Highly Active Silica Gel-Supported Metathesis (Pre)Catalysts

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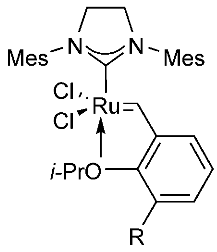
Abstract: Highly active Hoveyda–Grubbs and Hoveyda–Blechert type (pre)catalysts, immobilized on silica gel, are presented. These (pre)catalysts are synthesized in a few steps from readily available precursors and demonstrate high activity in a number of test metathesis reactions. The catalyst is easily separated by simple filtration of the non-swelling material.

Keywords: alkenes; immobilization; metathesis; ruthenium; silica gel; supported catalysts

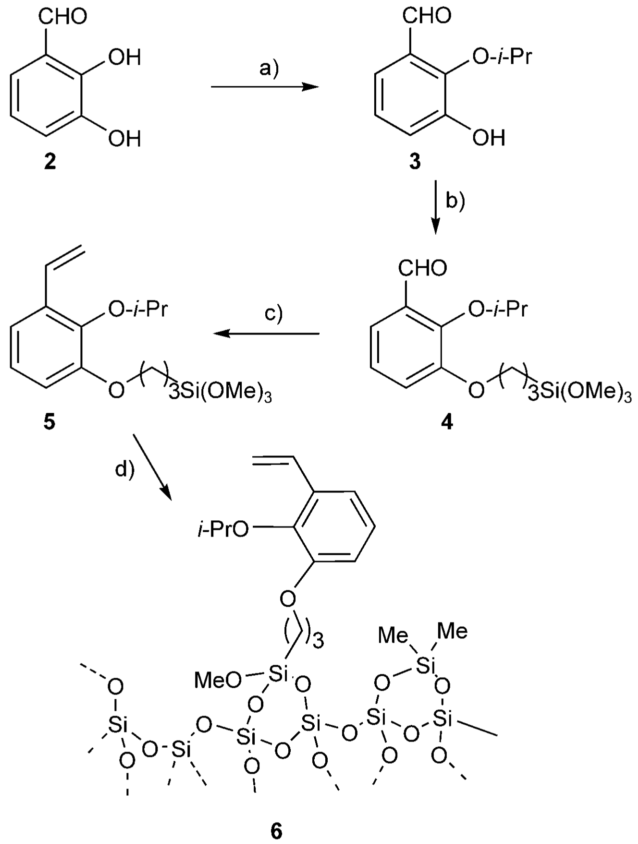
Since the development of commercially available Grubbs[1] and Grubbs–Herrmann[2] catalysts, olefin metathesis has emerged as a standard reaction in organic chemistry.[3] Further developments within this group and by others have led to more stable derivatives of these complexes containing a chelating isopropoxybenzylidene ligand.[4] These Hoveyda–Blechert type complexes have the advantage of increased stability over their phosphine-containing counterparts, whilst retaining functional group tolerance and are even purifiable by silica gel chromatography. Immobilized variants of these complexes have been developed and combine the functional group tolerance of homogeneous systems, with the possibility of recyclability and the advantage of simple work-up.[5] However, these supported systems are generally immobilized on organic polymers which typically suffer from a number of disadvantages including diffusion-related disadvantages[6] or the requirement for the addition of solvent for precipitation of the soluble carrier.[7]

Therefore, supported metathesis (pre)catalysts which are easily separated by simple filtration are highly desirable.

Previous work from our group[8] and others[9] has shown that different substitution on the chelating *o*-isopropoxystyrene can greatly influence catalyst activity. In particular, introduction of steric bulk at the *ortho* position has led to some of the fastest initiating (pre)catalysts developed to date (**1a**/**1b**).[10] It was envisaged that this increase of activity could be coupled with im-



1a: R = Ph
1b: R = OMe



Scheme 1. a) i) Ac_2O, AcOH, reflux, 12 h; ii) *i*-PrBr (7 equivs.), K_2CO_3 (2 equivs.), N_2, DMF, 50 °C, 12 h; iii) NaOMe, MeOH, yield 43% (over 3 steps); b) (3-iodopropyl)-trimethoxysilane (0.7 equivs.), NaH, DMF, N_2, 0 °C, 1 h, 30%; c) Ph_3PCH_3Br (2 equivs.), KO-*t*-Bu (1.9 equivs.), Et_2O, 0 °C, 10 min, 70%; d) i) silica gel, toluene, N_2, 80 °C, 12 h, 62%; ii) dimethoxydimethylsilane, 80 °C, 12 h.

