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An Immobilised Grubbs 2nd Generation Catalyst for Application in Flow-Through Devices

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Abstract: An improved immobilised Grubbs 2nd generation catalyst and its application in flow-through devices, shown for on-column reaction gas chromatography (ocRGC), has been studied. The coupling of a reaction capillary and a separation column in GC/MS allows direct reaction monitoring and analysis of conversion as well as reaction kinetics. The presented permanently bonded N-heterocyclic carbene ligand shows a great stability and activity in ring closing metathesis reactions. A salt-free approach was used to generate the carbene ligand, which can be directly monitored by mass spectrometry. The very flexible design of the immobilised ligand system in reaction channels and capillaries of flow through systems allows the preparation of various catalysts using a broad variety of metal precursors. This strategy of immobilised catalytically active complexes offers a wide range of on-column reactions combinable with fast reaction screening by high throughput experimentation.

Keywords: carbene ligands; heterogeneous catalysis; high throughput screening; homogeneous catalysis; metathesis

Recent developments in organic synthesis verify the important role of homogeneous catalysis.[1] Yet, it is still challenging to completely remove the catalyst from the reaction solution. In particular this can trigger manifold problems, when the remaining catalytic complex causes undesirable side reactions, for example, decomposition of the product.[2] These difficulties can be solved using immobilised ligands and complexes. For example, permanently bonded ruthenium-based catalysts are highly active in metathesis reactions and show great stability in addition to the desired recyclability.[3] Metathesis catalysts containing N-heterocyclic carbene (NHC) ligands[4] show an even higher level of thermal and air stability compared to phosphine ligands.[5] Many groups have investigated strategies for immobilisation of the Grubbs catalysts of the second and third generations.[6] There are various known routes to obtain a polymer bonded ligand system.[7] Barrett et al., for example, immobilised the Grubbs 2nd generation catalyst on vinyl modified polystyrene *via* the alkylidene group.[8] The results of the ring closing metathesis studies show that the activity of the immobilised catalyst is independent of the polymeric support, combining with the benefits of a reusable catalytic system.[6]

Here we have realized the concept of a polymer-bonded NHC precursor, which is permanently immobilised on a fused silica micro capillary and therefore suitable for application in flow-through devices, which is demonstrated in the present contribution for on-column reaction gas chromatography (ocRGC).[9] Like we have demonstrated in several studies hitherto, this concept of integrating catalytic activity and separation selectivity in a single chromatographic micro reactor system offers the opportunity of reliable reaction screening under constant and defined reaction conditions.[10,11] The here introduced ligand system can easily be converted into a metathesis catalyst based on the structural design of the Grubbs 2nd generation catalyst. This mode of solid-state homogeneous catalysis opens an easy access to an improved reaction screening system, which is not limited to a particular catalyst but allows the screening of NHC ligand-based catalysts.

The immobilisable pre-ligand was prepared by using the common strategy introduced by Blechert et al. which establishes the modification of the NHC backbone.[12] The advantage of this approach is that the steric and electronic properties[13] of the chemical environment of the carbene adjacent to the active metal centre are not affected. As shown in Figure 1 we started with the *N*,*N*-dimesityl-2,3-diaminopropane

