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A Set of Olefin Metathesis Catalysts with Extraordinary Stickiness to Silica

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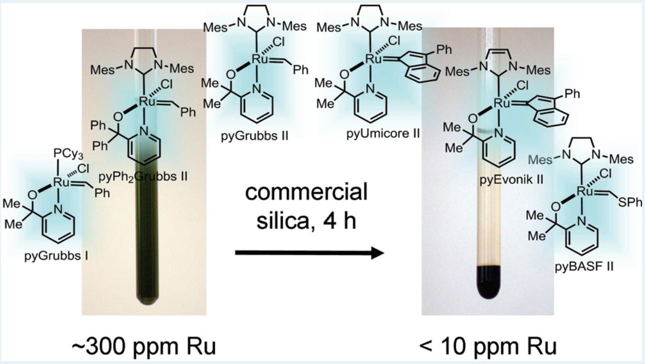
S *Supporting Information*

ABSTRACT: We report on a series of six new pyridinealkoxide-bridged first and second generation ruthenium carbenes with similar or even higher activity in ring-opening metathesis polymerization (ROMP), cross metathesis (CM), and ring closing metathesis (RCM) reactions than state-of-the-art catalysts. The new precatalysts show an extraordinarily high stickiness to commercially available silica, which significantly enhances their adsorptive separation from unprocessed reaction mixtures.

KEYWORDS: metathesis, adsorption, trace impurities, ruthenium



INTRODUCTION

Ruthenium-carbenes are industrially interesting metathesis catalysts (cf. commercially available precatalysts **1**−**5**, Figure 1) that continue to receive much attention. Catalyst loadings in the parts per million (ppm)-range are sufficient for high substrate conversion, if the starting materials have been thoroughly purified, and the reaction is conducted under inert and dry conditions.[1,2] This has been elegantly established by several industrial development teams[3−7] that have also emphasized the need to reduce residual catalyst and/or catalyst degradation products to a minimum, especially for end products used in pharmaceutical applications (e.g. < 10 ppm of Ru).[8]

Preferred methods for removal of ruthenium traces include oxidative treatments (H_2O_2,[10] $Pb(OAc)_4$,[11] PPh_3O, or DMSO[12]), which still require column chromatography to remove the last traces of residual catalyst decomposition products (ligand or metal), a problem also associated with extractive techniques. Captive ligands such as tris(hydroxymethyl)phosphine (THP)[13] or polar isocyanides,[14] work only well in a large excess and in combination with silica gel adsorption. Furthermore, THP occasionally promotes byproduct formation with sensitive products.[4]

Other techniques, that is, covalent immobilization of modified ruthenium carbenes on surfaces,[15,16] or the use of elaborate ligands to increase polarity or steric bulk of the ruthenium carbene for better catalyst separation,[17−24] are interesting concepts but have had little industrial impact as a consequence of notable catalyst manufacturing costs.

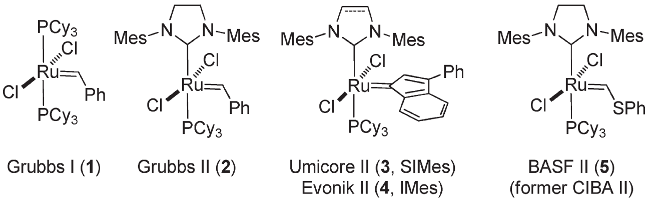


Figure 1. Commercially available ruthenium-based metathesis precatalysts **1**−**5** and their commonly used names.[9].

Adsorption techniques are an interesting and economically viable option for removing residual ruthenium traces, but so far, modified[25] and unmodified[26] inorganic materials and even cascades of purification beds (e.g. consecutive adsorption on silica, carbon, and silica gel column chromatography)[27] lead, at best, to residual ruthenium amounts of ~10 ppm.