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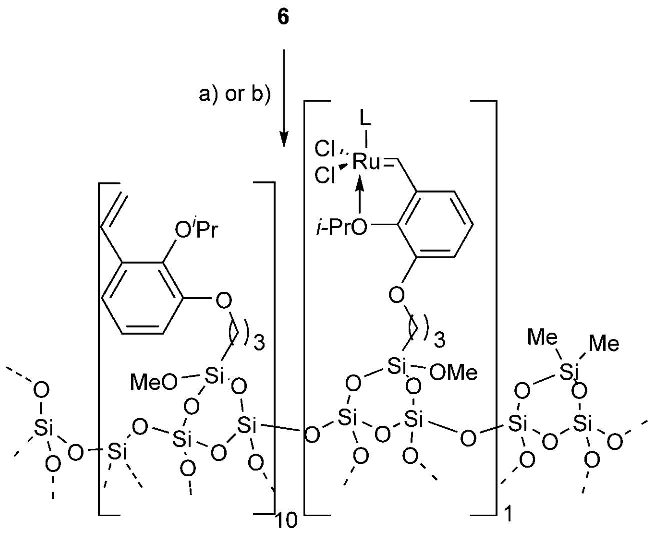
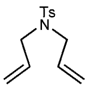
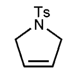
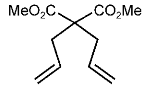
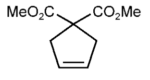
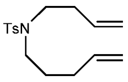
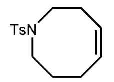
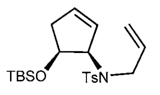
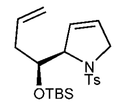
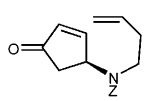
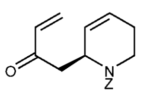
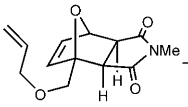
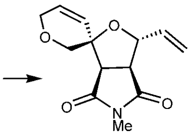
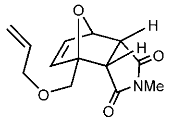
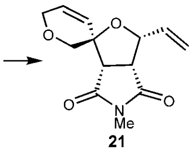
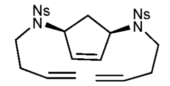
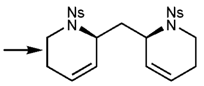
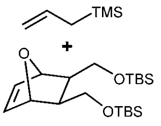
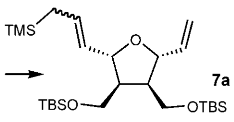


7a: L = IH_2Mes
7b: L = PCy_3

Scheme 2. a) Grubbs–Herrmann catalyst (0.1 equiv.), CuCl (0.1 equiv.), CH_2Cl_2, N_2, 45 °C, 3 h, loading 33.6 μmol/g; b) Grubbs catalyst (0.1 equiv.), CH_2Cl_2, N_2, 45 °C, 3 h, loading 17.4 μmol/g

Table 1. Metathesis reactions with **7a**/**7b**.

Substrate	Product	Conditions[a]	Yield
 **8**	 **9**	**7a** (1%, 1 h) **7b** (0.5%, 3 h)	>99%[b] >99%[b]
 **10**	 **11**	**7a** (1%, 2 h) **7b** (0.5%, 20 h)	79%[b] >99%[b]
 **12**	 **13**	**7a** (1%, 3 h) **7b** (0.5%, 20 h)	89%[b] >99%[b]
 **14**	 **15**	**7a** (1%, 4 h)	>99%[b]
 **16**	 **17**	**7a** (1%, 1 h)	40%[c]
		Z = benzyloxycarbonyl	
 **18**	 **19**	**7a** (1%, 1 h)	95%[c]
 **20**	 **21**	**7a** (1%, 1 h)	92%[c]
 **22**	 **23**	**7a** (1%, 1 h)	>99%[b]
		Ns = 2-nitrobenzenesulfonyl	
 **24**	 **25**	**7a** (1%, 0.5 h)	>99%[c]

[a] Conditions: 0.05 M, CH_2Cl_2, N_2, 25 °C.

