N, 12.53.

1-Dimethylsulfamoyl-5-vinyl-1*H*-imidazole-4-carboxaldehyde (14): A 3.0 M solution of EtMgBr in Et_2O (1.2 mL, 3.7 mmol) was added to a solution of **13** (1.00 g, 3.06 mmol) in dry CH_2Cl_2 (13 mL). The resulting solution was stirred at rt for 30 min and then *N*-methyl-*N*-2-pyridylformamide (0.49 mL, 4.10

mmol) was added. After stirring at rt for a further 2 h the mixture was diluted with CH_2Cl_2 and poured into half saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 4:1) to yield product **14** (613 mg, 88%) as colorless solid: mp 114.0-115.0 °C; ^{1}H NMR: δ = 2.91 (s, 6H), 5.86 (d, 1H, *J* = 11.4 Hz), 6.20 (d, 1H, *J* = 17.6 Hz), 6.98 (dd, 1H, *J* = 11.4, 17.6 Hz), 7.97 (s, 1H), 9.93 (s, 1H); ^{13}C NMR: δ = 38.4, 121.93, 126.9, 137.1, 138.8, 139.1, 185.0; IR (KBr, cm^{-1}): 3355, 3127, 3090, 2959, 2844, 2756, 1679, 1487, 1190; EIMS (*m/z*): 65 (100%), 97, 108, 123, 204, 230 (M^+ + 1); Anal. Calcd for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 42.02; H, 5.01; N, 18.05.

1-(1-Dimethylsulfamoyl-5-vinyl-1*H*-imidazol-4-yl)prop-2-en-1-ol (15): Aldehyde **14** (156 mg, 0.680 mmol) was dissolved in dry THF (5 mL). The mixture was cooled to 0 °C and vinylmagnesium bromide (0.56 mL, 1.2 M in THF) was added dropwise. The mixture was allowed to warm to rt and stirred for 2 h. Saturated aqueous NH_4Cl solution was added to the mixture and it was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was separated by flash chromatography (EtOAc) to furnish **15** (73 mg, 41%) as yellow oil: ^{1}H NMR: δ = 2.79 (s, 6H), 4.00 (br s, 1H), 5.11 (d, 1H, *J* = 5.9 Hz), 5.15 (d, 1H, *J* = 10.6 Hz), 5.21 (d, 1H, *J* = 17.2 Hz), 5.50 (dd, 1H, *J* = 1.1, 11.4 Hz), 5.53 (dd, 1H, *J* = 1.1, 17.2 Hz), 6.14 (ddd, 1H, *J* = 5.9, 10.3, 17.2 Hz), 6.78 (dd, 1H, *J* = 11.4, 17.2 Hz), 7.84 (s, 1H); ^{13}C NMR: δ = 38.3, 68.0, 115.8, 121.7, 123.6, 126.8, 137.9, 139.0, 142.2; IR (KBr, cm^{-1}): 3339, 1474, 1391, 1159; EIMS (*m/z*): 59, 84 (100%), 133, 216, 240, 258 (M^+ + 1); Anal. Calcd for $C_{10}H_{15}N_3O_3S$: C, 46.68; H, 5.88; N, 16.33. Found: C, 46.65; H, 6.27; N, 16.16.

5-Allyl-1-dimethylsulfamoyl-4-iodo-1*H*-imidazole (19): A 3.0 M solution of EtMgBr in Et_2O (4.3 mL, 12.9 mmol) was added to a solution of the diiodo compound **5** (5.00 g, 11.7 mmol) in dry CH_2Cl_2 (50 mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl (prepared by dissolving 1 equivalent CuCN and 2 equivalent LiCl (which was vacuum dried at 110 °C for 1 hour) in THF)[19] in dry THF (11.7 mL, 11.7 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (1.1 mL, 12.0 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h the reaction solution was partitioned with half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (50 mL). The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/Hexane, 1:1) to yield the 5-allylimidazole **19** (3.84 g, 96%) as yellow solid: mp 54.5-55.0 °C; ^{1}H NMR: δ = 2.88 (s, 6H), 3.53 (ddd, 2H, *J* = 1.5, 1.5, 5.5 Hz),

5.01 (dd, 1H, *J* = 1.5, 17.2 Hz), 5.11 (dd, 1H, *J* = 1.5, 10.3 Hz), 5.83 (ddt, 1H, *J* = 5.5, 10.3, 17.2 Hz), 7.85 (s, 1H); ^{13}C NMR: δ = 29.3, 38.2, 89.3, 117.1, 131.0, 132.9, 139.3; IR (KBr, cm^{-1}): 3128, 3085, 3012, 2981, 1639, 1461, 1391, 1157; EIMS (*m/z*): 108, 147, 233, 255, 302, 341 (M^+), 342 (M^+ + 1, 100%); Anal. Calcd for $C_8H_{12}IN_3O_2S$: C, 28.16; H, 3.55; N, 12.32. Found: C, 28.29; H, 3.94; N, 11.95.