To overcome this limitation, we initially focused on pyridinealkoxide-bridged first[28] and second[29] generation ruthenium carbenes **8**−**13** (cf. Scheme 1, Table 1), which show promising,[30,31] albeit scarcely explored activity, and have so far only been separated from crude reaction products by immobilization onto dendrimers[32] or nanofiltration.[33]

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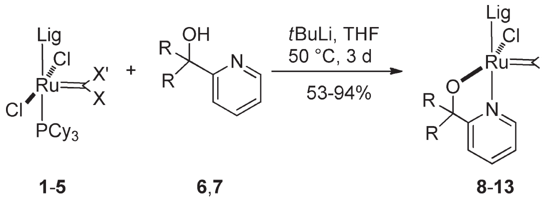
■ RESULTS AND DISCUSSION

Synthesis of Complexes 8−13. In C_6D_6 the reaction of **2**−**4** and lithiated *gem*-diphenylpyridine alkoxide **7** was sluggish (75% conversion of **2** at 60 °C over 6.5 d) and unselective (at 40 °C an ^{1}H NMR signal at ∼14 ppm which appeared concomitantly, might be assigned to the P-containing nonchelated complex, with the corresponding product's decreasing carbene signal at 15.45 ppm). We attributed the low reactivity of **7** to the steric hindrance resulting from the combination of the bulky *gem*-diphenyl substituent and the NHC. This assumption was supported by the straightforward synthesis of pyGrubbs I (**8**) and pyGrubbs II (**9**) from Grubbs I (**1**) and Grubbs II (**2**) and the less bulky *gem*-dimethyl substituted **6** in 76 and 86% yield, respectively, at 50 °C in tetrahydrofuran (THF). Thus, over a reaction time of 3 d, additionally $pyPh_2$Grubbs II (**9**), pyUmicore II (**11**), pyEvonik II (**12**), and pyBASF II (**13**) were accessible in 53−94% yield (Scheme 1) and purified by simple precipitation from hexane to remove excess PCy_3.[30,31] For selected complexes, such as **9**, the reaction could be followed by thin layer chromatography (TLC; color change from red-brown to bright green, cf. Experimental Section).

Scheme 1. Synthesis of Pyridine-Alkoxide Substituted Pre-Catalysts 8−13[a]



[a] For details cf. Table 1.

Table 1. Yields in the Synthesis of Pyridine-Alkoxide Substituted Pre-Catalysts 8−13

SM[a]	ligand	product	trivial name	ligand	X	X′	R	yield (%)[b]
1	6	8	pyGrubbs I	PCy_3	Ph	H	Me	76
2	7	9	pyGrubbs II	SIMes[c]	Ph	H	Me	86
2	6	10	$pyPh_2$Grubbs II	SIMes	Ph	H	Ph	53
3	6	11	pyUmicore II	SIMes	indenylidene		Me	75
4	6	12	pyEvonik II	IMes[d]	indenylidene		Me	82
5	6	13	pyBASF II	SIMes	SPh	H	Me	94

[a] Starting material. [b] Isolated yield after workup. [c] *N*,*N*′-bis[2,4,6-(trimethyl)-phenyl]imidazolidin-2-ylidene. [d] *N*,*N*′-bis[2,4,6-(trimethyl)phenyl]-imidazol-2-ylidene.

Crystals of pyGrubbs I (**8**) and pyGrubbs II (**9**) suitable for X-ray analysis were obtained by layering hexane over a saturated THF solution of **8** at −30 °C and over a saturated toluene solution of **9** at −36 °C (Figure 2).[34]

Once the six new catalysts **8**−**13** had been successfully prepared, their catalytic activity was evaluated using different metathesis reactions, that is, in the ROMP of cyclooctene (COE, **14**) to give poly-COE (**15**),[35,36] the CM of 5-decene (**16**) with 5-hexenyl acetate (**17**) to give 5-decenyl acetate (**18**)[37] and the RCM of 5-hexen-1-yl-10-undecenoate (**19**) to give pentadec-10-en-15-olide (**20**).[38,39]

In the ROMP experiments (cf. Figure 3), Grubbs II precatalyst (**2**) gave full conversion of COE in less than 2 min, followed by Umicore II (**3**) and BASF's latent Fischer carbene (formerly Ciba's precatalyst) BASF II (**5**). Reactions employing **3** and **5** reached full conversion in 20 and 30 min, respectively. While Evonik II (**4**) reached 50% conversion in 60 min, Grubbs I precatalyst (**1**) was unreactive at room temperature.