[b] Determined by HPLC.

[c] Determined by ^1H NMR.

mobilization on silica gel to afford a highly active, filterable (pre)catalyst.

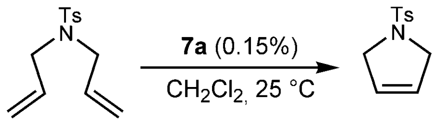
Styrene **5** required for immobilization, was readily synthesized starting from catechol **2**. Selective monoacylation, isopropylation and deprotection of the acetate furnished the desired *o*-isopropyl ether **3** in good overall yields. Alkylation with (3-iodopropyl)trimethoxysilane afforded aldehyde **4** which was purified by kugelrohr distillation. Subsequent Wittig olefination and purification through a short pad of silica gel afforded **5** in high purity in an overall yield of 9%.

The styrene **5** was immobilized on LiChroprep Si 60® 40–63 μm and 25–40μm[11] by heating a mixture of 1 g of silica gel per 1 mmol of **5** in toluene to give a loading of 0.63 mmol/g. The ligand concentration on the surface of the silica gel was determined by quantitative measurement of remaining **5** by ^1H NMR against stilbene as internal standard. The free Si-OH groups were subsequently capped with dimethoxydimethylsilane before immobilization of the (pre)catalyst.

In the condensation of trialkoxysilanes on silica gel the connection can be achieved by one, two or even three bonds. It is know that two bonds dominate so we assume **6** to be the structure of the functionalized silica gel.[12]

By refluxing the Grubbs–Herrmann catalyst[2] with 1 equivalent CuCl in dichloromethane with the functionalized silica gel in a ratio of 10:1 to the immobilized ligand, the immobilized (pre)catalyst was isolated, following filtration and drying as a stable green-colored silica gel **7a**, with a loading of 0,034 mmol/g.[13] The product showed good stability on storing at +4 °C under nitrogen over two weeks without any sign of decomposition. When quantitative loading of the styrene with ruthenium was achieved the (pre)catalyst decomposed within days at −20 °C. Synthesis of **7b** was achieved in a similar manner by reacting the Grubbs catalyst[1] to afford a brown-colored silica gel with 0.017 mmol/g active (pre)catalyst.

Table 2. Recycling with 0.15% immobilized catalyst **7a**.



8 **9**

Run	Time	Conversion[a]	Ru-residue[b, c]
1	1 h	>99%	32 ppm
2	1 h	93%	12 ppm
3	1 h	68%	6 ppm
4	12 h	76%	12 ppm

[a] Determined by HPLC.

[b] Without purification.

[c] Determined by TXRF[15] (±15%).

(Pre)catalyst **7a** was tested in a variety of metathesis reactions and the results are summarized in Table 1. The particle size of the carrier had no effect on the activity and work-up was accomplished by simple filtration with an average ruthenium residue corresponding to 65 ppm (±15%).

Cyclization of **8** catalyzed by **7a** at room temperature was completed within one hour, but as can be seen by the cyclization of **10** and **12**, just 0.5% of catalyst **7b** was much more effective for the other two RCM reactions attempted, albeit with a significantly lower turnover frequency. Afterwards **7a** was tested in ROM-RCM, RCM-ROM-RCM and ROM-CM sequences, where conversion in general was excellent. An exception is the transformation of **16** to **17**, which reached an equilibrium at 40%, an effect also seen with homogeneous catalysts.[14]

After we had proven the metathesis capability of **7a**, we were interested in its reusability. Most often immobilized metathesis (pre)catalyst are used with 5 mol % of the ruthenium complex. In our opinion this loading is much too high and does not give reliable information on reusability. Therefore a loading of 0.15% was chosen and the results are given in Table 2.