5-Allyl-1-dimethylsulfamoyl-4-vinyl-1*H*-imidazole (20): Iodide **19** (205 mg, 0.599 mmol) was combined with $Pd_2(dba)_3$ (17.3 mg, 0.019 mmol) and PPh_3 (19.7 mg, 0.075 mmol) and vinyltributyltin (0.34 mL, 1.2 mmol) in DMF (3.5 mL) under Ar protection. The mixture was heated at 85-90 °C for 19 h, then cooled to rt and filtered through Celite. The filtrate was diluted with EtOAc, washed with H_2O several times. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane, 1:1) to afford an oily product **20** (144 mg, 99%) which turned into a yellow solid on storage in the refrigerate: mp 41.5-42.0 °C; ^{1}H NMR: δ = 2.87 (s, 6H), 3.60 (d, 2H, *J* = 5.5 Hz), 4.96 (d, 1H, *J* = 16.9 Hz), 5.09 (d, 1H, *J* = 9.9 Hz), 5.27 (dd, 1H, *J* = 1.5, 11.0 Hz), 5.88 (ddt, 1H, *J* = 5.5, 9.9, 16.9 Hz), 5.97 (dd, 1H, *J* =1.5, 17.2 Hz), 6.52 (dd, 1H, *J* = 11.0, 17.2 Hz), 7.88 (s, 1H); ^{13}C NMR: δ = 27.2, 38.0, 115.1, 116.5, 125.3, 126.1, 134.2, 138.1, 139.5; IR (KBr, cm^{-1}): 3128, 2977, 1639, 1488, 1390, 1180; EIMS (*m/z*): 108, 133 (100%), 226, 241 (M^+), 242 (M^+ + 1); Anal. Calcd for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.70; H, 5.87; N, 17.85.

4-Allyl-1-dimethylsulfamoyl-5-vinyl-1*H*-imidazole (22): A 3.0 M solution of EtMgBr in Et_2O (1.2 mL, 3.6 mmol) was added dropwise to a solution of compound **13** (1.05 g, 3.21 mmol) in dry CH_2Cl_2 (14 mL) at rt The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (3.2 mL, 3.2 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (0.3 mL, 3.5 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (10 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield **22** (561 mg, 72%) as colorless liquid: ^{1}H NMR: δ = 2.74 (s, 6H), 3.31 (ddd, 2H, *J* = 1.5, 1.8, 5.9 Hz), 4.95 (ddt, 1H, *J* = 1.5, 1.8, 17.2 Hz), 5.01 (ddt, 1H, *J* = 1.5, 1.5, 10.3 Hz), 5.39 (dd, 1H, *J* = 1.5, 11.4 Hz), 5.40 (dd, 1H, *J* = 1.5, 17.6 Hz), 5.91 (ddt, 1H, *J* = 5.9, 10.3, 17.2 Hz), 6.76 (dd, 1H, *J* = 11.4, 17.6 Hz), 7.77 (s, 1H); ^{13}C NMR: δ = 32.6, 38.2, 116.2, 119.5, 124.1, 126.1, 135.4, 137.5, 140.2; IR ($CHCl_3$, cm^{-1}): 2978, 1638, 1470, 1390, 1178, 1153; EIMS (*m/z*): 108, 133, 242 (M^+, 100%); Anal. Calcd for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.70; H, 6.60; N, 17.84.

4,5-Diallyl-1-dimethylsulfamoyl-1*H*-imidazole (24): A 3.0 M solution of EtMgBr in Et_2O (0.24 mL, 0.73 mmol) was added to a solution of compound **19** (227 mg, 0.67 mmol) in dry CH_2Cl_2 (2.5 mL) at rt The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl (prepared by dissolving 1 equivalent CuCN and 2 equivalents LiCl (which was vacuum dried at 110 °C for 1 h) in THF)[19] in dry THF (0.67 mL, 0.67 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (0.15 mL, 1.74 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h, half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (5 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield compound **24** (100 mg, 60%) as colorless liquid: ^{1}H NMR: δ = 2.84 (s, 6H), 3.23 (ddd, 2H, *J* = 1.5, 1.8, 6.6 Hz), 3.51 (ddd, 2H, *J* = 1.5, 1.8, 5.9 Hz), 4.92 (ddt, 1H, *J* = 1.5, 1.8, 17.2 Hz), 4.99 (ddt, 2H, *J* = 1.5, 1.8, 9.9 Hz), 5.01 (ddt, 1H, *J* = 1.5, 1.8, 16.9 Hz), 5.90 (m, 2H), 7.83 (s, 1H); ^{13}C NMR: δ = 27.3, 31.8, 38.0, 116.1, 116.2, 124.3, 134.5, 135.2, 137.4, 139.9; IR ($CHCl_3$, cm^{-1}): 3130, 3081, 2979, 2920, 1640, 1477, 1393; EIMS (*m/z*): 108, 147, 255 (M^+), 256 (M^+ + 1, 100%); Anal. Calcd for $C_{11}H_{17}N_3O_2S$: C, 51.74; H, 6.71; N, 16.46. Found: C, 51.66; H, 6.78; N, 16.56.

General procedure for the RCM reactions with *p*-TsOH using second generation Grubbs' catalyst: The metathesis substrate (1 equivalent) and *p*-TsOH (1.1 equivalent) were dissolved in CH_2Cl_2 to prepare a 0.1 M solution under Ar protection. The mixture was heated at reflux for 30 min. Then the second generation Grubbs' catalyst (5 mol%) was added to the reaction mixture in solid form. The mixture was refluxed for 20 min, then either refluxed for an additional period or stirred at rt for an additional period until reaction finished as indicated by TLC and NMR of the crude reaction mixture. After the reaction finished, the solvent was concentrated and aqueous $NaHCO_3$ solution was added to the residue, some K_2CO_3 solid was also added until the solution was basic. The solution was extracted with CH_2Cl_2 several times and the combined organic phase was dried over $MgSO_4$ and concentrated. Flash chromatography afforded pure product.

