Olefin metathesis catalysts bearing a pH-responsive NHC ligand: a feasible approach to catalyst separation from RCM products†

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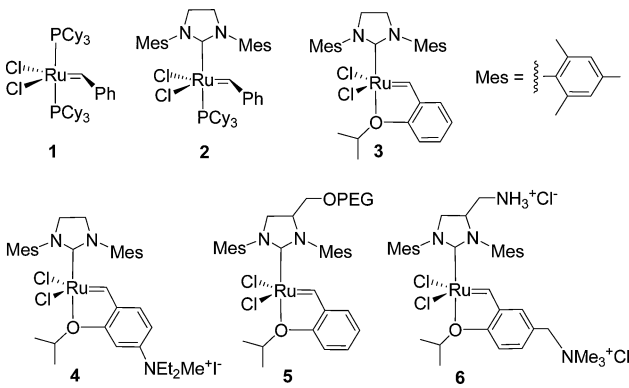
Two novel ruthenium-based olefin metathesis catalysts, $H_2ITap(PCy_3)Cl_2Ru{=}CH{-}Ph$ **12** and $H_2ITapCl_2Ru{=}CH{-}(C_6H_4{-}O{-}i Pr)$ **13** (H_2ITap = 1,3-bis(2′,6′-dimethyl-4′-dimethylaminophenyl)-4,5-dihydroimidazol-2-ylidene), were synthesized bearing a pH-responsive NHC ligand with two aromatic NMe_2 groups. The crystal structures of complexes **12** and **13** were determined *via* X-ray crystallography. Both catalysts perform ring opening metathesis polymerization (ROMP) of cyclooctene (COE) at faster rates than their commercially available counterparts $H_2IMes(PCy_3)Cl_2Ru{=}CH{-}Ph$ **2** and $H_2IMesCl_2Ru{=}CH{-}(C_6H_4{-}O{-}i Pr)$ **3** (H_2IMes = 1,3-bis(2′,4′,6′-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene) and perform at similar rates during ring closing metathesis (RCM) of diethyldiallylmalonate (DEDAM). Upon addition of 2 equiv. of HCl, catalyst **12** is converted into a mixture of several mono and diprotonated Ru-carbene species **12′** which are soluble in methanol but degrade within a few hours at room temperature. Catalyst **13** can be protonated with 2 equiv. of HCl and the resulting complex **13′** is moderately water-soluble. The complex is stable in aqueous solution in air for >4 h, but over prolonged periods of time shows degradation in acidic media due to hydrolysis of the NHC–Ru bond. Catalysts **12** and **13** perform RCM of diallylmalonic acid in acidic protic media with only moderate activity at 50 °C and do not produce polymer in the ROMP of cationic 7-oxanorbornene derivative **14** under the same conditions. Catalyst **13** was used for Ru-seperation studies when RCM of DEDAM or 3,3-diallypentadione (DAP) was conducted in low-polar organic solution and the Ru-species was subsequently precipitated by addition of strong acid. The Ru-species were removed by (1) filtration and (2) filtration and subsequent extraction with water. The residual Ru-levels could be reduced to as far as 11 ppm (method 2) and 24 ppm (method 1) without the use of chromatography or other scavenging methods.

Introduction

Over the last decade, olefin metathesis has emerged as a powerful technique in organic[1] and polymer synthesis.[2] Ru-based, single-site catalysts such as Grubbs' first and second generation catalysts **1** and **2**, and Hoveyda–Grubbs' catalyst **3** have become the center of attention for many scientists due to their high tolerance towards moisture and functional groups,[3] and thus have significantly expanded the scope of metathesis substrates. Furthermore, due to their elevated inertness towards molecular oxygen in solution, as particularly demonstrated for catalyst **3**,[4b] several derivatives have been successfully recycled and reused.[4,5] Catalyst removal after reaction is a major issue associated with homogeneous systems. Most commonly, column chromatography over silica gel is employed. However on a large scale, this method is not economically feasible and, additionally, often does not reduce the ruthenium content in the product sufficiently below 10 ppm Ru, the upper limit for pharmaceutical products.[6,7] Ruthenium scavenging based on chemical reagents[8] and physical adsorption[9] have been reported but often their utility is limited due to economic reasons, high toxicity and/or long processing times. More recent approaches have been based on using catalysts with a modified solubility profile such as catalysts **4**[10a] and **5**



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† Electronic supplementary information (ESI) available: ^1H, ^{13}C and ^{31}P NMR spectra of the synthesized ligand precursor and its synthetic intermediates **8–11**, and Ru-complexes **12** and **13**, as well as detailed kinetic experimental data. CCDC reference numbers 690483 (for **12**) and 690484 (for **13**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b809793c

which can be efficiently removed after reaction by flash column chromatography or *via* extraction with water.[10b,11] The application of these separation methods dramatically reduced the amount of ruthenium in the final product but did not accomplish the reduction of the ruthenium contamination within the limits of the pharmaceutical standard without additional purification.

