Imidazole Backbone Functionalization with Olefin Cross-Metathesis

Francesco Angelucci,[a] Davide Cirillo,[a] and Hans-René Bjørsvik*[a]

A selective and high-rate Ru-catalyzed cross-metathesis reaction of alkenes with vinylimidazole is disclosed. Cross-metathesis is known to operate less efficiently on *N*-heterocycles, but through optimization by means of statistical experimental design and multiple regression, optimal reaction conditions were identified that allowed for consistent high-yields without the need of overly complicated set-ups or additives. The method was tested on a series of terminal alkene reagents with a variety of different functional groups and it provides the corresponding target molecules in good to high yields.

Introduction

A longstanding objective of our research group has been the exploration of the synthetic possibilities borne from using imidazoles as starting materials given their near-ubiquity in nature.[1] Because of this, imidazoles have found multiple applications in medicinal chemistry[2], from bio-molecules co-opted by researchers in the treatment of patients (i.e. AICAR[3]) to synthetic analogues and derivatives that exploit their affinity for biological targets to afford cytotoxic,[4] antifungal,[5] and anti-histaminic[6] activities.

Beyond their role in biochemistry, imidazoles such as NHC-ligands have become key components in organometallic chemistry reactions as stabilized carbenes that can bind reversibly to transition metals. Particularly, these have taken a special role in the air/moisture stabilization of the olefin metathesis Ru-catalysts of the second generation,[7] but have also found application as potential new anti-cancer drugs, where designed NHCs are coordinated with silver.[4] Given this breadth of possibilities, we have avoided the traditional formation of backbone substituted imidazoles obtained through multi-component reactions[8] and instead focused on the functionalization of preformed imidazoles as cheap and promising starting materials, with the hope of contributing to the research of novel late-stage backbone functionalization of imidazole-containing molecules.[9] We have achieved this initially through the di- and mono-halogenation of the imidazole backbone,[10] which has allowed Suzuki,[11] Stille,[12] and Sonogashira[13] cross-coupling reactions. Partially dissatisfied with the production of halogen waste, we have more recently explored a greener approach that involved the C–H functionalization of 4-vinylimidazoles with aromatic boronic acids.[14]

However, this oxidative Heck cross-coupling reaction has the limitation of working only with aromatic sp^2 carbons on the organometallic counterpart, so we decided to investigate the vinylimidazole functionalization with sp^3-carbons.

Alkene metathesis unlike cross-coupling reactions does not require pre-formed reaction partners, be they aryl, alkenyl or alkynyl halides or benign organometallics but relies on a "partner swap" between the two ends of two alkenes. Especially after the clarification of the mechanism by Chauvin in 1971[15] and then the developments from Schrock[16] and Grubbs[17] on bench-stable highly active catalysts, alkene metathesis has become one of the go-to standard reactions for C–C bond formation[18] and its importance was of Nobel-prize winning rank.[19]

While the general reaction has by now been described in great detail,[20] applications involving hetero-aromatic rings are few and far between, probably because aromatic amines are amongst the less reactive substrates for alkene metathesis.[21]
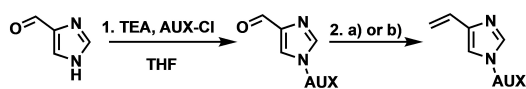
Results and Discussion

Starting material and early screenings

As with our recent oxidative Heck cross-coupling project[14], our starting point had to be an imidazole with an unencumbered olefin and we opted for a 1-AUX-4-vinyl-1*H*-imidazole. As in our previous work developing the oxidative Heck reaction[14] we used 1*H*-imidazole-4-carbaldehyde as starting material. After introducing a protective group, we decided to explore the Tebbe reagent[22] as an alternative to the Wittig reaction, with the aim of improving the atomic economy of the synthetic pathway, Scheme 1. However, the results were underwhelming, as the achieved yield was $\approx 25\%$ only when tested on a small scale and we were unable to scale-up the synthetic process. This, with the added consideration of the high cost of the Tebbe reagent, convinced us to rely once again on the Wittig reaction which afforded stable yields of $\approx 50\%$ even on gram-scale quantities.

[a] F. Angelucci, Dr. D. Cirillo, Prof. Dr. H.-R. Bjørsvik
Department of Chemistry
University of Bergen
Allégaten 41, N-5007 Bergen, Norway
E-mail: hans.bjorsvik@kj.uib.no
https://folk.uib.no/nkjhn/

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Scheme 1. Syntheses of 1-AUX-4-vinyl-1*H*-imidazole. 1. Protection of the imidazole with the AUX group 2. a) Wittig Reaction: *t*-BuOK, Me—P(Ph)₃Br, THF, 3 h, 20 °C. b) Tebbe Reaction: Tebbe reagent, THF, 3 h, 20 °C.

The work truly commenced by screening a vast array of different reaction conditions of which we present a selection in Table 1. Our initial screening informed our subsequent optimization allowing us to identify the best performing catalyst and the starting conditions for our set-up.

In accordance with previous studies[23] on aromatic *N*-heterocycles, it was clear that the choice of catalysts was only between Grubbs II (G II) and Hoveyda-Grubbs II (H—G II), as first-generation catalysts failed to give any conversion (entries 2, 3

of Table 1). It also showed that the choice of protecting group has a large influence on the reaction therefore we believe it more accurate to refer to it as an Auxiliary Group (AUX). In our screening only electron-withdrawing protecting groups, tosyl (Tos) and dimethyl-aminosulfonyl (DMAS) gave satisfactory yields, possibly by reducing the basicity/nucleophilicity of the nitrogens and preventing catalyst decomposition. However the use of a sterically hindering group like trityl (entry 6 of Table 1) did not achieve better yields as had also been suggested.[23]

While initially we had aimed for a combination of Grubbs II as the catalyst and Tosyl as a cheap and widely known protective group these gave consistently inferior yields compared to the DMAS-protected 4-vinylimidazole **1a** paired with the Hoveyda-Grubbs II catalyst. We thus decided to continue testing by focusing exclusively on this second combination and after having identified some initial working conditions that afforded consistent results (entry 18, Table 1), we used these to proceed to a traditional optimization approach "one-variable-at-a-time."

Solvents and Dilution

In accordance with literature,[24] our initial screening results suggested that the aromatic or polar and non-coordinating solvents were beneficial for a high-yielding reaction. Furthermore, the ideal solvent should withstand higher temperatures, as these appeared to be necessary for the reaction to proceed. This held true in our further screenings, Figure 1a, where 1,2-dichloroethane (DCE) proved to give the best yields. Moreover, in accordance with the previously cited literature, the reaction also achieved the best results when conducted at higher concentration or even neat as seen in Figure 1b.

Catalyst Loading and Reaction time

An early observation was that the reaction outcome was extremely variable and occasionally good results were difficult to reproduce. Despite our efforts to eliminate possible sources of variability by controlling factors such as (a) the order of addition, (b) the purity of the catalyst and of the reagents, (c) the presence of moisture and oxygen both in the solvents and in the overhead volume, a certain irreproducibility persisted at our preferred catalyst loading of 5%.

In our first screenings, we identified that the variability in the results was only present at lower catalyst loadings but disappeared at 10% loadings, and this also appeared to give higher yields than other tested catalyst loadings as visible in Figure 1c.

To evaluate whether increased reaction times would achieve the same results with lower catalyst loadings, we investigated the loadings of 5 and 10% over a 20 h period, Figure 1e. This was not observed as the yields of the 5% catalyst load remained lower and less consistent whilst the 10% loadings appeared to achieve an equilibrium after a period of 4 h.