The new catalysts **8**−**13** performed quite differently. Full conversion was reached with pyGrubbs II (**9**) within 50 min, whereas its *gem*-diphenyl derivative $pyPh_2$Grubbs II (**10**) reached only 50% conversion in that time. This could result from the larger Thorpe-Ingold effect of *gem*-diphenyl versus the smaller *gem*-dimethyl substituent,[40] which forces precatalyst **10** to the five-membered internal chelate resting state (cf. Figure 2) thereby increasing its stability. Indenylidene carbene pyUmicore II (**11**) was more active than pyBASF II (**13**) (70 vs 50% conversion in 60 min). Both first generation complexes pyGrubbs I (**8**) and Grubbs I (**1**) exhibited high latency: no conversion after 60 min at room temperature, which increased to 70 and 40% at 60 °C, respectively.

In contrast to the moderate ROMP activity, many of the new complexes were highly active in CM of 5-decene (**16**) and 5-hexenyl acetate (**17**) to give **18**,[6,37] which is the major component of the Peach Twig Borer's (PTB) sex attractant pheromone (Figure 4).[41]

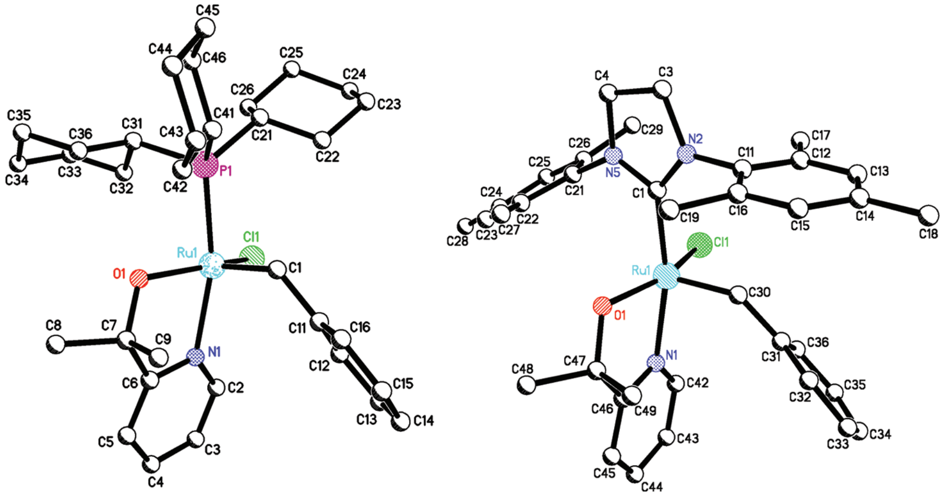


Figure 2. Ortep plot of pyGrubbs I (**8**) and pyGrubbs II (**9**) at 50% probability. H-atoms are omitted for clarity.

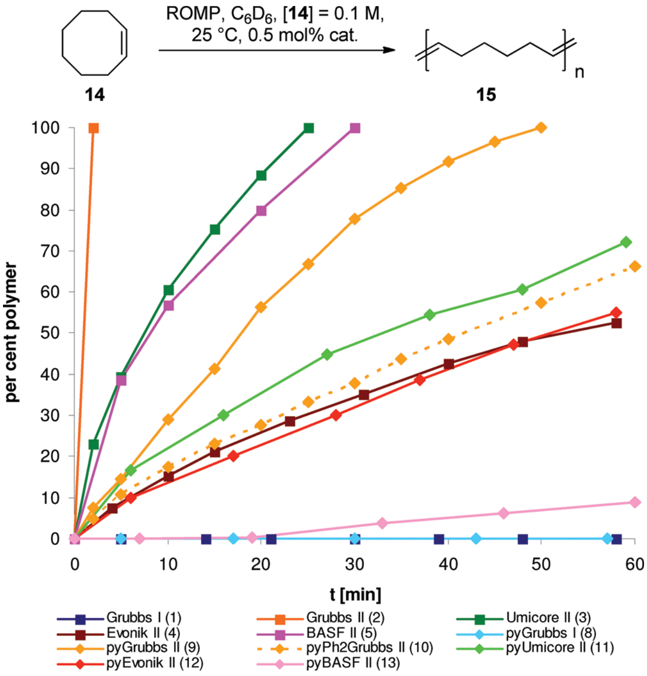


Figure 3. ROMP of COE at 25 °C.