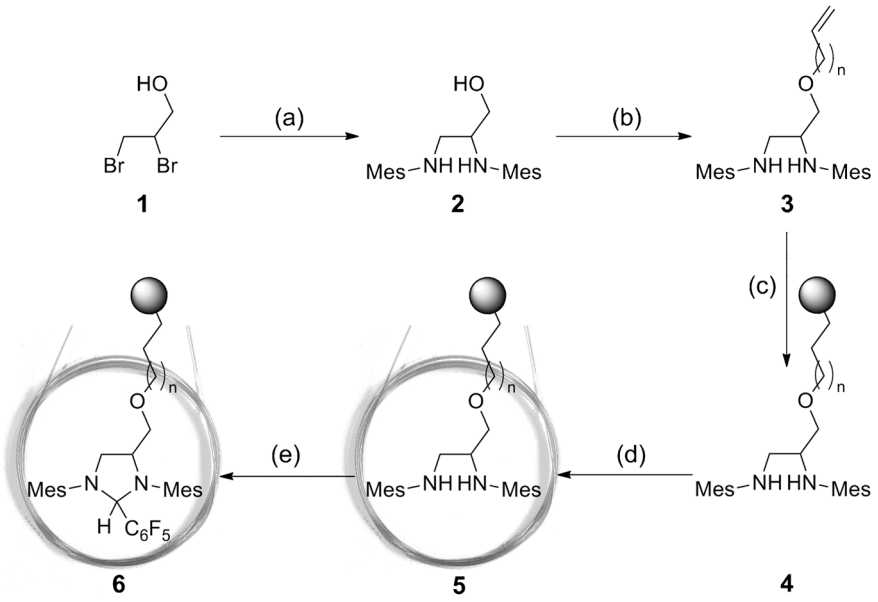

Figure 1. Synthesis of the permanently immobilised diamine ligand **5** and conversion into the immobilised 1,3-dimesitylated imidiazolidine-type carbene precursor **6**. (a) 2,4,6-Trimethylaniline, 120 °C, 15 h. (b) NaH, ω-bromoalkene ($n = 1, 4, 6$), 78 °C, 20 h. (c) Hydridomethyldimethylpolysiloxane (HMPS), Karstedt's catalyst, THF, sonication, 3 h ($n = 1, 4, 6$). (d) Fused silica capillary (i.d. 250 μm). (e) Pentafluorobenzaldehyde, AcOH, THF, room temperature, 20 h.

2 to introduce alkene chains with variable spacer lengths to investigate the influence of the linker in the on-column reaction gas chromatographic set-up, used as a precise flow-through device.

Compound **2** was prepared starting with the commercially available reactants 2,3-dibromo-1-propanol **1** and 2,4,6-trimethylaniline.[14] The reaction of **2** with NaH and an ω-bromoalkene results in the isolation of the etherified product **3**. Afterwards the modified diamine **3** reacts with hydridomethyldimethylpolysiloxane (HMPS) using Karstedt's catalyst by hydrosilylation to give the immobilised precursor **4**.

Here we present an improved synthetic protocol for the immobilisation reaction of the ligand **3** with the polymer HMPS.[15] It is quite challenging to obtain a polymer with a proper concentration of remaining Si–H groups, which are required for permanent attachment to the fused silica surface *via* Si–OH groups of chips and fused silica capillaries, low enough to avoid unintended reduction of the later introduced metal ion to form the catalytically active (precursor) complex. We optimised the reaction time and conditions by systematic ^{1}H NMR investigations (cf. the Supporting Information, Figure S9), providing reasonable certainty that a sufficient amount of Si–H groups are remaining for a permanent immobilisation on the inner surface of the fused silica capillary *via* a condensation reaction with surface silanol groups. To achieve a permanent immobilisation the fused silica capillary containing the ligand system was heated to 190 °C at a rate of 0.5 K min^{-1} and maintained at this temperature for 62 h under a very slow and constant nitrogen flow. Cyclisation of the bonded diamine **5** with pentafluorobenzaldehyde afforded 2-(pentafluorophenyl)-imidazolidine **6**.[16] At this stage we took advantage of solid-phase chemistry using the derivatisation reagent in great excess to achieve complete conversion. In that respect the capillary was flushed with a solution of the pentafluorobenzaldehyde in tetrahydrofuran. We used a syringe pump with a speed rate of 0.25 mL h^{-1} to accomplish the formation of the desired carbene precursor on-column. Former studies discussed the advantages to create a carbene *via* thermal activation in comparison with the use of a strong base to convert the corresponding imidazolium salt into the carbene. It was also shown that the combination of a strong base and remaining Si–H groups in the polymer will lead to the decomposition of the ligand system.[17] Therefore a salt-free route was chosen.