Table 1. Cross-metathesis early screening using 4-vinylimidazole as substrate.[a]

#	AUX	Cat.	T [°C]	Solvent	Yield [%][b]
1	Tosyl	G II	40	Dichloromethane	30
2	Tosyl	G I	80	1,2 Dichloroethane	35
3	Tosyl	H—G I	80	1,2 Dichloroethane	Traces
4	H	G II	80	1,2 Dichloroethane	Traces
5	THP	G II	80	1,2 Dichloroethane	Traces
6	Trityl	G II	80	1,2 Dichloroethane	13
7	Tosyl	H—G II	90	1,2 Dichloroethane	51
8	Tosyl	NO₂ Gr	90	1,2 Dichloroethane	19
9	Tosyl	G II	100	1,4 Dioxane	43
10	Tosyl	G II	100	DMF	Traces
11	Tosyl	G II	70	THF	48
12	Tosyl	H—G II	90	Cl-Benzene	46
13	Tosyl	G II	90	Toluene anhydrous	51
14	Tosyl	G II	90	1,2 Dichloroethane	58
15	Tosyl	H—G II	90	1,2 Dichloroethane	64
16	DMAS	G II	90	Toluene anhydrous	57
17	DMAS	G II	90	1,2 Dichloroethane	67
18	DMAS	H—G II	90	1,2 Dichloroethane	75

[a] Reaction conditions: 1-AUX-4-vinylimidazole (248 μmol), 1-hexene (3 equiv.), catalyst (10% mol), and solvent (1 mL) were placed in an Argon flushed sealed microwave reaction tube (0.5–2 mL) for 8 h at a temperature of T [°C]. [b] Yield measured by means of GC.

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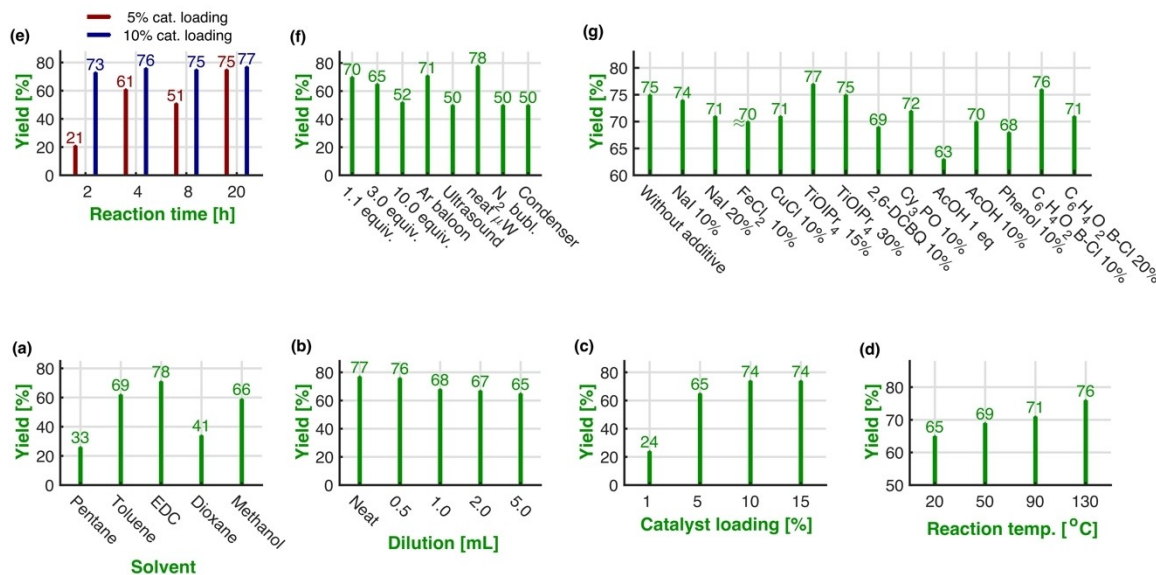European Chemical
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Figure 1. Screening of experimental variables (a) Screening of solvents (b) Screening of dilution (selected 0.5 mL), (c) Screening of catalyst loading (d) Screening of reaction time with two catalyst loadings (e) Screening of reaction temperature, (f) Screening of other variables (g) Screening of additives: Sodium iodide, Iron(II)chloride, Copper(II)chloride, Titanium(IV)isopropoxide, 2,6-Dichloro-1,4-benzoquinone, Tricyclohexylphosphine oxide, Acetic acid, Phenol, B-chlorocatecholborane. The basic set-up for the screenings was: 1-DMAS-4-vinylimidazole (248 μmol) and catalyst H–G II (10%) were placed in a Microwave reactor tube (0.5–2 or 2–5 mL) that was sealed and flushed for 1 minute with Ar. 1-hexene (3 equiv.) and DCE (1 mL) were added, and the reaction mixture was stirred at 90 °C in a pre-heated oil bath for 8 h. From screening to screening a single parameter (solvent, dilution, catalyst loading, reaction time, reagent equivalents) was varied and all the other conditions kept the same. For the screening of the additives the additive in the reported amount was added to the reactor tube after the catalyst and before the flushing. For the screening of the other variables, the reaction was run according to the general conditions except in the case of the condenser which was fitted on a 5 mL round-bottom flask. The crude of each reaction was then diluted in DCE, filtered and analyzed on GC.

Reaction temperature and reagent equivalents

Our investigation of the role of an increased reaction temperature was inconclusive. While a general trend towards higher conversions was observed with increasing temperatures, the results were close to one another and in the range of variability of the reaction, Figure 1d. With regards to the equivalents of reagent we observed that adding an excess of the reagent olefin reduced the overall conversion of the reaction. An ideal ratio was 1:1.1 between our vinyl imidazole **1a** and 1-hexene **3a**.

This result, combined with the observation that if the reaction was conducted with the product of self-metathesis of our test alkene (*trans*-decene) that resulted in full conversion suggested that the issue we were facing was connected at least in part to decomposition of the catalyst due to the presence of ethylene as a side product of the reaction.[25]

We decided to explore this by using different reaction set-ups to investigate if by allowing the fast escape of the produced ethylene we would achieve higher yields, Figure 1f. To this end we: (a) conducted the reaction connected to an Argon balloon to increase the overhead volume, (b) ran the reaction neat in a microwave reactor so that the ethylene would not be able to be dissolved in the solvent and be in contact with the catalyst, (c) conducted a reaction in the ultrasound bath to facilitate the evaporation of ethylene through cavitation, (d) ran one open to the air, and (e) ran one with bubbling of nitrogen through the reaction mixture. Next, we decided to

identify if the produced ethylene was coming from both **1a** and **3a**, or if it was only coming from the latter. To test this, we employed several combinations of 2-heptene and 1-DMAS-4-(alk-1-en-1-yl)-1*H*-imidazole to obtain propylene or 2-butene as the leaving gas (Table 2).

This series of experiments helped us to build a Grubbs-like model of reactivity[35] and selectivity of our cross-metathesis set-up, where we could place our starting material **1a** as a type III alkene, reactive but unable to undergo self-metathesis, the reacting olefins as type I olefins that quickly produce homo-dimers and that these were still active and undergo secondary metathesis with **1a**.

This ensures a selective cross-metathesis and a non-statistical distribution of products as **3b** is instead far less likely to undergo secondary metathesis and accumulates over time as the final product. These experiments also quickly revealed that the conversion was less affected by the presence of the propenyl starting material (**2a**), confirming that the fast-reacting type I alkene was responsible for most of the release of ethylene and subsequent formation of the methylidene complex and degradation of the catalyst. However, as expected from the reaction of an asymmetrical alkene, part of the starting material converted into the propenyl-imidazole (**2b**). In our screening we also confirmed that the reaction is at least partially reversible and **3b** can react in this set-up.