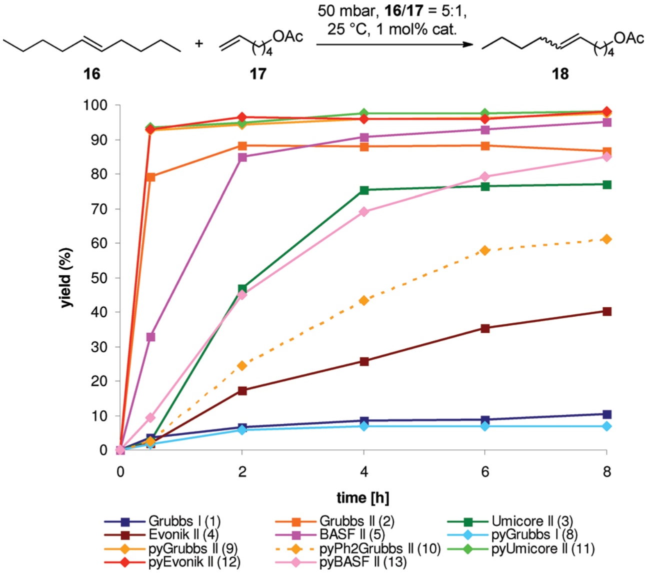
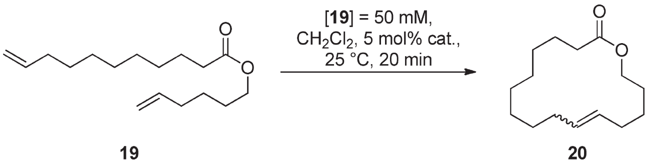


Figure 4. CM of 5-decene (**16**) with 5-hexenyl acetate (**17**) to the peach twig borer-pheromone 5-decenyl acetate (**18**).

Scheme 2. RCM Reaction of 5-Hexen-1-yl-10-undecenoate (19) to the Macrolactone Pentadec-10-en-15-olide (20)[a]



[a] For details cf. Table 2.

Table 2. RCM Reaction of 5-Hexen-1-yl-10-undecenoate (19) to the Macrolactone Pentadec-10-en-15-olide (20)

catalyst	conv. (%)[a]	catalyst	conv. (%)	catalyst	conv. (%)
Grubbs I (**1**)	94	Grubbs II (**2**)	88	Umicore II (**3**)	81
Evonik II (**4**)	85	BASF II (**5**)	90	pyGrubbs I (**8**)	91
pyGrubbs II (**9**)	94	$pyPh_2Grubbs$ II (**10**)	99	pyUmicore II (**11**)	96
pyEvonik II (**12**)	100	pyBASF II (**13**)	100		

[a] Conversion after 20 min.

The new pyridinealkoxide catalysts pyGrubbs II (**9**), pyUmicore II (**11**), and pyEvonik II (**12**) give **18** in nearly quantitative yield within ~15 min. In comparison, the best commercial catalysts, that is, Grubbs II (**2**) and BASF II (**5**), give **18** in 85 and 90% yield within 3 h, respectively, whereas **2** quickly deactivates and **5** reacts slowly. Precatalyst Umicore II (**3**) deactivates fast and gives within 4 h yields of 75%, followed by Evonik II (**4**) being latent but steadily producing **18** in 40% yield within 8 h. The first generation catalysts Grubbs I (**1**) and pyGrubbs I (**8**) have similar activity but are significantly less reactive than their second generation counterparts Grubbs II (**2**) and pyGrubbs II (**9**) (<10% vs 87 and 98% yield after 8 h). Once again because of the Thorpe-Ingold effect, complex $pyPh_2$-Grubbs II (**10**) is significantly less reactive than **9** (95 vs 20% yield after 2 h).

In the RCM reaction of 5-hexen-1-yl-10-undecenoate (**19**) the new complexes show similar or even better reactivity than their commercial counterparts to give the macrolactone pentadec-10-en-15-olide (**20**),[38,39] a congener of Firmenich's Exaltolide (Scheme 2). And under high dilution, now also the first generation precatalysts Grubbs I (**1**) and pyGrubbs I (**8**) gave high conversion (94 vs 91% after 20 min). The conversion obtained with Grubbs II (**2**) was surpassed by pyGrubbs II (**9**) (88 vs 99%), which is once again more active than analoguous $pyPh_2$Grubbs II (**10**) (94% yield). The same is true for the couples BASF II/pyBASF II (**5**/**13**: 90 vs 100% yield), Umicore II/pyUmicore II (**3**/**11**: 81 vs 96% yield), and Evonik II/pyEvonik II (**4**/**12**: 85 vs 100% yield).