Finally the fused silica capillary coated with the permanently bonded imidazolidine **6** was coated once again with a solution of the Grubbs 1st generation catalyst in *n*-pentane to obtain the immobilised Grubbs 2nd generation catalyst **7**. The on-column ligand exchange reaction can be controlled by GC/MS. Here, the *in situ* formation of the carbene was monitored by continuous analysis of the generated pentafluorobenzene upon application of a temperature programme to the coated capillary installed in a GC/MS (Figure 2).

Therefore the capillary is heated from 40 °C to 80 °C with a rate of 4 K min^{-1}. The reaction starts after 15 min at a temperature of about 55 °C as shown

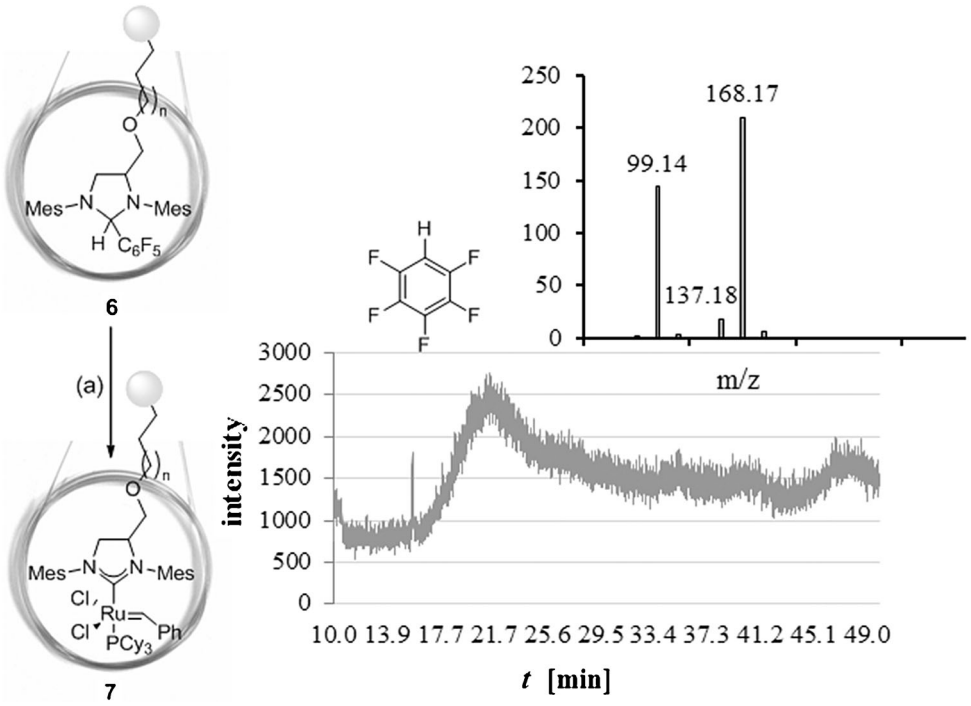

Figure 2. Mass spectrometric reaction control of the on-column ligand exchange by *in situ* carbene formation to achieve a permanently immobilised Grubbs 2nd generation catalyst **7**. (a) $(PCy_3)_2Cl_2Ru{=}CHPh$, *n*-pentane.

by recording the mass trace (Figure 2). The characteristic MS (EI) fragmentation pattern of pentafluorobenzene ($m/z = 168$ Da) confirms the successful formation of the free carbene. Dissociated tricyclohexylphosphine (PCy_3), formed by the ligand exchange with the Grubbs 1st generation catalyst was not detected. This fact leads to the conclusion that the phosphine remains on the fused silica column. It will be dissolved in the polymer and supports the stabilization of the resting state of the immobilised catalyst **7**.[18]

The synthesised and immobilised ligand system was used to investigate the influence of the spacer length to ensure a sufficient flexibility of the ligand by reduced interactions with the polymeric backbone.[19] We studied the system in the ring closing metathesis of *N*,*N*-diallyltrifluoroacetamide **8**. The catalytically active column (length = 50 cm) was installed between a pre-separation and a separation column in the GC/MS. This set-up offers an *in situ* reaction monitoring of the ring closing metathesis of **8** injected onto this column arrangement. Figure 3 gives an overview of the examined diamine **3** in relation to the different linker lengths ($n = 1$, 4, 6). It can be shown that the activity of the immobilised catalyst system strongly depends on the length of the spacer. We observed under these reaction conditions with relatively short contact times a maximum turnover of about 40%. These high reaction rates are observed using the ligand system **3b** (at 80 °C with $n = 4$) and **3c** (at 60 °C with $n = 6$).