These adjustments showed that the ethylene itself appeared to react at a high rate *in situ* and adjustments like increasing the overhead volume or having a nitrogen flow did not

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Table 2. Screening for the origin and role of ethylene gas in catalyst decomposition.[a]

#	R_1	R_2	Conv.[a]		
1	H	H	76%	4	1
2	H	C_4H_9	99%	1	<0.1
3	H	CH_3	99%	2	1
4	CH_3	H	87%	10	1
5	CH_3	CH_3	>96%	2	1
6	C_4H_9	H	7%	10	1

[a] Reaction conditions: 1-DMAS-4-(alk-1-en-1-yl)-1*H*-imidazole (248 μmol), the olefin (1.1 equiv.), H–G II (10% mol), and DCE (1 mL) were placed in an Argon flushed sealed Microwave reactor tube (0.5-2 mL) and stirred for 2 h at 90 °C. The crude product was then diluted in DCE, filtered, and analyzed on GC. [b] The conversion was measured on GC and the ratio was calculated between **3b** and **SP** (side-product). [c]In this case $R_1 = R_2$, a total inversion of configuration was observed around the double bond, from (*Z*) to (*E*) in the cross-metathesis product. [d] In this case the reaction proceeded in reverse and 7% of **1a** was obtained according to GC conversion

significantly affect the outcome, only the reaction run neat gave better than average results, even if this could be attributed also to the reaction being more concentrated.

Additives

A known issue of running cross-metathesis reactions in the presence of amines is catalyst decomposition,[26] and this has often been addressed by the ingenious use of additives.[27] We tested some of the most commonly used additives, Figure 1g. However, in our method, the presence of additives did not appear to significantly improve the reaction outcome. In fact, in some cases, the presence of the additive even increased the variability of the results, so we ultimately decided to proceed without any additive present.

Reaction optimization using empirical modelling

Our initial experimental screening (results portrayed in Figure 1) revealed that several of the experimental variables were concomitantly responsible for the reaction outcome, which called for a systematic and in-depth investigation and optimization by means of empirical modelling using statistical experimental design,[28] multiple linear regression,[29] and response surface methodology.[30] The model approximation and graphical projections in terms of *iso*-contour maps were herein carried out using the MATLAB software.[31] In this context, we suggested that the reaction temperature [°C] (z_1), the catalyst loading [%] (z_2), the solvent volume [mL] (z_3), and reaction time [h, min.] (z_4) were the experimental variables that affected the performance of the reaction. By using the experimental

variables $z_1, ..., z_4$ a statistical experimental design matrix **D** composed of $2^k + c = 2^4 + 3 = 19$ experiments were generated and listed in standard order,[32] Table 3.

Each of the experimental variables $z_1, ..., z_4$ were investigated at two experimental levels. All the other experimental variables were kept at a fixed experimental level throughout the investigation.

The design matrix **D** (Table 3) was scaled[33] according to equation (1), in order to facilitate the subsequent modelling and ultimately the model interpretation. By means of equation (2), the scaled design matrix **D** was used to produce the model matrix **M**. The multiple linear regression (MLR)[29] expressed by equation (3) was used to calculate the regression coefficients (β).

Table 3. Statistical experimental design $(2^k + c = 2^4 + 3) = 19$ experiments for four experimental variables $z_1, ..., z_4$ where measured response $y =$ yield-% was used to investigate and optimize the olefine cross-metathesis with 1-DMAS-4-vinylimidazole as reaction substrate.[a]

Experimental levels

#	Experimental variables	Low	Centre	High
z_1	Reaction Temp. [°C]	90	120	150
z_2	Catalyst loading [mol-%]	1	5	10
z_3	Solvent volume [mL]	0.5	1.0	1.5
z_4	Reaction time [h]	2	4	6

#[a]	Experimental variables				Responses[b]		
	z_1	z_2	z_3	z_4	y	c	s
1	90	1	0.5	2	1.1	1.2	89.0
2	150	1	0.5	2	5.9	7.1	83.0
3	90	10	0.5	2	72.9	82.3	89.0
4	150	10	0.5	2	74.4	88.0	84.0
5	90	1	1.5	2	30.0	36.6	82.0
6	150	1	1.5	2	11.3	14.6	77.0
7	90	10	1.5	2	72.0	79.9	90.0
8	150	10	1.5	2	69.8	83.6	83.0
9	90	1	0.5	6	6.7	7.8	86.0
10	150	1	0.5	6	5.0	5.0	100
11	90	10	0.5	6	76.4	85.5	89.0
12	150	10	0.5	6	0	100.0	0
13	90	1	1.5	6	0	0	0
14	150	1	1.5	6	8.5	8.5	100
15	90	10	1.5	6	68.5	76.6	89.0
16	150	10	1.5	6	0	100	0
17	120	5	1.0	4	41.0	50.2	82.0
18	120	5	1.0	4	45.5	55.6	82.0
19	120	5	1.0	4	41.9	48.5	86.0

[a] The design matrix is listed in standard order, but conducted in randomized order. Reaction conditions: 1-DMAS-4-vinyl-1*H*-imidazole (248 μmol), 1-hexene (1.1 equiv.), H–G II (% mol), and DCE (mL) were placed in an Argon flushed sealed microwave reactor tube (0.5–2 mL) and stirred for reaction time [h] at reaction temperature [°C]. The crude product was then diluted in DCE, filtered, and analyzed on GC. [b] $y =$ yield-%, c = conversion-%, s = selectivity-%.

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$$x_k = \frac{z_k - \left[z_{k,L} + \frac{1}{2} \times (z_{k,H} - z_{k,L}) \right]}{z_{k,H} - \left[z_{k,L} + \frac{1}{2} \times (z_{k,H} - z_{k,L}) \right]}, \begin{cases} z_{k,L} \; low \; level \\ z_{k,L} \; high \; level \\ k = 1, \dots, 4 \end{cases} \quad (1)$$

$$\mathbf{M} = \begin{bmatrix} 1 & x_1 & x_2 & x_3 & x_4 & x_1 x_2 & x_1 x_3 & x_1 x_4 & x_2 x_3 & x_2 x_4 & x_3 x_4 & \dots \\ & & x_1 x_2 x_3 & x_1 x_2 x_4 & x_1 x_3 x_4 & x_2 x_3 x_4 & x_1 x_2 x_3 x_4 \end{bmatrix} \quad (2)$$

$$\mathbf{y} = \mathbf{M\beta} \Rightarrow \mathbf{\beta} = (\mathbf{M}^T \mathbf{M})^{-1} \mathbf{M}^T \mathbf{y} \quad (3)$$

With the purpose of keeping better control over the reaction and its reaction conditions and to be able to conduct several experiments during a single day, we decided to limit the reaction time $\leq 8\,$h, explored the reaction space of catalyst loadings $\leq 15\%$ and to keep the reaction temperatures $\leq 150\,°C$. At this temperature, the reaction mixture was observed to degraded over time and we were unable to detect either substrate, reagent, or any reaction products. We considered for our model the conversion (c) (percentage of starting material that has been converted during the defined time of reaction), the selectivity (s) (percentage of converted substrate converted into target molecule), and yield (y) (percentage of target molecule). The selectivity was calculated based on the observation that in the GC a small percentage of the (Z) product was observed to be formed, however it was not possible to isolate it during the purification.