4,7-Dihydro-1-dimethylsulfamoyl-1*H*-benzimidazole (25): Compound **25** was synthesized from compound **24** (200 mg, 0.784 mmol) in 77% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt overnight and worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 1:1) afforded product **25** (137 mg, 77%) as colorless

solid: mp 115.0-116.0 °C; ^{1}H NMR: δ = 2.87 (s, 6H), 3.30 (m, 2H), 3.43 (m, 2H), 5.81 (m, 1H), 5.88 (m, 1H), 7.84 (s, 1H); ^{13}C NMR: δ = 24.7, 26.4, 38.2, 122.4, 122.9, 124.6, 136.2, 136.5; IR (KBr, cm^{-1}): 3128, 3041, 2890, 2849, 1655, 1602, 1476, 1380, 1181, 1152; EIMS (*m/z*): 65, 119, 228 (M^+ + 1, 100%); Anal. Calcd for $C_9H_{13}N_3O_2S$: C, 47.56; H, 5.77; N, 18.49. Found: C, 47.52; H, 6.04; N, 18.52.

5-Allyl-4-(2-methylprop-2-enyl)-1-dimethylsulfamoyl-1*H*-imidazole (26): A 3.0 M solution of EtMgBr in Et_2O (0.32 mL, 0.96 mmol) was added to a solution of **19** (300 mg, 0.88 mmol) in dry CH_2Cl_2 (3 mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (0.88 mL, 0.88 mmol) was added. The reaction mixture was cooled to –30 °C and methallyl chloride (0.17 mL, 1.77 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h half saturated NH_4Cl solution containing 2% concentrated NH_3 (5 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/Hexane, 3:2) to yield **26** (156 mg, 66%) as yellow liquid: ^{1}H NMR: δ = 1.64 (s, 3H), 2.78 (s, 6H), 3.13 (s, 2H), 3.46 (ddd, 2H, *J* = 1.8, 1.8, 5.9 Hz), 4.62 (s, 1H), 4.74 (s, 1H), 4.88 (ddt, 1H, *J* = 1.5, 1.8, 17.2 Hz), 4.99 (ddt, 1H, *J* = 1.5, 1.8, 10.3 Hz), 5.78 (ddt, 1H, *J* = 5.9, 10.3, 17.2 Hz), 7.78 (s, 1H); ^{13}C NMR: δ = 22.4, 27.4, 35.7, 38.0, 112.0, 116.1, 124.9, 134.4, 137.3, 139.6, 143.0; IR ($CHCl_3$, cm^{-1}): 2914, 1640, 1389, 1171; EIMS (*m/z*): 74, 108, 125, 161, 216, 269 (M^+), 270 (M^+ + 1, 100%); Anal. Calcd for $C_{12}H_{19}N_3O_2S$: C, 53.51; H, 7.11; N, 15.60. Found: C, 53.58; H, 7.45; N, 15.64.

4,7-Dihydro-5-methyl-1-dimethylsulfamoyl-1*H*-benzimidazole (27): Compound **27** was synthesized from compound **26** (156 mg, 0.579 mmol) in 81% yield according to the general procedure for the RCM reactions with *p*-TsOH by using Grubbs' second generation catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt for 2 h and worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 1:1) afforded product **27** (114 mg, 81%) as colorless solid: mp 121.0-121.5 °C; ^{1}H NMR: δ = 1.79 (d, 3H, *J* = 1.5 Hz), 2.83 (s, 6H), 3.18 (t, 2H, *J* = 7.0 Hz), 3.35 (m, 2H), 5.50 (m, 1H), 7.80 (s, 1H); ^{13}C NMR: δ = 23.4, 24.7, 30.9, 38.1, 116.8, 123.0, 132.1, 136.65, 136.69; IR (KBr, cm^{-1}): 3128, 2968, 2908, 1601, 1480, 1387, 1153; EIMS (*m/z*): 55, 65, 73, 125, 133, 230, 241 (M^+), 242 (M^+ + 1, 100%); Anal. Calcd for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.62; H, 6.33; N, 17.76.

1-(5-Allyl-1-dimethylsulfamoyl-1*H*-imidazol-4-yl)prop-2-en-1-ol (28): A 3.0 M solution of EtMgBr in Et_2O (2.5 mL, 7.5 mmol) was added to a solution of compound **19** (2.00 g, 5.86 mmol) in dry CH_2Cl_2 (40

mL). The resulting solution was stirred at rt for 30 min and then acrolein (1.6 mL, 23.9 mmol) in CH_2Cl_2 (5 mL) was added. After stirring at rt for a further 2 h the mixture was diluted with CH_2Cl_2 and poured into a half saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc) to yield product **28** (777 mg, 49%) as yellow oil: ^{1}H NMR: δ = 2.82 (s, 6H), 3.57 (m, 2H), 3.82 (s, 1H), 4.92 (d, 1H, *J* = 17.2 Hz), 5.04 (d, 1H, *J* = 10.3 Hz), 5.06 (d, 1H, *J* = 6.2 Hz), 5.13 (d, 1H, *J* = 10.3 Hz), 5.26 (d, 1H, *J* = 17.2 Hz), 5.84 (m, 1H), 6.05 (m, 1H), 7.84 (s, 1H); ^{13}C NMR: δ = 27.3, 38.0, 68.3, 115.5, 116.6, 125.0, 134.5, 137.8, 138.8, 141.9; IR ($CHCl_3$, cm^{-1}): 3307, 2981, 1481, 1390, 1178; EIMS (*m/z*): 89, 108, 125, 163, 254 (100%), 271 (M^+), 272 (M^+ + 1); Anal. Calcd for $C_{11}H_{17}N_3O_3S$: C, 48.69; H, 6.32; N, 15.49. Found: C, 48.76; H, 6.79; N, 15.33.