In contrast to these results the allyl linker system **3a** ($n = 1$) shows a turnover of only 4% under these reaction conditions and is therefore not the first choice to be used to coat columns for flow-through experiments. In addition there is no observable temperature influence on the NHC complex **3a**.

For the ring closing metathesis the ligand system **3b** with a spacer length $n = 4$ affords the best results due to a sufficient flexibility and minimised *gauche* interactions with the polymeric framework.[20] Next we examined the turnover depending on the length of the reaction capillary, which decreases on shortening as would be expected due to the reduced contact time. However, the 10 cm long catalyst column still shows a yield of about 7% in the mentioned ring closing metathesis, which demonstrates the great activity of the here presented system. It features stable measurements over a period of 24 h as well as a wide temperature range (up to 150 °C!) and emphasises the great reproducibility in the here presented study. These temperature and long-term stabilities are remarkable characteristics of the here presented material, which exceed by far those of the commonly used homogeneous system. We can explain this by three factors: (i) the catalytic centres are well separated by the here employed polysiloxane avoiding metal-metal interactions, (ii) the polymeric matrix stabilises the catalyst and prevents oxidative decomposition by traces of air,

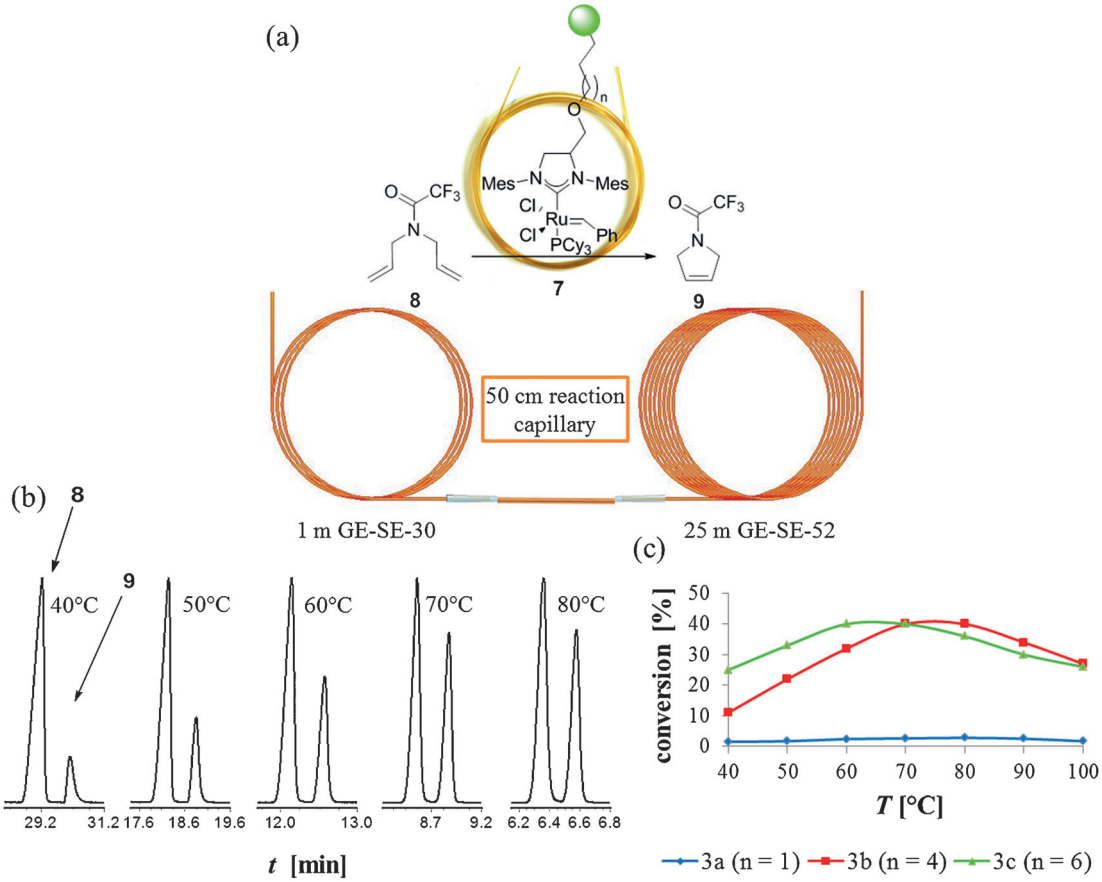

Figure 3. (a) Experimental set-up: the reaction capillary is coupled between a pre-separation column (1 m, GE-SE-30) and a separation column (25 m, GE-SE-52). (b) Elution profiles between 40 °C and 80 °C of the ocRGC ring closing metathesis experiment using *N*,*N*-diallyltrifluoroacetamide **8** as model substrate (first eluted peak) converted to *N*-trifluoroacetamide-3-pyrroline **9** (second eluted peak) using the catalyst column **7b** ($n=4$). Helium was used as carrier gas ($p=80$ kPa). (c) Turnover of the on-column ring closing metathesis of *N*,*N*-diallyltrifluoroacetamide in dependence on the length n of the linker and the temperature T ($p=80$ kPa helium).