Full conversion of **8** was achieved again within 1 hour and after filtration the next RCM run was filtered again after 1 hour and showed 93% conversion. The conversion dropped off significantly for the third run after 1 hour, but by increasing the reaction time in the forth run it was possible to achieve a respectable conversion. Ruthenium contamination of the products were measured by TXRF, and in all cases were significantly lower than previous reports of metathesis following silica gel chromatography.[15]

The presented heterogeneous ruthenium complex is a highly active metathesis catalyst. Standard silica gel was functionalized within a few steps, immobilization of the ruthenium complex has been achieved and the catalyst is easily separated from the reaction mixture by simple filtration. In different test reactions the silica gel immobilized catalysts **7a** and **7b** reached high conversion with just 1% or, respectively, 0.5% ruthenium and showed higher activity than the parent Grubbs catalyst.

Experimental Section

2-Isopropoxy-3-propyl-(3-trimethoxysilyl)-benzaldehyde (4)

Under N_2 compound **3**[3i] (3 g, 16.6 mmol) was placed in dry DMF and treated with NaH (380 mg, 15.8 mmol). After 30 minutes (3-iodopropyl)trimethoxysilane (2.15 mL, 11.0 mmol) was added at 0 °C. After 30 minutes at room temperature the reaction mixture was treated with saturated aqueous K_2CO_3 and extracted with Et_2O. The organic layer was washed with saturated aqueous K_2CO_3/NaCl, dried over $MgSO_4$ and purified by kugelrohr distillation; yield: 1.1 g (30%); ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 10.45$ (s, 1H), 7.46 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz, 1H), 7.13–7.04 (m, 2H), 4.66 (sep, $J = 6.2$ Hz, 1H), 3.99 (t, $J = 6.5$ Hz, 2H), 3.59 (s, 9H), 1.96 (tt, $J_1 = 8.2$ Hz, $J_2 = 6.5$ Hz, 2H), 1.33 (d, $J = 6.2$ Hz, 6H), 0.84–0.78 (m, 2H); ^{13}C NMR (126.3 MHz, $CDCl_3$): $\delta = 191.1$ (d), 152.7 (s), 150.8 (s), 131.0 (s), 123.7 (d), 118.92 (d), 118.90 (d), 76.2 (d), 70.8 (t), 50.7 (q, 3C), 22.8 (t), 22.4 (q, 2C), 5.5 (t); IR (film): $\nu =$ 2974, 2943, 2842, 1748, 1687, 1582, 1085 cm^{-1}; MS (70 eV): *m/z* (%) = 342 (5) [M$^+$], 121 (100), 163 (29), 226 (36).

2-Isopropoxy-1-propyl-(3-trimethoxysilyl)-3-vinylbenzene (5)

Under N_2 Ph_3PCH_3Br (1.4 g, 3.84 mmol) was placed in Et_2O at −10 °C and KO-*t*-Bu (393 mg, 3.50 mmol) was slowly added. After 30 minutes **4** (600 mg, 1.75 mmol) was slowly added and stirred for 15 minutes. The organic layer was washed with saturated aqueous K_2CO_3/NaCl, dried over $MgSO_4$ and filtered over a pad of silica gel; yield: 418 mg (70%); ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 7.15$–7.06 (m, 2H), 6.97 (t, $J = 7.9$ Hz, 1H), 6.82–6.78 (m, 1H), 5.69 (dd, $J_1 = 17.8$ Hz, $J_2 = 1.1$ Hz, 1H), 5.24 (dd, $J_1 = 11.1$ Hz, $J_1 = 1.1$ Hz, 1H), 4.45 (sept, $J = 6.2$ Hz, 1H), 3.94 (t, $J = 6.5$ Hz, 2H), 3.58 (s, 9H), 1.94 (tt, $J_1 = 8.2$ Hz, $J_2 = 6.5$ Hz, 2H), 1.28 (d, $J = 6.2$ Hz, 6H), 0.82 (m, 2H); ^{13}C-NMR (126.3 MHz, $CDCl_3$): $\delta = 152.6$ (s), 144.8 (s), 132.8 (s), 132.3 (d), 123.4 (d), 117.5 (d), 114.5 (t), 112.6 (d), 75.4 (d), 70.5 (t), 50.4 (q), 22.9 (t), 22.6 (q), 5.5 (q); IR (film): $\nu = 2973$, 2942, 2840, 1574, 1459, 1086 cm^{-1}; MS (70 eV): *m/z* (%) = 340 (14) [M$^+$], 121 (100), 224 (47), 266 (19).