1-Dimethylsulfamoyl-1*H*-benzimidazole (29): Compound **29** is a known compound[25] and was synthesized from compound **28** (172 mg, 0.634 mmol) in 45% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt for 1.5 h. The reaction was worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 1:1) afforded product **29** (64 mg, 45%) as colorless solid: mp 77.0-78.0 °C; ^{1}H NMR: δ = 2.90 (s, 6H), 7.38 (m, 2H), 7.83 (m, 2H), 8.23 (s, 1H); ^{13}C NMR: δ = 38.4, 112.9, 121.0, 124.5, 125.4, 131.8, 141.9, 143.6; IR (KBr, cm^{-1}): 3066, 2984, 1607, 1445, 1390, 1256, 1162, 1138, 1029; EIMS (*m/z*): 65, 108, 119, 144, 226 (M^+ + 1, 100%).

5-Allyl-1-benzyl-4-iodo-1*H*-imidazole (31): A 3.0 M solution of EtMgBr in Et_2O (14.3 mL, 42.9 mmol) was added to a solution of 1-benzyl-4,5-diiodo-1*H*-imidazole **30**[30] (16.0 g, 39.0 mmol) in dry CH_2Cl_2 (160 mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (39.0 mL, 39.0 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (3.67 mL, 42.6 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (100 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield **31** (9.69 g, 77%) as yellow liquid: ^{1}H NMR: δ = 3.22 (ddd, 2H, *J* = 1.5, 1.8, 5.9 Hz), 4.93 (ddt, 1H, *J* = 1.5, 1.8, 17.2 Hz), 5.04 (ddt, 1H, *J* = 1.5, 1.5, 10.3 Hz), 5.06 (s, 2H), 5.70 (ddt, 1H, *J* = 5.9, 10.3, 17.2 Hz), 7.02-7.06 (m, 2H), 7.27-7.35 (m, 3H), 7.45 (s, 1H); ^{13}C NMR: δ = 29.1, 49.6, 85.2, 116.9, 127.0, 128.4, 129.2, 131.5, 133.5, 135.5, 139.4; IR ($CHCl_3$, cm^{-1}): 3080, 3031, 2978, 2906, 1638; EIMS (*m/z*): 65, 148, 275 (100%), 303, 324 (M^+), 325 (M^+ + 1);

Anal. Calcd for $C_{13}H_{13}IN_2$: C, 48.17; H, 4.04; N, 8.64. Found: C, 48.03; H, 4.27; N, 8.73.

4,5-Diallyl-1-benzyl-1*H*-imidazole (32): A 3.0 M solution of EtMgBr in Et_2O (0.45 mL, 1.35 mmol) was added to a solution of **31** (360 mg, 1.11 mmol) in dry CH_2Cl_2 (4 mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (1.1 mL, 1.1 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (0.25 mL, 2.24 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h, half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (5 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield **32** (154 mg, 58%) as yellow liquid: ^{1}H NMR: δ = 3.14 (m, 2H), 3.27 (m, 2H), 4.87 (ddt, 1H, *J* = 1.1, 1.5, 17.2 Hz), 4.96 (s, 2H), 4.97-4.99 (m, 2H), 5.04 (ddt, 1H, *J* = 1.1, 1.5, 17.2 Hz), 5.69 (ddt, 1H, *J* = 5.5, 9.9, 17.2 Hz), 5.94 (ddt, 1H, *J* = 6.2, 10.3, 17.2 Hz), 6.97-7.02 (m, 2H), 7.21-7.30 (m, 3H), 7.37 (s, 1H); ^{13}C NMR: δ = 27.4, 32.3, 48.6, 115.2, 116.1, 124.3, 126.7, 128.0, 129.0, 134.9, 136.55, 136.61, 136.9, 137.6; IR ($CHCl_3$, cm^{-1}): 3077, 2977, 2907, 1639; EIMS (*m/z*): 65, 91, 147, 238 (M^+), 239 (M^+ + 1, 100%). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.77; H, 7.84; N, 11.74.

1-Benzyl-4,7-dihydro-1*H*-benzimidazole (33): Compound **33** was synthesized from compound **32** (300 mg, 1.26 mmol) in 87% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 1 h and worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 4:1) afforded product **33** (230 mg, 87%) as colorless solid: mp 140.0–140.5 °C; ^{1}H NMR: δ = 3.06 (m, 2H), 3.32 (m, 2H), 5.01 (s, 2H), 5.72 (m, 1H), 5.89 (m, 1H), 7.04-7.08 (m, 2H), 7.24-7.33 (m, 3H), 7.46 (s, 1H); ^{13}C NMR: δ = 23.0, 26.7, 48.7, 122.1, 123.2, 125.9, 126.9, 128.1, 129.0, 134.5, 136.1, 136.5; IR (KBr, cm^{-1}): 3089, 3030, 2871, 2835, 1651, 1594; EIMS (*m/z*): 65, 91, 119, 172, 210 (M^+), 211 (M^+ + 1, 100%). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.73; H, 6.71; N, 12.97.

5-Allyl-1-benzyl-4-(2-methylprop-2-enyl)-1*H*-imidazole (34): A 3.0 M solution of EtMgBr in Et_2O (1.84 mL, 5.52 mmol) was added to a solution of compound **31** (1.62 g, 5.00 mmol) in dry CH_2Cl_2 (18 mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (5 mL, 5 mmol) was added. The reaction mixture was cooled to –30 °C and methallyl chloride (1 mL, 10.2 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h, half saturated NH_4Cl solution containing 2% concentrated NH_3 (20 mL) was added to the

reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 4:1) to yield **34** (879 mg, 70%) as yellow liquid: ^{1}H NMR: δ = 1.70 (s, 3H), 3.16 (d, 2H, *J* = 5.5 Hz), 3.23 (s, 2H), 4.71 (s, 1H), 4.76 (s, 1H), 4.90 (dd, 1H, *J* = 1.5, 17.2 Hz), 4.99 (dd, 1H, *J* = 1.5, 10.3 Hz), 5.00 (s, 2H), 5.70 (ddt, 1H, *J* = 5.5, 10.3, 17.2 Hz), 6.98-7.01 (m, 2H), 7.23-7.32 (m, 3H), 7.42 (s, 1H); ^{13}C NMR: δ = 22.4, 27.5, 36.4, 48.7, 111.3, 116.1, 126.6, 128.0, 129.0, 134.9, 136.7, 144.5; IR ($CHCl_3$, cm^{-1}): 3076, 2976, 2909, 1639; EIMS (*m/z*): 59, 84 (100%), 239, 252 (M^+), 253 ($M^+ + 1$); Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.13; H, 8.27; N, 11.23.