and (iii) the remaining tricyclohexylphosphine (PCy_3) acts as stabiliser[18] and oxygen scavenger.

We determined the activation parameters for the ring closing metathesis of *N*,*N*-diallyltrifluoroacetamide **8** on the basis of a permanently immobilised Grubbs 2nd generation catalyst **7** with an optimised spacer length ($n=4$).

Temperature-dependent measurements between 40 and 80 °C were used to calculate these parameters (Figure 4):[9a] $\Delta G^{\neq}$ (298 K) = 89.3 kJ mol^{-1}, $\Delta H^{\neq}$ = 62.5 ± 5.1 kJ mol^{-1} and $\Delta^{\neq} = -89 \pm 13$ J mol^{-1} K^{-1}. Reaction temperatures above 40 °C are necessary for the elution of reactants and products. The negative value of $\Delta S^{\neq}$ refers to a highly ordered transition state. To classify the determined parameters we studied the on-column metathesis reaction of *N*,*N*-diallyltrifluoroacetamide **8** using Grubbs 1st and 2nd generation catalysts as well as the Grubbs–Hoveyda catalyst. These complexes were dissolved in dimethylpolysiloxane and coated onto the inner surface of micro capillaries by the static method introduced by Grob.[11,21] The resulting activation energies of the on-column measurements are summarised in Table 1.

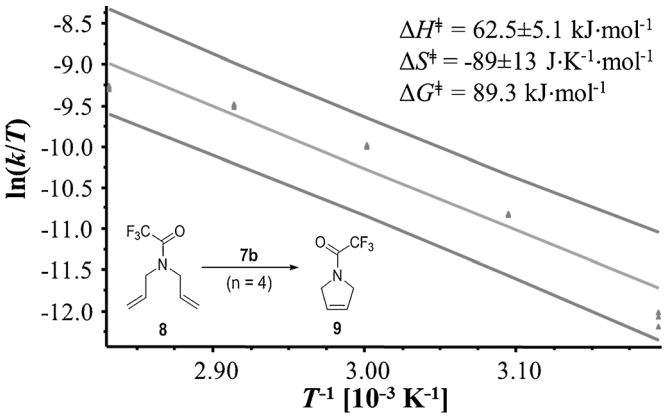

Figure 4. Eyring plot to determine activation parameters of the on-column ring closing metathesis of *N*,*N*-diallyltrifluoroacetamide **8** using the Grubbs catalyst column **7b** ($n=4$).

Table 1. Results of the on-column gas chromatographic ring closing metathesis of *N,N*-diallyltrifluoroacetamide **8** using different Grubbs-type catalysts. Gibbs activation energy $\Delta G^{\neq}$ is determined at 25 °C.