One of the most surprising features of complexes **8**−**13** is their extraordinary affinity to silica gel. Whereas $pyPh_2$ Grubbs II (**10**), the precatalyst with the largest organic ligand, can be purified by column chromatography eluting with cyclohexane, precatalysts **9**−**13** migrate only upon addition of methanol, which might be a consequence of the protonation of the pyridine's nitrogen by silica.

The adsorption from unprocessed reaction mixtures resulting from the CM of **16** and **17** to **18** is fast (<10 min) as seen by the almost complete decoloration of the deep-green solution upon addition of commercially available silica gel (60A-Acros). Quantitative measurement of residual amounts of ruthenium in solution by ICP-MS (cf. Figure 5) show that pyEvonik II (**12**) and pyBASF II (**13**) have the highest affinitiy to commercial silica: Even in the presence of only 100 mg of silica residual amounts of ruthenium in the unprocessed reaction mixture could be reduced to 1 ppm, whereas the commercial congeners are reduced to 43 ppm for BASF II (**5**) or even only 105 ppm for Evonik II (**4**) even in the presence of the 3-fold amount of silica (300 mg).

The same is true for pyGrubbs II (**9**) and Grubbs II (**2**): The amount of residual ruthenium found in the crude reaction

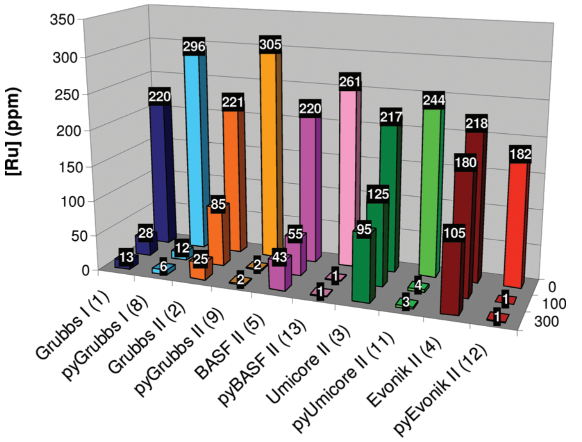


Figure 5. ICP-MS adsorption isotherme of the unprocessed cross metathesis reaction of 5-decene (**16**) with 5-hexenyl acetate (**17**) catalyzed by precatalysts **8**, **9**, and **11**−**13** and their commercially available counterparts **1**, **2**, and **4**.

mixture for **9** is after 1 h only a tenth even in the presence of 300 mg of silica compared to the commercial precatalyst **2** (2 vs 25 ppm). The biggest difference between modified and commercial precatalyst is observed between Umicore II (**3**) and pyUmicore II (**11**): The amount of residual ruthenium found for **3** surpasses the amount detected for **11** by a factor 30 (95 vs 3 ppm). The residual amount of ruthenium found for the first generation precatalysts Grubbs I (**1**) exceeds that found for pyGrubbs I (**8**) by ~100% (6 vs 13 ppm).

Thus, after 1 h the residual amount of ruthenium in all crude reaction mixtures obtained with the new catalysts **8**−**13** was close to or even well below the 10 ppm threshold. This is of particular importance in pharmaceutical applications, thus making the new catalysts particularly attractive for use in this context.

CONCLUSIONS

In summary, we have synthesized and fully characterized six new first and second generation metathesis precatalysts incorporating a pyridylalkoxide-ligand. All new second generation catalysts show a very high affinity to untreated, unmodified, and commercially available chromatography-grade silica. The concentration of residual ruthenium in unprocessed reaction mixtures was reduced to well below 10 ppm, which is a prerequisite for fine-chemical applications. Some of those new catalysts show superior reactivity to state-of-the-art catalysts as shown in a CM and RCM reaction. Their latent behavior in ROMP is also valuable for some industrial applications.

ASSOCIATED CONTENT

Ⓢ Supporting Information. Crystallographic data in CIF format. Experimental details and spectral characterization for Ru-complexes **8**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org. Files CCDC 807154 (**8**) and 807155 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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