1-Benzyl-4,7-dihydro-5-methyl-1*H*-benzimidazole (35): Compound **35** was synthesized from compound **34** (433 mg, 1.72 mmol) in 82% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 3 h and then stirred overnight. The reaction was worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 4:1) afforded **35** (315 mg, 82%) as colorless solid: mp 122.0-123.0 °C; ^{1}H NMR: δ = 1.80 (d, 3H, *J* = 1.5 Hz), 3.01 (m, 2H), 3.21 (t, 2H, *J* = 6.6 Hz), 5.01 (s, 2H), 5.44 (m, 1H), 7.04-7.08 (m, 2H), 7.24-7.33 (m, 3H), 7.46 (s, 1H); ^{13}C NMR: δ = 23.1, 23.7, 31.2, 48.8, 116.5, 123.4, 126.9, 128.0, 129.0, 133.4, 135.0, 136.3, 136.5; IR (KBr, cm^{-1}): 3031, 2836; EIMS (*m/z*): 65, 91, 224 (M^+), 225 ($M^+ + 1$, 100%); Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.14; H, 7.25; N, 12.59.

1,2-Diallyl-4,5-dibromo-1*H*-imidazole (37): A 3.0 M solution of EtMgBr in Et_2O (2.7 mL, 8.1 mmol) was added to a solution of compound **36** (2.50 g, 7.25 mmol) in dry CH_2Cl_2 (25 mL) at rt The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (8.0 mL, 8.0 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (1.5 mL, 15 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (20 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 3:7) to yield **37** (1.68 g, 76%) as yellow liquid: ^{1}H NMR: δ = 3.47 (ddd, 2H, *J* = 1.3, 1.5, 6.2 Hz), 4.53 (ddd, 2H, *J* = 1.7, 1.8, 4.8 Hz), 4.92 (ddt, 1H, *J* = 1.8, 1.8, 17.0 Hz), 5.10 (ddt, 1H, *J* = 1.3, 1.5, 17.0 Hz), 5.15 (ddt, 1H, *J* = 1.3, 1.3, 10.1 Hz), 5.23 (ddt, 1H, *J* = 1.7, 1.8, 10.4 Hz), 5.78 (m, 1H), 5.87 (m, 1H); ^{13}C

NMR: δ = 32.7, 47.9, 103.3, 115.6, 117.9, 118.1, 131.2, 132.4, 147.1; IR ($CHCl_3$, cm^{-1}): 3083, 2983, 1643; EIMS (*m/z*): 227, 265, 306 (M^+), 307 (M^+ + 1, 100%); Anal. Calcd for $C_9H_{10}Br_2N_2$: C, 35.33; H, 3.29; N, 9.15. Found: C, 35.38; H, 3.41; N, 8.84.

2,3-Dibromo-5,8-dihydroimidazo[1,2-*a*]pyridine (38): Compound **38** was synthesized from compound **37** (475 mg, 1.55 mmol) in 78% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt overnight. The reaction was worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 1:1) afforded product **38** (336 mg, 78%) as colorless solid.: mp 159.0–160.0 °C; ^{1}H NMR: δ = 3.48 (m, 2H), 4.42 (m, 2H), 5.89 (m, 1H), 6.00 (m, 1H); ^{13}C NMR: δ = 25.8, 45.3, 100.9, 116.2, 119.2, 122.8, 143.3; IR ($CHCl_3$, cm^{-1}): 1472, 1414, 1226, 1003, 680; EIMS (*m/z*): 199, 278 (M^+), 279 (M^+ + 1, 100%); Anal. Calcd for $C_7H_6Br_2N_2$: C, 30.25; H, 2.18; N, 10.08. Found: C, 30.35; H, 2.21; N, 9.65.

1-Allyl-4,5-diiodo-1*H*-imidazole (40): 4,5-Diiodoimidazole **39** (8.00 g, 25.0 mmol) was dissolved in 40 mL THF. The solution was cooled to 0 °C and NaH (1.10 g, 60% in mineral oil, 27.5 mmol) was added portionwise. The mixture was allowed to warm up to rt and stirred for 1.5 h. Then the mixture was cooled to 0 °C again, and allyl bromide (4.00 mL, 35.8 mmol) was added. The mixture was warmed up to rt and then heated to 40 °C and stirred overnight. Saturated aqueous NH_4Cl solution was added to the mixture and it was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to furnish **40** (6.87 g, 76%) as colorless solid: mp 134.0-135.0 °C; ^{1}H NMR: δ = 4.57 (d, 2H, *J* = 5.5 Hz), 5.10 (d, 1H, *J* = 16.9 Hz), 5.31 (d, 1H, *J* = 10.3 Hz), 5.88 (ddt, 1H, *J* = 5.5, 10.3, 16.9 Hz), 7.62 (s, 1H); ^{13}C NMR: δ = 52.0, 82.9, 96.1, 119.6, 131.5, 141.1; IR (KBr, cm^{-1}): 3098, 1642; EIMS (*m/z*): 107, 157, 172, 234, 360 (M^+, 100%); Anal. Calcd for $C_6H_6I_2N_2$: C, 20.02; H, 1.68; N, 7.78. Found: C, 20.18; H, 1.54; N, 7.60.