Catalyst[a]	k[b] [10^{-3} s^{-1}]	$\Delta G^{\neq}$ [kJ mol^{-1}]	$\Delta H^{\neq}$ [kJ mol^{-1}]	$\Delta S^{\neq}$ [J mol^{-1}·K^{-1}]
Grubbs 1st	7.6	83.2	18.3 ± 1.2	−218 ± 29
Grubbs 2nd	4.8	90.2	24.9 ± 0.7	−219 ± 17
Grubbs–Hoveyda	0.6	92.7	39.6 ± 0.7	−178 ± 22
7b	6.4	89.3	62.5 ± 5.1	−89 ± 13

[a] Grubbs 1st and 2nd generation catalysts as well as Grubbs–Hoveyda catalyst were dissolved in polysiloxane GE-SE-30;[11] catalyst **7b** ($n=4$) was immobilised on hydridomethyldimethylpolysiloxane.

[b] Reaction rate constants reported at 50 °C and 80 kPa helium.

The determined Gibbs activation energy $\Delta G^{\neq}$ of catalyst **7b** ($n=4$) is comparable with the dissolved Grubbs 2nd generation catalyst (Table 1). The activation energy is about 6 kJ mol^{-1} higher than for the dissolved Grubbs 1st generation catalyst used in on-column metathesis reactions. These experimentally determined data are in very good agreement with previously performed measurements and are also in accordance with experimental findings by Grubbs et al.[18] Additionally the observed reaction rate constants using the permanently immobilised system **7b** ($k=6.4\cdot10^{-3}$ s^{-1}) are in agreement to reported results obtained by NMR experiments of Grubbs et al. ($k=1.0\cdot10^{-3}$ s^{-1}) and the given data of the dissolved catalysts in Table 1. The higher activation barrier of the Grubbs–Hoveyda catalyst indicates a slower initiation, which is also in accordance with NMR studies.[22]

In conclusion, we have developed an advanced and reproducible synthetic protocol for the permanent immobilisation of Grubbs 2nd generation catalyst onto the inner surface of reaction channels and provided enhanced insights into the kinetics of flow-through reaction systems. We can assume that using permanently immobilised ligand systems coated onto the inner surface of fused silica capillaries offers a high potential for kinetic characterisation of catalytic reactions,[23] in particular for NHC-carbene ligands, which require tedious and time-consuming synthetic steps to prepare sufficient material for classic reaction screening schemes. In our set-up the free carbene ligand can be easily thermally generated and monitored, and we are able to build bonded catalysts with various metal precursors by on-column ligand exchange. This advantage could open the access to a broad variety of flow-through catalytic processes which can be analysed in high-throughput measurements to kinetically evaluate these catalysts and to elucidate reaction mechanisms.

Experimental Section

N,N'-Dimesityl-2,3-diamino-1-propanol (2)

A solution of 2,3-dibromopropan-1-ol (2.36 mL, 23.0 mmol, 1.00 equiv.) and 2,4,6-trimethylaniline (8.36 mL, 60.0 mmol, 2.60 equiv.0) was stirred for 15 h at 120 °C. Afterwards 400 mL of 1.7 M NaOH and 400 mL of dichloromethane were added. The organic layer was separated, washed with distilled water and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, *n*-pentane/diethyl ether, v/v 3:1) to afford a colourless, crystalline solid: yield: 5.52 g (16.9 mmol, 74 %). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.20$–2.42 (m, 18 H, Ar-CH_3), 3.05 (dd, $^2J_{H,H}=11.9$ Hz, $^3J_{H,H}=4.3$ Hz, 1 H, NH-CH_2-), 3.31 (dd, $^2J_{H,H}=12.0$ Hz, $^3J_{H,H}=5.2$ Hz, 1 NH-CH_2-), 3.41–3.56 (m, 1 H, NH-C*H*-), 3.71 (br. s, 3 H, N*H*, O*H*), 3.80–3.91 (m, 1 H, -CH_2-OH), 3.91–4.04 (m, 1 H, -CH_2-OH), 6.89 (d, $^4J=5.0$ Hz, 4 H, Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C, TMS): $\delta=17.7$, 18.7, 20.3, 20.4, 51.7, 56.9, 65.1, 128.7, 129.4, 129.6, 130.2, 130.6, 132.0, 141.6, 142.5; HR-MS: $m/z=327.2432$, calcd. for $C_{21}H_{30}N_2O$ [M + H$^+$]: 327.2436.