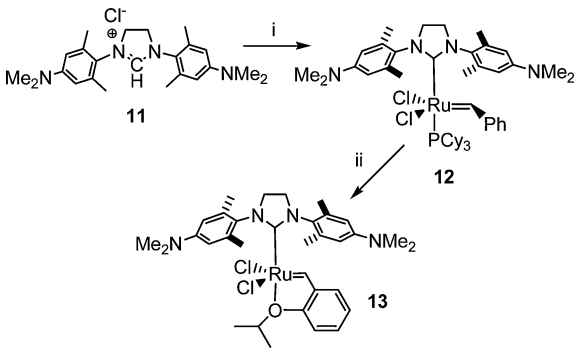
Olefin metathesis in aqueous media was successfully carried out with hydrophobic catalysts by sonication[12] or in the presence of an organic co-solvent[13] or surfactant.[14] Modifications of phosphine[15] or pyridine ligands,[16] reactive carbene moieties,[17,18] and particularly N-heterocyclic carbene (NHC) ligands,[10a,19,20] or combinations thereof[20] have furnished Ru-based catalysts with solubility in protic and aqueous media. Neutrally-charged derivatives bearing polyethyleneglycol (PEG) substituted NHC ligands, such as catalyst **5**, have been demonstrated to perform metathesis reactions homogeneously in aqueous as well as non-protic organic media.[10] Ionic NHC ligands which produce water-soluble metal complexes have been previously reported,[21–24] however not in conjunction with Ru-based olefin metathesis catalysts. This is mainly due to a solubility problem. The direct NHC/phosphine ligand exchange reaction from first generation olefin metathesis catalysts, to date the most common approach to obtain NHC-ligated derivatives, requires low-polar solvent conditions such as hexanes or toluene to go to completion.[25,26] Under these conditions, ionic NHC ligands are not sufficiently soluble. Therefore, to enable successful ligand exchange, the N-heterocyclic carbene must be neutrally charged at this stage. Grubbs *et al.* have produced metathesis catalyst **6**, the only derivative bearing a charged NHC ligand. The ammonium group was initially introduced into the complex as a Boc-protected moiety which is hydrolyzed and simultaneously protonated after attachment to the metal center.[20] To provide sufficient solubility in aqueous media however, an additional positive charge was introduced *via* the reactive carbene moiety.

We wish to report the synthesis of the first pH-responsive, highly active olefin metathesis catalysts with variable solubility profiles. After performing ring closing metathesis (RCM), the catalysts can be removed from the reaction mixture in a straightforward protocol by acid addition and subsequent filtration to give products with residual Ru levels as low as 24 ppm after simple filtration and 11 ppm after additional extraction with water.

Results and discussion

Catalyst syntheses

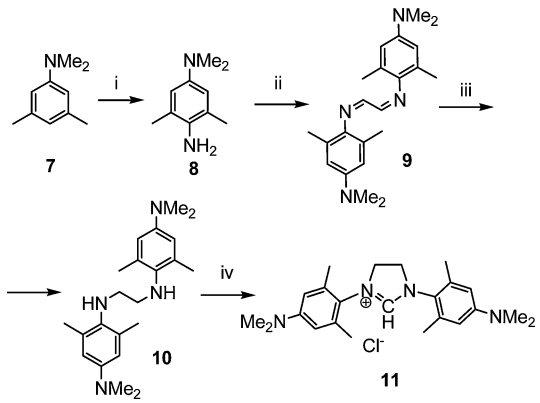
Dimethylamino groups are ideal pH-responsive groups in Ru-based olefin metathesis catalysts as they are compatible with Ru-based olefin metathesis catalysts.[27] We synthesized ligand precursor **11** which contains two dimethylamino groups bound to the aromatic NHC ligand substituents. The precursor salt was directly used *in situ* with base and Grubbs' catalyst **1** to produce the second generation Grubbs-type catalyst **12** (Scheme 1) bearing the H_2ITap ligand (H_2ITap = 1,3-bis(2′,6′-dimethyl-4′-dimethylaminophenyl)-4,5-dihydroimidazol-2-ylidene). The solid complex has a light brownish color. Catalyst **12** was then converted into the green-colored Hoveyda–Grubbs-type catalyst **13** with 2-*i*-propoxystyrene in the presence of CuCl applying the literature procedure for catalyst **2** (Scheme 1).[4a] The work-up is conducted in air which is in agreement with the previously observed superb