1,5-Diallyl-4-iodo-1*H*-imidazole (41): A 3.0 M solution of EtMgBr in Et_2O (2.6 mL, 7.8 mmol) was added to a solution of compound **40** (2.50 g, 6.95 mmol) in dry CH_2Cl_2 (30 mL) at rt The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN·2LiCl in dry THF (6.95 mL, 6.95 mmol) was added. The reaction mixture was cooled to –30 °C and allyl bromide (0.65 mL, 7.5 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 h, half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (20 mL) was added to the reaction mixture. The mixture was stirred for 20 min, the color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined

organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield **41** (1.37 g, 72%) as yellow liquid: ^{1}H NMR: δ = 3.31 (ddd, 2H, *J* = 1.5, 1.8, 5.5 Hz), 4.47 (ddd, 2H, *J* = 1.5, 1.8, 5.5 Hz), 4.94 (ddt, 1H, *J* = 1.5, 1.8, 17.2 Hz), 5.04 (ddt, 1H, *J* = 1.1, 1.8, 17.2 Hz), 5.07 (ddt, 1H, *J* = 1.5, 1.5, 10.6 Hz), 5.24 (ddt, 1H, *J* = 1.1, 1.5, 10.6 Hz), 5.75 (ddt, 1H, *J* = 5.5, 10.6, 17.2 Hz), 5.85 (ddt, 1H, *J* = 5.5, 10.6, 17.2 Hz), 7.42 (s, 1H); ^{13}C NMR: δ = 29.0, 48.2, 84.7, 116.8, 118.6, 131.4, 132.4, 133.6, 138.9; IR ($CHCl_3$, cm^{-1}): 3081, 3009, 2980, 2911, 1640; EIMS (*m/z*): 148, 274 (M^+), 275 (M^+ + 1, 100%); Anal. Calcd for $C_9H_{11}IN_2$: C, 39.44; H, 4.04; N, 10.22. Found: C, 39.19; H, 3.99; N, 9.94.

1-Iodo-5,8-dihydroimidazo[1,5-*a*]pyridine (42): Compound **42** was synthesized from compound **41** (274 mg, 1.00 mmol) in 92% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt for 2 h. The reaction was worked up according to the general procedure. Flash chromatography (EtOAc/hexane, 3:2) afforded **42** (227 mg, 92%) as an off-white solid, which is very unstable and quickly converted to uncharacterized black species after purification: ^{1}H NMR: δ = 3.18 (m, 2H), 4.56 (m, 2H), 5.83 (m, 1H), 5.99 (m, 1H), 7.44 (s, 1H); ^{13}C NMR: δ = 22.7, 43.4, 79.3, 119.6, 122.6, 128.0, 136.5; IR (KBr, cm^{-1}): 3110, 3044, 2908, 2871, 1662; EIMS (*m/z*): 120, 134, 246 (M^+), 247 (M^+ + 1, 100%).

1-(1-Allyl-4-iodo-1*H*-imidazol-5-yl)ethanol (43): A 3.0 M solution of EtMgBr in Et_2O (2.2 mL, 6.6 mmol) was added to a solution of compound **40** (2.14 g, 5.94 mmol) in dry CH_2Cl_2 (25 mL). The resulting solution was stirred at rt for 30 min and then cooled to 0 °C. Acetaldehyde (1.1 mL, 20 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was allowed to warm up to rt and stir for a further 3 h. The mixture was diluted with CH_2Cl_2 and poured into half saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 2:3) to yield product **43** (1.01 g, 61%) as colorless oil which changed to colorless solid slowly: mp 92.0-93.0 °C; ^{1}H NMR: δ = 1.47 (d, 3H, *J* = 7.0 Hz), 3.40 (br s, 1H), 4.76 (dddd, 1H, *J* = 1.5, 1.5, 5.5, 16.1 Hz), 4.84 (dddd, 1H, *J* = 1.5, 1.5, 5.9, 16.1 Hz), 5.02 (q, 1H, *J* = 7.0 Hz), 5.10 (dddd, 1H, *J* = 1.1, 1.5, 1.5, 17.2 Hz), 5.25 (dddd, 1H, 1.1, 1.5, 1.5, 10.3 Hz), 5.95 (ddt, 1H, *J* = 5.5, 10.3, 17.2 Hz), 7.28 (s, 1H); ^{13}C NMR: δ = 23.0, 48.6, 62.6, 81.1, 118.7, 133.1, 135.5, 139.7; IR ($CHCl_3$, cm^{-1}): 3220, 2977, 2929, 1645; EIMS (*m/z*): 153, 221, 235, 261, 278 (M^+), 279 (M^+ + 1, 100%); Anal. Calcd for $C_8H_{11}IN_2O$: C, 34.55; H, 3.99; N, 10.07. Found: C, 34.63; H, 3.95; N, 9.94.