General Procedure for the Synthesis of the Immobilisable Diamine Ligands 3

Sodium hydride (2.0 equiv.) was suspended in anhydrous tetrahydrofuran at 0 °C. A mixture of 1.0 equiv. *N,N'*-dimesityl-2,3-diamino-1-propanol **2** in anhydrous tetrahydrofuran was added dropwise and the solution was allowed to stir for 30 min at 0 °C. Afterwards 1.1 equiv. ω-bromoalkene, dissolved in anhydrous tetrahydrofuran was added dropwise. The mixture was refluxed for 20 h under stirring. Subsequently it was quenched with a saturated solution of NH_4Cl, extracted with *n*-pentane and washed with distilled water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure.

1-(Allyloxy)-*N,N'*-dimesityl-2,3-diamino-1-propanol (3a): The general procedure was used for the synthesis of **3a**. The crude product was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, v/v 9:1) to obtain a yellow oil; yield: 2.93 g (8.00 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.25$–2.42 (m, 18 H, Ar-CH_3), 3.13 (dd, $^2J_{H,H}=11.9$ Hz, $^3J_{H,H}=6.0$ Hz, 1 H, NH-CH_2-), 3.39 (dd, $^2J_{H,H}=11.8$ Hz, $^3J_{H,H}=5.6$ Hz, 1 NH-CH_2-), 3.45–3.53 (m, 1 H, NH-C*H*-), 3.54–3.82 (m, 4 H, N*H*, -CH_2-O-), 4.02 (dd, $^2J_{H,H}=5.5$ Hz, $^3J_{H,H}=1.4$ Hz, 2 H, -O-CH_2-), 5.16–5.43 (m, 2 H, -CH=CH_2), 5.87–6.06 (m, 1 H, -C*H*=CH$_2$), 6.90 (s, 4 H, Ar-*H*); ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C, TMS): $\delta=18.2$, 18.7, 20.4, 20.5, 50.8, 56.5, 70.6, 72.1, 116.9, 129.2, 129.3, 129.5, 129.8, 140.7, 131.2, 134.7, 141.6, 143.5; HR-MS: $m/z=367.2745$, calcd. for $C_{24}H_{34}N_2O$ [M + H$^+$]: 367.2749.

1-(Hex-5-en-1-yloxy)-*N,N'*-dimesityl-2,3-diamino-1-propanol (3b): The general procedure was used for the synthesis of **3b**. The crude product was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, v/v 9:1) to obtain a yellow oil; yield: 1.67 g (4.09 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.42$–1.58 (m, 2 H, -CH_2-), 1.59–1.72 (m, 2 H, -CH_2-), 2.07–2.14 (m, 2 H, -CH_2-), 2.22–2.46 (m, 18 H, Ar-CH_3), 3.06 (dd, $^2J_{H,H}=11.8$ Hz, $^3J_{H,H}=5.8$ Hz, 1 H, NH-CH_2-), 3.62–3.49 (m, 4 NH-CH_2-, NH-C*H*-,

-O-CH_2-), 3.52–3.54 (m, 4H, NH, -CH_2-O-), 4.93–5.18 (m, 2H, -CH=CH_2), 5.87–5.90 (m, 1H, -CH=CH$_2$), 6.85 (d, ^4J = 3.9 Hz, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C, TMS): δ = 18.3, 18.7, 20.5, 25.4, 29.1, 33.5, 50.8, 56.5, 71.1, 71.2, 114.6, 129.2, 129.4, 129.5, 129.8, 130.6, 131.2, 138.5, 141.7, 143.5; HR-MS: m/z = 409.3214, calcd. for $C_{27}H_{40}N_2O$ [M+H$^+$]: 409.3219.