Functionalized Silica Gel (6)

Under N_2 toluene-washed silica gel (380 mg) was suspended in toluene (20 mL). (*E*)-Stilbene (68.7 mg, 0.38 mmol) was added as NMR standard. Compound **5** (130 mg, 0.38 mmol) was added and the suspension was stirred at 80 °C. After 12 hours dimethoxydimethylsilane (0.5 mL, 3.54 mmol) was added and stirred for an additional 12 hours. The silica gel was filtered, washed with CH_2Cl_2, Et_2O, and then with pentane, before being dried in vacuum; yield: 457 mg; loading (0.622 mmol/g); IR (KBr): $\nu = 2980$, 2880, 1773, 1743, 1099, 805 cm^{-1}.

Hoveyda–Blechert Catalyst Loaded Silica Gel (7a)

Silica gel **6** (200 mg) was suspended in CH_2Cl_2 (20 mL) treated with Grubbs–Herrmann catalyst (10.56 mg, 12.4 μmol) and CuCl (1.231 mg, 12.4 μmol) and stirred for 3.5 h at 40 °C. The green silica gel was filtered and washed again with CH_2Cl_2, Et_2O, pentane and dried in vacuum. Silica gel **7a** (10 mg) was treated with ethyl vinyl ether (0.5 mL)/PPh_3 (0.8 mg) in refluxing CH_2Cl_2 (3 mL) for 1 h. The ruthenium amount in the filtrate was determined by TXRF. IR (KBr): $\nu = 2980$, 2879, 1755, 1472, 1099, 805 cm^{-1}; Ru: (0.0336 mmol/g).

Hoveyda–Grubbs Catalyst Loaded Silica Gel (7b)

Silica gel **6** (100 mg) was suspended in CH_2Cl_2 (10 mL) and treated with Grubbs catalyst (5.25 mg, 6.38 μmol) for 2 h at 40 °C. The brown silica gel was filtered, washed with CH_2Cl_2, Et_2O and pentane and dried in vacuum. Silica gel **7b** (10 mg) was treated with ethyl vinyl ether (0.5 mL)/PPh_3 (0.8 mg) in refluxing CH_2Cl_2 (3 mL) for 1 h. The ruthenium amount in the filtrate was determined by TXRF. IR (KBr): $\nu = 2981$, 2945, 2879, 2859, 1630, 1577, 1470, 1461, 1097, 952, 934, 805 cm^{-1}; Ru: (0.0174 mmol/g).

Acknowledgements

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References and Notes

[1] Grubbs catalyst refers to benzylidenebis(tricyclohexylphosphine)dichlororuthenium, $RuCl_2(PCy_3)_2{=}CHPh$.

[2] Grubbs–Herrmann catalyst refers to benzylidene-1,3-[bis-(2,4,6-trimethylphenyl)-imidazolidinylidene]dichloro-(tricyclohexylphosphine)ruthenium; $RuCl_2PCy_3H_2IMes{=}CHPh$.

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[11] Purchased from Merck; specifications LiChroprep Si 60® 40–63 μm: specific surface area 460–580 m^2/g, pore volume 0.70–0.90 mL/g, particle size 40–63 μm; specifications LiChroprep Si 60® 25–40 μm: specific surface area 480–540 m^2/g, pore volume 0.74–0.84 mL/g, particle size 25–40 μm.

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[13] Catalyst loading was determined by treating 10 mg of **7a**/**7b** with ethyl vinyl ether/triphenylphosphine in dichloromethane to detach the (pre)catalyst and measure the content of ruthenium in the filtrate quantitatively by total X-ray fluorescence (TXRF);[15] see: A. Wittershagen, P. Rostam-Khani, M. Mertens, C. Rittmeyer, B. O. Kolbesen, *Totalreflexions-Röntgenfluorenszenzanalyse (TXRF). Eine vielfältig einsetzbare Methode zur Mikro-, Spuren- und Oberflächenanalyse*, CLB Chemie in Labor und Biotechnik, 48. Jahrgang, 12, 506, **1997**.

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