The estimated model (the β-coefficients) for the response "yield" constitutes crucial information about the investigated olefin cross-metathesis reaction is listed in Table 4.

The graphical representation of these coefficients is given in a stem plot and a CND (cumulative normal probability) plot[34] in Figure 2, from which it is possible to determine that the following regression coefficients: $β_1, β_2, β_4, β_{12}, β_{14}, β_{24}, β_{124}$, and

$β_{234}$ (in addition to $β_0$) are significant and which contributes to the final model that describes the developed olefin metathesis reaction.

Final model that includes the significant variables and interaction terms is given in equation (4). The product statistics demonstrates a good model fit and acceptable prediction error.

$$\begin{aligned} y = f(x_1 x_2 x_4) = & \; 33.28 - 9.750 \times x_1 + 22.637 \times x_2 - \\ & 10.975 \times x_4 - 8.634 \times x_1 \times x_2 - 7.696 \times x_1 \times x_4 - \\ & 7.234 \times x_2 \times x_4 - 10.309 \times x_1 \times x_2 \times x_4 + 2.829 \times x_1 \times x_3 \times x_4 \end{aligned} \quad (4)$$

$R^2 = 0.9567$, $R^2_{Adj} = 0.9221$, RMSEP $= 6.2502$, and RSD $= 6.6182$

iso-Contour projection

The final model, equation (4), was then used to produce the *iso*-contour projection map portrayed in Figure 3. By means of this *iso*-contour projection we could predict optimized conditions and subsequently conduct the experiments in the laboratory to evaluate (and confirm) how the predicted results fitted the derived model (Equation 4).

We conducted three reactions in parallel (O1, O2 O3) by selecting a running temperature of 120 °C and a reaction time of 6 h. The reaction was run neat, with a 10% loading of catalyst, and two more with 0.5 mL of DCE and catalyst loadings of 10% and 15% respectively, see Table 5. The GC yields of the experiments neatly aligned with the results predicted by the *iso*-contour map (Figure 3). Based on these results, we decided to continue working with the lower catalyst loading of 10%, striking a compromise between high cost of the catalyst and achieved conversion. While in the instrumental analysis the neat reaction afforded the best yield, we proceeded to isolate and measure compound **3b** from the two reactions.

We achieved a 70% isolated yield from the neat reaction and 77% for the one with 0.5 mL of DCE. We therefore selected the latter as model reaction for our further experiments as this had given the higher yield and it also helped to reduce uncertainties in reactions with solid reagents that did not achieve conversion.

Table 4. Empirical predictive model (1st model, no variable pruning) for the response yield-% produced in the novel cross-metathesis reaction.[a]

$β_0$	33.31	$β_{12}$	−8.633	$β_{123}$	1.091
$β_1$	−9.753	$β_{13}$	−0.546	$β_{124}$	−10.309
$β_2$	22.634	$β_{14}$	−7.696	$β_{134}$	2.829
$β_3$	0.897	$β_{23}$	−2.758	$β_{234}$	2.191
$β_4$	−10.978	$β_{24}$	−7.233	$β_{1234}$	−1.381
		$β_{34}$	−2.471		

[a] Product statistics for the regression model: $R^2 = 0.9778$, $R^2_{Adj} = 0.8670$, RMSEP $= 4.4786$, and RSD $= 4.7348$.
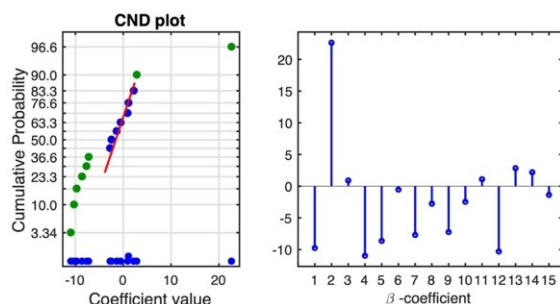

Figure 2. Right hand side: A stem plot displaying the estimated regression coefficients (except of $β_0$). Left hand side: The cumulative normal probability (CND) plot of the regression coefficients (the β's) of the derived predictive model. The CND plot suggest $β_1, β_2, β_4, β_{12}, β_{14}, β_{24}, β_{124}$ and $β_{134}$ (in addition to $β_0$) to be significant.

Table 5. Optimization experiments. Reaction conditions predicted by means of the *iso*-contour plot of Figure 3.

#[a]	Experimental variables [a]				Responses [b]
	z_1	z_2	z_3	z_4	y
O1	120	15	0.5	6	85.3
O2	120	10	0.5	6	76.1
O3	120	10	0.0	6	91.8

[a] Reaction conditions: 1-DMAS-4-vinyl-1*H*-imidazole (248 μmol), 1-hexene (1.1 equiv.), H–G II (% mol), and DCE (mL) were placed in an Argon flushed sealed microwave reactor tube (0.5–2 mL) and stirred for reaction time [h] at reaction temperature [°C]. The crude was then diluted in DCE, filtered, and analyzed on GC. [b] $y =$ yield-%.

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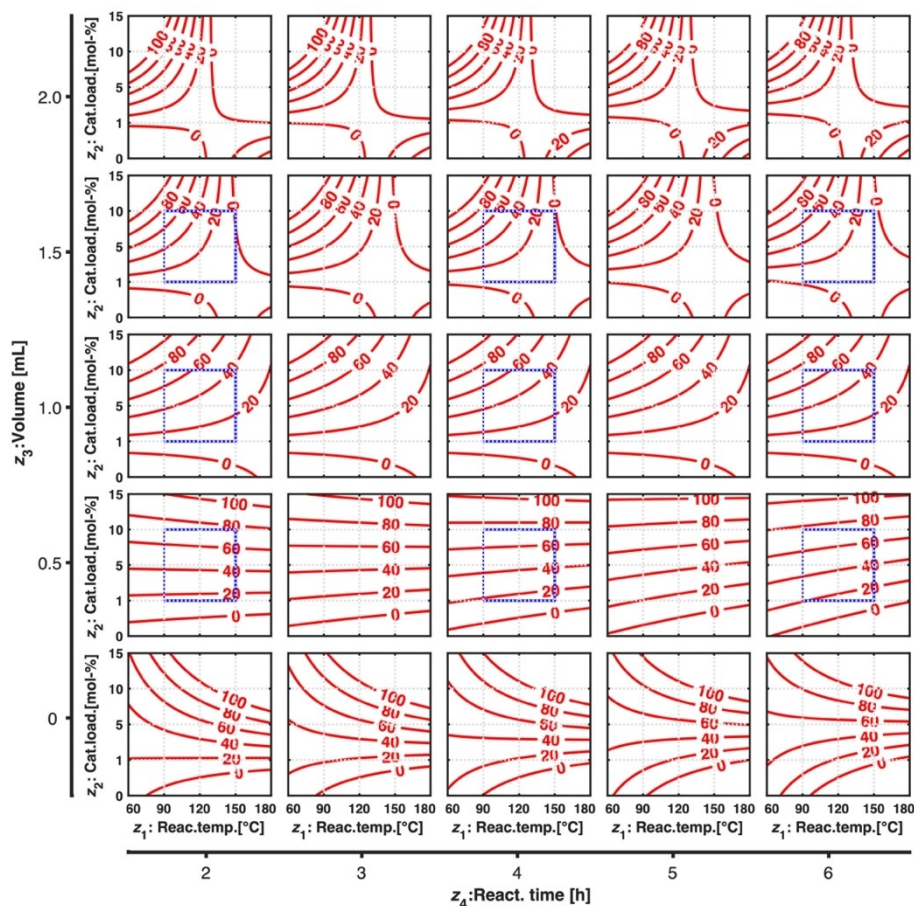European Chemical
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Figure 3. *Iso*-contour projections of the response surfaces that display the yield of **3b**. The plots above display the variations of the response "yield of **3b**" (the red colored *iso*-contour lines) when the four experimental variables z_1 (reaction temperature [°C]), z_2 (catalyst loading [mol-%]), z_3 (solvent volume [mL]), and z_4 (reaction time [h]) were varied. The multi-dimensional *iso*-contour projections plot is read in the following way: the large frame shows the variation (abscissa) in solvent volume (z_3) and (ordinate) the reaction time (z_4), each on five discrete levels. Within this frame, twenty-five subplots displaying the *iso*-contour projections of the response surface when the abscissa, that is the quantity of (z_1) and the ordinate, that is the reaction temperature (z_2) were varied. The squares drawn in blue line make up the experimental space defined by the design matrix (outlined in Table 1).