1-Allyl-4-iodo-5-vinyl-1*H*-imidazole (44): A mixture of compound **43** (1.01 g, 3.63 mmol) and $CuSO_4$ (5.80 g, 36.3 mmol) was refluxed in *o*-xylene (15 mL) overnight. The mixture was allowed to cool down to rt and filtered through Celite. The solvent was removed and the residue was purified by flash chromatography (EtOAc/hexane, 1:1) to yield product **44** (103 mg, 11%) as yellow oil: ^{1}H NMR: δ = 4.56 (m, 2H), 5.03 (m, 1H), 5.26 (dd, 1H, *J* = 1.5, 10.3 Hz), 5.35 (dd, 1H, *J* = 1.1, 12.1 Hz), 5.82 (dd, 1H, *J* = 1.1, 18.0 Hz), 5.89 (ddt, 1H, *J* = 5.1, 10.3, 17.2 Hz), 6.41 (dd, 1H, *J* = 12.1, 18.0 Hz), 7.39 (s, 1H); ^{13}C NMR: δ = 48.3, 84.7, 117.8, 118.6, 123.0, 130.9, 132.1, 139.7; IR ($CHCl_3$, cm^{-1}): 3089, 1629; EIMS (*m/z*): 134, 261 (M^+ + 1, 100%); Anal. Calcd for $C_8H_9IN_2$: C, 36.95; H, 3.49; N, 10.77. Found: C, 37.05; H, 3.33; N, 10.54.

1-Iodo-5*H*-pyrrolo[1,2-*c*]imidazole (46): Compound **46** was synthesized from **44** (130 mg, 0.498 mmol) in 53% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt for 3 h. The reaction was worked up according to the general procedure. Flash chromatography (80/20, EtOAc/hexane) afforded product **46** (61 mg, 53%) as grey solid. Compound **46** is unstable and rapidly converted to an uncharacterized black species after purification: ^{1}H NMR: δ = 4.58 (m, 2H), 6.32 (m, 1H), 6.47 (m, 1H), 7.59 (s, 1H); ^{13}C NMR: δ = 51.6, 67.6, 120.8, 130.5, 134.7, 145.1; IR (KBr, cm^{-1}): 3390, 3114, 2921; EIMS (*m/z*): 96, 107, 232 (M^+), 233 (M^+ + 1, 100%).

1-Allyl-5-vinyl-1*H*-imidazole (45): A 3.0 M solution of EtMgBr in Et_2O (1.5 mL, 4.4 mmol) was added to a solution of compound **44** (575 mg, 2.21 mmol) in dry CH_2Cl_2 (15 mL) at rt The resulting suspension was stirred at rt for 30 min and then quenched with saturated NH_4Cl solution (5 mL). The mixture was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 3:2) to yield product **45** (165 mg, 56%) as colorless liquid: ^{1}H NMR: δ = 4.51 (m, 2H), 4.99 (d, 1H, *J* = 16.9 Hz), 5.17 (d, 1H, *J* = 11.4 Hz), 5.22 (d, 1H, *J* = 10.3 Hz), 5.55 (d, 1H, *J* = 17.2 Hz), 5.90 (m, 1H), 6.42 (dd, 1H, *J* = 11.4, 17.2 Hz), 7.20 (s, 1H), 7.40 (s, 1H); ^{13}C NMR: δ = 47.3, 114.8, 117.9, 122.9, 127.4, 131.0, 132.7, 138.1; IR ($CHCl_3$, cm^{-1}): 3387, 3090, 2988; EIMS (*m/z*): 107, 119, 134 (M^+, 100%); Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.47; H, 8.03; N, 20.40.

5*H*-Pyrrolo[1,2-*c*]imidazole (47): Compound **47** was synthesized from compound **45** (91 mg, 0.68 mmol) in 32% yield according to the general procedure for the RCM reactions with *p*-TsOH by using second generation Grubbs' catalyst. After adding the catalyst, the mixture was refluxed for 20 min and then stirred at rt overnight. The reaction was worked up according to the general procedure. Flash

chromatography (EtOAc) afforded product **47** (23 mg, 32%) as off-white solid. Compound **47** is a known compound and is very unstable and quickly changed to an uncharacterized black species after purification.[29] The ^{1}H NMR of compound **47** is identical to that in the literature:[29] ^{1}H NMR: δ = 4.51 (m, 2H), 6.28 (m, 1H), 6.61 (m, 1H), 6.83 (s, 1H), 7.67 (s, 1H); IR (KBr, cm^{-1}): 3385, 1476, 1217, 1091, 964, 800, 734, 663.

5-(3-Trimethylsilylprop-2-ynyl)-1-dimethylsulfamoyl-4-iodo-1*H*-imidazole (49): A 3.0 M solution of EtMgBr in Et_2O (4.3 mL, 12.9 mmol) was added to a solution of **5** (5.00 g, 11.7 mmol) in dry CH_2Cl_2 (50 mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN.2LiCl (prepared by dissolving 1 equivalent of CuCN and 2 equivalent LiCl in THF) in dry THF (11.7 mL, 11.7 mmol) was added. Then the reaction mixture was cooled to -30 °C and TMS protected propargyl bromide (2.45 g, 12.8 mmol) was added. The temperature was allowed to increase to 0 °C and then stirred for an additional 4 h. Then half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (50 mL) was added to the reaction mixture and stirred for 20 min. The color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (EtOAc/hexane, 3:7) to yield **49** (3.17g, 66%) as a pale yellow solid: mp 100.0-101.0 °C; ^{1}H NMR: δ = 0.13 (s, 9H), 2.99 (s, 6H), 3.78 (s, 2H), 7.87 (s, 1H); ^{13}C NMR (75 MHz): δ = 0.0, 17.1, 38.2, 86.3, 89.3, 100.5, 128.2, 139.5; IR ($CHCl_3$, cm^{-1}): 3129, 2959, 2179, 1536, 1459, 1251, 1150, 1099; HRMS (ESI) Calcd for $C_{11}H_{18}IN_3O_2NaSSi$ $[M+Na]^+$*m/z*, 433.9826, found 433.9826.