1-(Oct-7-en-1-yloxy)-*N*,*N*'-dimesityl-2,3-diamino-1-propanol (3c): The general procedure was used for the synthesis of **3c**. The crude product was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, v/v 9:1) to obtain a yellow oil; yield: 3.04 g (6.97 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24–1.51 (m, 6H, -CH_2-), 1.53–1.67 (m, 2H, -CH_2-), 2.05–2.09 (m, 2H, -CH_2-), 2.19–2.51 (m, 18H, Ar-CH_3), 3.07 (dd, $^2J_{H,H}$ = 11.8 Hz, $^3J_{H,H}$ = 5.9 Hz, 1H, NH-CH_2-), 3.25–3.47 (m, 4H, NH-CH_2-, NH-CH-, -O-CH_2-), 3.53 (m, 2H, -CH_2-O-), 4.84–5.22 (m, 2H, -CH=CH_2), 5.70–5.96 (m, 1H, -CH=CH$_2$), 6.85 (d, ^4J = 4.4 Hz, 4H, Ar-H); ^{13}C NMR (126 MHz, $CDCl_3$, 23 °C, TMS): δ = 18.3, 18.7, 20.5, 26.1, 28.8, 28.9, 29.7, 33.7, 50.8, 56.5, 71.1, 71.4, 114.2, 129.5, 129.7, 130.7, 131.2, 139.0, 141.7, 143.5; HR-MS: m/z = 437.3527, calcd. for $C_{29}H_{44}N_2O$ [M+H$^+$]: 437.3532.

General Procedure for the Immobilised Diamine Ligand 4

Hydridomethyldimethylpolysiloxane (HMPS, 1.0 equiv., 10.2% Si–H groups) and 0.10 equiv of the substrate **3** were dissolved in anhydrous tetrahydrofuran and 10 μL of Karstedt's catalyst (2% by weight of platinum in xylene) were added. The mixture was stirred in an ultrasonic bath for 3 h at room temperature. The solvent was removed under reduced pressure and the residue passed through a short silica column (dichloromethane/methanol, v/v 20:1). The solvent was evaporated to give a pale yellow oil; yield: quantitative.

Coating of Fused Silica Columns

The immobilised compound **4** (24.0 mg) was dissolved in 3.00 mL anhydrous diethyl ether for use as coating solution. Capillaries were coated by the static method of Grob.[21] The fused silica column (i.d. 250 μm) was coated with this solution giving a 500 nm film at the inner wall of the capillary. Immobilisation was achieved in a stream of nitrogen using a temperature programme starting at 40 °C for 10 min, then heating up to 190 °C for 62 h at the rate of 0.5 K min^{-1}.

Preparation of the Ring Closing Metathesis Column

Pentafluorobenzaldehyde (30.0 mg) was dissolved in anhydrous tetrahydrofuran (5.00 mL) and mixed with a catalytic amount of acetic acid. A 1 m fused silica capillary **5** was rinsed with this solution at the rate of 0.25 mL h^{-1}. Afterwards the capillary was rinsed with anhydrous tetrahydrofuran (2.00 mL) at the rate of 1.00 mL h^{-1} and flushed with argon. In the next step Grubbs 1st generation catalyst (2.0 mg) was dissolved in absolute *n*-pentane (4.00 mL). The capillary was coated with this solution by the static method of Grob.[21] The ligand exchange was achieved by using a temperature programme starting at 40 °C for 10 min, then heating up at 80 °C for 30 min at the rate of 4 K min^{-1}. Helium was used as carrier gas (p = 120 kPa).

On Column Ring Closing Metathesis Measurements

Ring closing metathesis experiments of the *N*,*N*-diallyltrifluoroacetamide were performed by on-column reaction gas chromatography. The catalyst capillary was coupled between a pre-separation column, coated with GE-SE-30 (1 m, i.d. 250 μm, 500 nm film thickness) and a separation column, coated with GE-SE-52 (25 m, i.d. 250 μm, 250 nm film thickness). Helium was used as carrier gas (p = 80 kPa).

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