Scope and limitation of the method.

With the optimized reaction conditions in hand, we proceeded to test our method on *N,N*-dimethyl-4-vinyl-1*H*-imidazole-1-sulfonamide **1a** and a series of alkenes, see Table 6.

We selected the reaction partners based on the presence of vicinal or isolated functional groups and aromatic rings and the reaction conditions proved to be a general, selective, and effective strategy to obtain (*E*)-4-alkyl and styryl imidazoles in good yields. The results appeared to neatly follow the reactivity groups for alkenes as described by Grubbs and collaborators[35] for their selected catalysts. However, some key differences were observed that might be attributed to the different catalyst employed and the reactivity of starting material **1a**. Based on these reactivity rules of thumb, our first observation was that starting material **1a** could be classified as a type III alkene,[35] as it reacted slowly with its metathesis partner, but no homo-dimerization was observed. Consequently, the best yields and most selective metathesis reactions, were achieved on type I olefins: terminal, unencumbered alkenes whose homodimers

could still react with **1a**, and which allowed the introduction of a variety of isolated functional groups.

Similarly, styrene and its derivatives converted to products in good yield making them likely type I and II alkenes, and so too the ethyl acrylate ester.

In line with previous observations, the unreactive compounds fell into one of two categories: presence of known "problematic" moieties or sterically hindered alkenes that were passive spectators (type IV alkenes). While we tested these compounds, they were not included in Table 3, but detailed information on these reactions can be found in the Supporting Information. So, for example it came as no surprise that acrylonitrile, allylglycine and 4-vinylpyridine, all containing N moieties known for causing catalyst decomposition,[36] were less or entirely unreactive.

This might also explain why the isolated cyano in 5-hexenenitrile gave the lowest yield of the series. Similarly, vinylbromide is known to decompose the catalyst[37] at a high rate, while the bulkiness of the vinyl tributyltin fits neatly the explanation of unreactivity of encumbered alkenes of the type

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Table 6. Scope and limitation of the olefine cross-metathesis method using *N,N*-dimethyl-4-vinyl-1*H*-imidazole-1-sulfonamide 1a as substrate.[a]

Type[b]	Reagent	Product	Type[b]	Reagent	Product	Type[b]	Reagent	Product
I	3a	3b 77%	I	9a	9b 66%	I	15a	15b 58%
I	4a	4b 65%	I	10a	10b 49%	I	16a	16b 55%
I	5a	5b 70%	I	11a	11b 62%	I	17a	17b 66%
I	6a	6b 39%	II	12a	12b 59%	II	18a	18b 58%
I	7a	7b 50%	I	13a	13b 58%	II	19a	19b 50%
I	8a	8b 68%	I	14a	14b 62%			

[a] Reaction conditions: 1-DMAS-4vinyl-1*H*-imidazole (248 μmol), the olefin (1.1 equiv.), H–G II (10% mol), and DCE (0.5 mL) were placed in an Argon flushed sealed microwave reactor tube (0.5–2 mL) and stirred for 6 h at 120 °C. The crude product was then purified by autoflash chromatography and the identified target compound analyzed using NMR and HRMS. [b] Olefin type classified according to Grubbs and collaborators.[35]

IV. More surprising was the unreactivity of vinylboronic acid pinacol ester and the olefins containing acidic moieties (acrylic acid, 4-pentenylboronic acid and 4-vinylbenzoic acid), but we assume this might be a consequence of these being electron poor substrates acting as type IV alkenes in our set-up or that the acidic moiety is interfering with our substrate and hindering the reaction.

Conclusion

We have designed, developed, and investigated a novel method for olefin cross-metathesis that operates with the usually unreactive 4-vinylimidazole as substrate. By means of empirical modelling using statistical experimental design, multiple linear regression, and response surface methodology, the olefin cross-metathesis method was optimized to afford high

regioselectivity and yield comprising a high reaction rate. The reaction produced (*E*)-4-alkylimidazole derivatives with broad functional group tolerance. The cross-metathesis reaction did not proceed in the presence of highly encumbered alkenes (type IV) and with known problematic alkenes such as vinyl bromide, other vinyl *N*-heterocycles and with other highly reactive moieties, which caused catalyst decomposition, it performed with good to high yields in the other examples we tested, significantly expanding our ability to intervene on the imidazole scaffold. The best results were achieved with terminal unencumbered olefins, or type I olefins, as well as with vinylarylic derivatives with both electron donating and electron withdrawing substituents. The partnering of olefins of different types, our type III starting material and the type I and II reagents, ensured a non-statistical distribution of products and high yields. We envision that the unveiled method will be a valuable tool for the construction of more complex imidazole-

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cantered frameworks, by either further functionalization of the olefin, of the functional groups located on the imidazole/heterocycle or on the newly bonded cross metathesis product.

Experimental Section

General Experimental Information. All reagents and solvents were purchased from commercial sources and used as received. Reagent-grade chemicals were purchased from commercial sources and used without further purification. All reaction mixtures and samples collected during column chromatography were monitored by means of TLC analysis (TLC plates Merck Kieselgel 60 F254). The TLC plates were observed under UV light at λ 254 nm and λ 366 nm. All final compounds were purified by autoflash chromatography on an Interchim Puriflash® XS420 with Biotage Sfär Silica HC D 10 g pre-packed columns. Fractions of equal purity were pooled and evaporated under reduced pressure by Rotavapor. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker instruments AV 500 and Biospin 850SB. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro YA263 instrument.

The substrates listed in Table 1, apart from **1a** and **2a**, were synthesized according to reference [14].

General Procedure for the Cross Metathesis Reaction, experiments reported in Table 3

Method: **1a** (50 mg, 248 μmol) and Hoveyda Grubbs Catalyst M720 (H–G II)(10%, 16 mg, 25 μmol) are added to an oven dried pressure-resistant reaction tube (0.5-2 mL). This is capped and flushed with Argon gas for 1 min. Then anhydrous 1,2-dichloroethane (0.5 mL) is added to the tube by syringe followed by the reactant olefin. Solid olefins were weighed in before capping and flushing. The mixture is stirred at RT for 30 seconds and then stirred at 120 °C for 6 h. After cooling, the solvent was evaporated under reduced pressure. The obtained crude was purified by means of column chromatography and the eluent system was a progressive gradient of the ratio of hexane to EtOAc. The UV-wavelength used for the purification of compounds is 254 nm for most products except the electron rich styrene derivatives that were visible at 300 nm.