5-(3-Trimethylsilylprop-2-ynyl)-1-dimethylsulfamoyl-4-allyl-1*H*-imidazole (50): A 3.0 M solution of EtMgBr in Et_2O (0.86 mL, 2.57 mmol) was added to a solution of **49** (0.96 g, 2.34 mmol) in dry CH_2Cl_2 (10mL) at rt. The resulting suspension was stirred at rt for 30 min and then a 1.0 M solution of CuCN.2LiCl (prepared by dissolving 1 equivalent of CuCN and 2 equivalent LiCl in THF) in dry THF (2.34 mL, 2.34 mmol) was added. Then the reaction mixture was cooled to -30 °C and allyl bromide (0.41 mL, 4.68 mmol) was added. The temperature was allowed to increase to 0 °C and then stirred for an additional 4 h. Then half saturated aqueous NH_4Cl solution containing 2% concentrated NH_3 (10 mL) was added to the reaction mixture and stirred for 20 min. The color of the mixture changed to blue and the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (EtOAc/hexanes, 3:2) to yield **50** (540 mg, 71%) as a pale yellow solid: mp 39.0-41.0 °C; ^{1}H NMR (300 MHz): δ = 0.12 (s, 9H), 2.95 (s, 6H), 3.38 (dt, 2H, *J* = 1.4, 6.5 Hz), 3.76 (s, 2H), 5.11 (td, 2H, *J* = 1.4, 16.9 Hz), 5.97 (ddt, 1H, *J* = 6.4, 10.0, 17.0 Hz), 7.85 (s, 1H); ^{13}C NMR (75 MHz): δ = 0.0, 14.8, 31.9,

38.0, 85.9, 101.8, 116.3, 121.5, 134.7, 137.5, 139.9; IR ($CHCl_3$, cm^{-1}): 3081, 2960, 2178, 1640, 1476, 3991, 1251, 1178; HRMS (ESI) Calcd for $C_{14}H_{24}N_3O_2SSi$ $[M+H]^+$ m/z, 326.1353, found 326.1353.

4,7-Dihydro-5-vinyl-1-dimethylsulfamoyl-1*H*-benzimidazole (51): Compound **50** (500 mg, 1.54 mmol) and *p*-TsOH (322 mg, 1.69 mmol) were dissolved in dry CH_2Cl_2 (30.8 mL) and heated at reflux for 30 min. Then the solution was cooled to rt and Grubbs' II catalyst (185 mg, 0.218 mmol) was added and the mixture again heated to reflux for 2 h. After that an aqueous $NaHCO_3$ solution followed by solid K_2CO_3 added to the reaction mixture until the solution was basic. After separating the layers, the aqueous solution was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (EtOAc/hexanes, 1:1) to yield **51** (215 mg, 55%) as a brownish solid: mp 122.0-124.0 °C; ^{1}H NMR (300 MHz): δ = 2.91 (s, 6H), 3.41 (dd, 2H, *J* = 2.8, 3.8 Hz), 3.53 (t, 2H, *J* = 6.9 Hz), 5.08 (d, 1H, *J* = 10.7 Hz), 5.19 (d, 1H, *J* = 17.5 Hz), 5.96 (broad s, 1H), 6.53 (dd, 1H, *J* = 6.5, 11.0 Hz), 7.87 (s, 1H); ^{13}C NMR (75 MHz): δ = 23.6, 26.7, 38.2, 111.9, 123.2, 126.7, 132.2, 136.0, 137.0, 138.7; IR ($CHCl_3$, cm^{-1}): 2892, 2360, 1615, 1472, 1390, 1274, 1182, 1145, 965; HRMS (ESI) Calcd for $C_{11}H_{16}N_3O_2S$ $[M+H]^+$ m/z, 254.0958, found 254.0959.

1-Dimethylsulfamoyl-4,4a,5,6,7,9-hexahydro-1-*H*-[3,4-*g*]-1-phenyl-pyrrolidine-2,5-dionenaphtho[2, 3-*d*]imidazole (52): Compound **51** (100 mg, 0.395 mmol) and *N*-phenylmaleimide (137 mg, 0.791 mmol) in dry CH_2Cl_2 (3.9 mL) were placed in a thick-walled resealable tube. Then the tube was purged with nitrogen and heated to 50 °C for 22 h. Then CH_2Cl_2 was evaporated and residue was purified by flash chromatography (EtOAc/hexanes, 3:1) to yield **52** (144 mg, 86%) as a white solid: mp 159.0-161.0 °C; ^{1}H NMR: δ = 2.44 (m, 1H), 2.75-2.84 (m, 2H), 2.82 (s, 6H), 2.93 (m, 1H), 2.99 (dd, 1H, *J* = 6.0, 14.2 Hz), 3.28 (dt, 1H, *J* = 2.9, 9.4 Hz), 3.39 (dd, 1H, *J* = 7.3, 9.2 Hz), 3.44 (d, 1H, *J* = 17.4 Hz), 3.56 (d, 1H, *J* = 17.4 Hz), 5.81 (t, 1H, *J* = 5.0 Hz), 7.25 (m 2H), 7.35 (m, 1H), 7.43 (m, 2H), 7.72 (s, 1H); ^{13}C NMR: δ = 22.3, 27.2, 31.0, 33.9, 38.0, 38.1, 42.1, 121.4, 124.3, 126.4, 128.7, 129.3, 131.8, 134.6, 136.6, 138.3, 177.3, 178.6; IR ($CHCl_3$, cm^{-1}): 2930, 2360, 1709, 1499, 1390, 1184, 1142, 964; HRMS (ESI) Calcd for $C_{21}H_{22}N_4NaO_4S$ $[M+Na]^+$ m/z, 449.1254, found 449.1253.

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