4-formyl-N,N-dimethyl-1H-imidazole-1-sulfonamide [140174-48-7]. 1H-imidazole-4-carbaldehyde (5.00 g, 52.0 mmol) and dimethylaminosulfamoyl chloride (2 equiv., 7.47 g, 5.59 mL, 52.0 mmol) were added to a Schlenk-tube under argon atmosphere. THF (dry, 30 mL) was then added to dissolve the mixture and triethylamine (1 equiv., 7.26 mL, 5.27 g, 52.0 mmol) was added by syringe. The reaction mixture was stirred under argon for 24 h at ambient temperature. Afterwards, the solvent was evaporated under reduced pressure. The crude product was extracted from sat. solution of NH$_4$Cl with EtOAc (3×150 mL), the organic phases were reunited and dried over Na$_2$SO$_4$. This was followed by purification using autoflash chromatography with an eluent system composed of hexane : EtOAc=80:20. Target product was isolated in a yield of 79% (8.32 g, 40.9 mmol) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.96 (s, 1H), 7.96 (d, J=1.2 Hz, 1H), 7.89 (d, J=1.3 Hz, 1H), 2.93 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 185.55, 142.18, 137.58, 122.49, 39.54, 38.20.

N,N-dimethyl-4-vinyl-1H-imidazole-1-sulfonamide [343880-85-3] **(1a)**. Methyltriphenylphosphonium bromide (2.5 equiv., 35.16 g, 98.4 mmol) was transferred to a three-neck round bottom flask (250 mL) under inert and anhydrous conditions. Then, was suspended in THF (dry, 30 mL), followed by the addition of potassium *tert*-butoxide in THF (1 M, 5.5 equiv., 98 mL, 98.4 mmol)

by syringe. No relevant increase of temperature was noticed during the addition and the suspension turns pale yellow. After 30 min, 4-formyl-N,N-dimethyl-1H-imidazole-1-sulfonamide (8 g, 39.4 mmol) was slowly added to the mixture as the addition is exothermic. The reaction mixture was stirred for 4 h at ambient temperature and checked through GC-MS. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The crude product was then dissolved in a saturated solution of NaHCO$_3$ (100 mL) and extracted with EtOAc (3 × 150 mL), the organic phases were combined and dried over Na$_2$SO$_4$. Finally, purification using column chromatography packed with silica and an eluent system composed of hexane : EtOAc=75:25. Target product was isolated in a yield of 64% (5.11 g, 25.4 mmol) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (s, 1H), 7.07 (d, J=0.8 Hz, 1H), 6.50 (dd, J=17.4, 11.0 Hz, 1H), 5.90 (dd, J=17.4, 1.4 Hz, 1H), 5.23 (dd, J=11.0, 1.5 Hz, 1H), 2.80 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.85, 136.82, 127.08, 115.54, 114.27, 38.19.

(Z)-N,N-dimethyl-4-(prop-1-en-1-yl)-1H-imidazole-1-sulfonamide [NEW] (2a). Ethyltriphenylphosphonium bromide (2.5 equiv., 9.13 g, 24.6 mmol) was transferred to a three-necks round bottom flask (100 mL) under inert and anhydrous conditions. Then, was suspended in THF (dry, 30 mL), followed by the addition of potassium *tert*-butoxide in THF (1 M, 2.5 equiv., 24,6 mL, 24,6 mmol) by syringe. No relevant increase of temperature was noticed during the addition and the suspension turned orange. After 30 min, 4-formyl-N,N-dimethyl-1H-imidazole-1-sulfonamide (2.0 g, 9.8 mmol), was added portion wise to the mixture. The addition was exothermic, and the aldehyde should never be added too quickly. The reaction mixture was stirred for 4 h at ambient temperature and the reaction progress controlled on GC-MS. Upon completion of the reaction, the solvent was evaporated under reduced pressure. The crude product was extracted from acidic water with DCM (3 × 200 mL), the organic phases were combined and dried over Na$_2$SO$_4$. Finally, purification using column chromatography packed with silica and an eluent system composed of hexane : EtOAc=80:20 provides target compound in a yield of 65% (1.37 g, 6.4 mmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, J=1.3 Hz, 1H), 7.15 (d, J=1.2 Hz, 1H), 6.28 (dq, J=11.4, 1.8 Hz, 1H), 5.83 (dq, J=11.5, 7.1 Hz, 1H), 2.86 (s, 6H), 1.98 (dd, J=7.2, 1.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.11, 136.03, 128.27, 121.10, 115.23, 38.32, 15.37. (ESI) m/z: [M+H]$^+$ calculated for C$_8$H$_{14}$N$_3$O$_2$S 216.08067; found 216.08011.

(E)-N,N-dimethyl-4-(prop-1-en-1-yl)-1H-imidazole-1-sulfonamide [NEW] (2b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and *trans*-2-heptene (1.1 equiv., 38 μL, 273 μmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated whereupon the crude product was purified by autoflash chromatography. The target compound was obtained in a yield of 26% (14 mg, 65 μmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (s, 1H), 7.02 (s, 1H), 6.48 (dq, J=15.6, 6.7 Hz, 1H), 6.29–6.20 (m, 1H), 2.85 (s, 6H), 1.87 (dd, J=6.7, 1.7 Hz, 3H).^{13}C NMR (126 MHz, CDCl$_3$) δ 136.71, 127.93, 121.23, 112.69, 38.20, 18.30. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_8$H$_{14}$N$_3$O$_2$S 216.08067; found 216.08010.

(E)-4-(hex-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide [NEW] (3b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and 1-hexene (1.1 equiv., 35 μL, 273 μmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was

purified by autoflash chromatography. Target product was isolated in a yield of 77% (49 mg, 190 µmol) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, J=1.3 Hz, 1H), 7.02 (d, J=1.5 Hz, 1H), 6.40 (dt, 1H), 6.25-6.00 (m, 1H), 2.84 (s, 6H), 2.19 (dd, J=7.2, 1.5 Hz, 2H), 1.47–1.32 (m, 4H), 0.90 (t, J=7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.15, 136.79, 133.37, 119.98, 112.92, 38.32, 38.30, 32.57, 31.36, 22.34, 14.03. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{11}$H$_{20}$N$_3$O$_2$S 258.12762; found 258.12733.

(E)-4-(dodec-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide [NEW] (4b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and 1-dodecene (1.1 equiv., 61 µL, 273 µmol) were added to a microwave reactor tube (0.5-2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, whereupon the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 65% (55 mg, 161 µmol) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (d, J=1.4 Hz, 1H), 7.03 (d, J=1.3 Hz, 1H), 6.47 (dt, J=15.7, 7.0 Hz, 1H), 6.26–6.19 (m, 1H), 2.85 (s, 6H), 2.19 (qd, J=7.1, 1.5 Hz, 2H), 1.25 (t, J=3.1 Hz, 16H), 0.87 (t, J=6.9 Hz, 3H).^{13}C NMR (126 MHz, CDCl$_3$) δ 142.18, 136.81, 133.47, 119.96, 112.94, 38.32, 32.93, 32.04, 29.75, 29.65, 29.47, 29.36, 29.27, 22.81, 14.25. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{17}$H$_{32}$N$_3$O$_2$S 342.22152; found 342.22098.

(E)-4-(6-chlorohex-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide [NEW] (5b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and 6-chlorohex-1-ene (1.1 equiv., 36 µL, 273 µmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath at 120 °C for 6 h. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 70% (51 mg, 175 µmol) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (d, J=1.4 Hz, 1H), 7.04 (d, J=1.3 Hz, 1H), 6.45 (dt, J=15.5, 7.0 Hz, 1H), 6.25 (dt, J=15.7, 1.5 Hz, 1H), 3.55 (t, J=6.7 Hz, 2H), 2.85 (s, 6H), 2.24 (qd, J=7.1, 1.5 Hz, 2H), 1.94–1.75 (m, 2H), 1.62 (tdd, J=10.0, 8.8, 5.3 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.77, 136.74, 132.06, 120.59, 113.08, 44.90, 38.20, 32.01, 26.32. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{11}$H$_{19}$ClN$_3$O$_2$S 292.08865; found 292.08814.

(E)-4-(5-cyanopent-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide [NEW] (6b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and hex-5-enenitrile (1.1 equiv., 31 µL, 273 µmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 39% (26 mg, 97 µmol) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (d, J=1.4 Hz, 1H), 7.06 (d, J=1.3 Hz, 1H), 6.39 (dt, J=15.7, 6.8 Hz, 1H), 6.34–6.27 (m, 1H), 2.86 (s, 6H), 2.42–2.34 (m, 4H), 1.84 (p, J=7.2 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.38, 136.96, 129.67, 122.26, 119.60, 113.72, 38.33, 31.48, 24.88, 16.56. HRMS (ESI) m/z: [M+Na]$^+$ calculated for C$_{11}$H$_{16}$NaN$_4$O$_2$S 291.08917; found 291.08879.

(E)-6-(1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl)hex-5-enoic acid [NEW] (7b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and hex-5-enoic acid (1.1 equiv., 33 µL, 273 µmol) were added to a microwave reactor

tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. The target compound was obtained in a yield of 50% (36 mg, 125 µmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (s, 1H), 7.05 (s, 1H), 6.43 (dt, J=15.7, 7.0 Hz, 1H), 6.26 (d, J=15.8 Hz, 1H), 2,86 (s, 6H), 2.41 (t, J=7.4 Hz, 2H), 2.28 (qd, J=7.2, 1.3 Hz, 2H), 1.83 (p, J=7.4 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.46, 136.87, 131.74, 120.79, 113.23, 38.22, 31.93, 24.14. HRMS (ESI) m/z: [M+Na]$^+$ calculated for C$_{11}$H$_{17}$NaN$_3$O$_4$S 310.08375; found 310.08318.

Methyl (E)-6-(1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl)hex-5-enoate [NEW] (8b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and methyl hex-5-enoate (1.1 equiv., 35 mg, 273 µmol) were added to a microwave reactor tube (0.5–2 mL) and reacted in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 68% (51 mg, 169 µmol) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, J=1.6 Hz, 1H), 7.04 (d, J=1.4 Hz, 1H), 6.43 (dt, J=15.7, 7.0 Hz, 1H), 6.24 (dt, J=15.7, 1.6 Hz, 1H), 3.66 (s, 3H), 2.85 (s, 6H), 2.36 (t, J=7.5 Hz, 2H), 2.24 (qd, J=7.2, 1.5 Hz, 2H), 1.81 (p, J=7.5 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 174.08, 141.85, 136.85, 131.65, 121.08, 113.25, 51.65, 38.32, 33.47, 32.14, 24.40. HRMS (ESI) m/z: [M+Na]$^+$ calculated for C$_{12}$H$_{19}$NaN$_3$O$_2$S 324.09940; found 324.09892.

(E)-4-(6-hydroxyhex-1-en-1-yl)-N,N-dimethyl-1H-imidazole-1-sulfonamide [NEW] (9b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and hex-5-en-1-ol (1.1 equiv., 33 µL, 273 µmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 66% (45 mg, 164 µmol) as an off-white solid. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.87 (s, 1H), 6.99 (d, J=1.3 Hz, 1H), 6.44 (dt, J=15.7, 7.0 Hz, 1H), 6.18 (d, J=15.7 Hz, 1H), 3.60 (t, J=6.5 Hz, 2H), 2.81 (s, 6H), 2.19 (qd, J=7.1, 1.5 Hz, 2H), 1.59–1.47 (m, 4H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.87, 136.73, 132.64, 120.30, 112.97, 62.78, 38.20, 32.45, 32.21, 25.22. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{11}$H$_{20}$N$_3$O$_2$S 258.12762; found 258.12733.

(E)-N,N-dimethyl-4-(4-(oxiran-2-yl)but-1-en-1-yl)-1H-imidazole-1-sulfonamide [NEW] (10b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg, 248 µmol), Hoveyda a Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloroethane (0.5 mL) and 2-(but-3-en-1-yl)oxirane (1.1 equiv., 31 µL, 273 µmol) were added to a microwave reactor tube (0.5-2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. Post-reaction the 1,2-dichloro-ethane was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 49% (33 mg, 122 µmol) as a dark yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, J=1.4 Hz, 1H), 7.04 (d, J=1.3 Hz, 1H), 6.48 (dt, J=15.7, 7.0 Hz, 1H), 6.38–6.21 (m, 1H), 2.97 (dtd, J=6.8, 4.4, 2.7 Hz, 1H), 2.85 (s, 6H), 2.76 (dd, J=5.0, 4.0 Hz, 1H), 2.51 (dd, J=5.0, 2.7 Hz, 1H), 2.37 (dddd, J=15.3, 8.5, 6.6, 1.5 Hz, 2H), 1.81–1.59 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.76, 136.88, 131.53, 120.89, 113.32, 51.92, 47.32, 38.31, 32.16, 29.35. HRMS (ESI) m/z: [M+Na]$^+$ calculated for C$_{11}$H$_{17}$NaN$_3$O$_3$S 294.08883; found 294.08805.

Diethyl (E)-(4-(1-(N,N-dimethylsulfamoyl)-1H-imidazol-4-yl)but-3-en-1-yl)phosphonate [NEW] (11b).

Using the general procedure for the cross-metathesis of imidazoles reported above, 1a (50 mg,

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248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and diethyl but-3-en-1-ylphosphonate (1.1 equiv., 52 μL, 273 μmol) were added to a microwave reactor tube (0.5-2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 62% (56 mg, 153 μmol) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, $J = 1.3$ Hz, 1H), 7.05 (d, $J = 1.3$ Hz, 1H), 6.46 (dt, $J = 15.6, 6.8$ Hz, 1H), 6.30–6.25 (m, 1H), 4.23–3.95 (m, 4H), 2.85 (s, 6H), 2.50 (ddt, $J = 9.6, 5.8, 1.6$ Hz, 2H), 1.93–1.83 (m, 2H), 1.32 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.42, 136.80, 131.05, 130.90, 120.79, 113.43, 61.63, 61.58, 38.20, 25.79, 25.75, 24.80, 16.50, 16.45. HRMS (ESI) m/z: [M+Na]$^+$ calculated for C$_{13}$H$_{24}$NaN$_3$O$_5$PS 388.10560; found 388.10720.

Ethyl (*E*)-3-(1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazol-4-yl)acrylate [NEW] (12 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and ethyl acrylate (1.1 equiv., 33 μL, 273 μmol) were added to a microwave reactor tube (0.5-2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated and the crude product was purified by autoflash chromatography. The target compound was obtained in a yield of 59% (40 mg, 146 μmol) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88 (d, $J = 1.0$ Hz, 1H), 7.49 (d, $J = 15.8$ Hz, 1H), 7.36 (d, $J = 1.2$ Hz, 1H), 6.65 (d, $J = 15.7$ Hz, 1H), 4.24 (d, $J = 7.1$ Hz, 2H), 2.88 (s, 6H), 1.31 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 166.88, 139.41, 137.52, 134.09, 119.73, 118.42, 60.50, 38.21, 14.29. HRMS (ESI) m/z: [M+Na]$^+$ calculated for C$_{10}$H$_{15}$NaN$_3$O$_4$S 296.06810; found 296.06776.

(*E*)-*N*,*N*-dimethyl-4-styryl-1*H*-imidazole-1-sulfonamide [2492345-60-3] (13 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and styrene (1.1 equiv., 31 μL, 273 μmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 58% (40 mg, 144 μmol) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (s, 1H), 7.46–7.39 (m, 2H), 7.35–7.24 (m, 3H), 7.22–7.13 (m, 2H), 6.87 (d, $J = 16.1$ Hz, 1H), 2.81 (s, $J = 6.0$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.85, 137.03, 136.87, 130.26, 128.71, 127.85, 126.55, 118.37, 114.48, 38.24.

(*E*)-*N*,*N*-dimethyl-4-(3-phenylprop-1-en-1-yl)-1*H*-imidazole-1-sulfonamide [NEW] (14 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and allylbenzene (1.1 equiv., 36 μL, 273 μmol) were added to a microwave reactor tube (0.5–2 mL) and reacted in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 62% (45 mg, 154 μmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, $J = 1.3$ Hz, 1H), 7.30 (dd, $J = 7.9, 6.9$ Hz, 2H), 7.25–7.18 (m, 3H), 7.05 (d, $J = 1.4$ Hz, 1H), 6.64 (dt, $J = 15.5, 6.8$ Hz, 1H), 6.25 (dt, $J = 15.7, 1.7$ Hz, 1H), 3.54 (dd, $J = 6.8, 1.6$ Hz, 2H), 2.84 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.72, 139.71, 136.73, 131.42, 128.76, 128.50, 126.21, 121.17, 113.31, 39.03, 38.19. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{14}$H$_{18}$N$_3$O$_2$S 292.11197; found 292.11135.

(*E*)-*N*,*N*-dimethyl-4-(4-phenylbut-1-en-1-yl)-1*H*-imidazole-1-sulfonamide [NEW] (15 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol),

Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and but-3-en-1-ylbenzene (1.1 equiv., 41 μL, 273 μmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 58% (44 mg, 144 μmol) as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.86 (d, $J = 1.3$ Hz, 1H), 7.37–7.18 (m, 5H), 7.08 (dd, $J = 7.9, 1.3$ Hz, 1H), 6.56 (dt, $J = 15.7, 6.9$ Hz, 1H), 6.33–6.27 (m, 1H), 2.89 (s, 6H), 2.83 (dd, $J = 9.1, 6.7$ Hz, 2H), 2.57 (dtd, $J = 8.3, 6.9, 1.5$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.82, 141.67, 136.74, 132.01, 128.42, 125.91, 120.54, 113.10, 38.20, 35.55, 34.64. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{15}$H$_{20}$N$_3$O$_2$S 306.12762; found 306.12699.

(*E*)-4-(4-fluorostyryl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide [NEW] (16 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and 4-fluorostyrene (1.1 equiv., 33 μL, 273 μmol) were added to a microwave reactor tube (0.5-2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 55% (40 mg, 135 μmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89 (s, 1H), 7.45 (dd, $J = 8.7, 5.5$ Hz, 2H), 7.33 (d, $J = 16.1$ Hz, 1H), 7.21 (d, $J = 1.4$ Hz, 1H), 7.06–7.01 (m, 2H), 6.85 (d, $J = 16.1$ Hz, 1H), 2.88 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.82, 137.18, 133.20, 129.23, 128.22, 128.16, 118.24, 115.90, 115.73, 114.58, 38.38. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{13}$H$_{15}$FN$_3$O$_2$S 296.08690; found 296.08648.

(*E*)-4-(4-methoxystyryl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide [NEW] (17 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and 4-methoxystyrene (1.1 equiv., 33 μL, 273 μmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 56% (43 mg, 140 μmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88 (d, $J = 1.3$ Hz, 1H), 7.45–7.40 (m, 2H), 7.32 (d, $J = 16.0$ Hz, 1H), 7.18 (d, $J = 1.3$ Hz, 1H), 6.92–6.84 (m, 2H), 6.80 (d, $J = 16.1$ Hz, 1H), 3.82 (s, 3H), 2.88 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.48, 142.13, 136.94, 129.86, 129.66, 127.80, 116.25, 114.16, 113.84, 55.33, 38.24. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{14}$H$_{18}$N$_3$O$_3$S 308.10689; found 308.10640.

(*E*)-*N*,*N*-dimethyl-4-(2-(thiophen-2-yl)vinyl)-1*H*-imidazole-1-sulfonamide [NEW] (18 b). Using the general procedure for the cross-metathesis of imidazoles reported above, **1 a** (50 mg, 248 μmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 μmol), anhydrous 1,2-dichloroethane (0.5 mL) and 2-vinylthiophene (1.1 equiv., 30 mg, 273 μmol) were added to a microwave reactor tube (0.5-2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 58% (41 mg, 145 μmol) as an off-white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89–7.87 (m, 1H), 7.49 (d, $J = 15.8$ Hz, 1H), 7.21–7.17 (m, 2H), 7.09–7.06 (m, 1H), 6.99 (dd, $J = 5.1, 3.5$ Hz, 1H), 6.75 (d, $J = 15.8$ Hz, 1H), 2.88 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.30, 141.40, 137.07, 127.69, 126.67, 124.62, 123.49, 117.84, 114.32, 38.24. HRMS (ESI) m/z: [M+H]$^+$ calculated for C$_{11}$H$_{14}$N$_3$O$_2$S$_2$ 284.05274; found 284.05232.

(*E*)-*N*,*N*-dimethyl-4-(2,4,5-trimethoxystyryl)-1*H*-imidazole-1-sulfonamide [NEW] (19 b). Using the general procedure for the cross-

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metathesis of imidazoles reported above, **1a** (50 mg, 248 µmol), Hoveyda Grubbs Catalyst M720 (H–G II) (10%, 16 mg, 25 µmol), anhydrous 1,2-dichloro-ethane (0.5 mL) and α-asarone (1.1 equiv., 53 µL, 273 µmol) were added to a microwave reactor tube (0.5–2 mL) and immersed in a pre-heated oil bath for 6 h at 120 °C. The post-reaction mixture was evaporated, and the crude product was purified by autoflash chromatography. Target product was isolated in a yield of 50% (46 mg, 125 µmol) as a brown solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, $J = 1.4$ Hz, 1H), 7.57 (d, $J = 16.3$ Hz, 1H), 7.20 (d, $J = 1.4$ Hz, 1H), 7.05 (s, 1H), 6.88 (d, $J = 16.3$ Hz, 1H), 6.52 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 2.87 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 152.08, 149.76, 143.31, 142.73, 136.88, 125.06, 117.65, 117.09, 113.53, 110.09, 97.59, 56.51, 56.10, 38.24. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{22}N_3O_5S$ 368.12802; found 368.12767.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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[32] A factorial design, 2^k, consist of 2^k experiments with experimental levels $(x_1, x_2,…, x_k) = (\pm 1, \pm 1,…, \pm 1)$ where every possible combination of $\pm$ signs is selected in turn. It is convenient for the sake of analysis to list the experiments in standard order, which is obtained by writing alternate–and $+$ sign (low level and high level) in the column headed x1 (or the corresponding actual value as z_1), alternated pairs—,$++$, in the x_2 column, alternated four—,$++++$, in the x_3 column, and so on.
[33] Scaling of the experimental variables z_1 - z_4 were carried out by using equation (1). The scaled low value is set at a value of zlow $=$-1, and the scaled high value was set at value of $z_{high} = +1$.
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