Scheme 1 Synthesis of pH-responsive catalysts **12** and **13**; (i) **1**/KO*t*Bu/heptane, 24 h, 60 °C (70%); (ii) 2-*i*-propoxystyrene/CuCl, 2 h, 35 °C (70%).

oxidative stability of Hoveyda–Grubbs-type catalysts.[4b,5] The yields (70% for **12** and 70% for **13**) are comparable to those for catalysts **1** and **2**.

The dimethylamino groups in the H_2ITap ligand were introduced by starting out from phenylenediamine derivative **8** which was synthesized from commercially available *N*,*N*-3,5-tetramethylaniline **7** in 45% overall yield.[28] Following the literature procedure for the synthesis of Grubbs' second generation catalyst **2** with few modifications,[25] aniline derivative **8** was converted into the respective NHC ligand precursor salt **11** in three steps (65% overall yield) *via* the intermediates **9** and **10** (Scheme 2). In this process, we have developed an improved hydrogenation procedure for diimine **9** with $NaBH_4$ to afford the diamine **10**. The previously described reaction conditions for the synthesis of analogous diamines[25] required a slow addition of conc. HCl_{aq} at 0 °C to the solution of the double-Schiff base in thf in the presence of excess $NaBH_4$. This procedure afforded hydrolysis side products in the synthesis of diamine **10** and therefore reduced the yields significantly. Furthermore, the pure diamine must be isolated as the hydrochloride salt first which then separately is extracted with base to afford the pure diamine. In the new procedure, we activated the $NaBH_4$ with anhydrous boric acid (1.33 equiv. relative to $NaBH_4$). As the acid exhibited low solubility in the solvent (thf), all reagents were added at once and the reaction was stirred at slightly elevated temperature. The end of the reaction was



Scheme 2 Preparation of H_2ITap·HCl **11**: (i) (1) $NaNO_2$/conc. HCl_{aq}, 60 min, −5 °C, (2) Sn/HCl, 70 °C (45%); (ii) $(CHO)_2$/MeOH [HCl], 24 h, RT (85%); (iii) $NaBH_4/H_3BO_3$/thf, 60 min, 30 °C (88%); (iv) $HC(OEt)_3/NH_4Cl$, 12 h, 130 °C (87%).

determined by complete discoloration of the orange-red reaction solution (usually between 30 and 60 min). The aqueous work-up directly afforded the pure diamine **10** in high yields and purity.

Catalyst structures

The structures of catalysts **12** and **13** in solid state could be determined *via* X-ray crystallography (Fig. 1 and 2). Relevant bond distances and angles for the complexes are summarized in Table 1. Both complexes exhibit a distorted square pyramidal ligand environment as usual for these Ru–carbene complexes. The base is formed by the donor ligands and the chlorides, and the benzylidene moiety is in the apex. In complex **12**, all bond distances and bond angles involving the ruthenium center are in the same range as for the $(PCy_3)Cl_2Ru$=CHPh complex bearing a 1,3-dimesityl-1,4,5,6-tetrahydropyrimidin-2-ylidene ligand[29] (the only other crystal structure published for a $(PCy_3)Cl_2Ru$=CHPh complex with a non-aromatic NHC ligand) within a margin of 0.01 Å and 0.6°. The only exception is the Ru–C_{NHC} distance of 2.075 Å which is actually shorter by more than 0.03 Å (2.106 Å). This bond distance is more similar to the Ru–C_{NHC} distance of the corresponding $IMes(PCy_3)Cl_2Ru$=CHPh complex with 2.069 Å (IMes = 1,3-bis(2′,4′,6′-trimethylphenyl)imidazol-2-ylidene).[30] This is not surprising as the mesityl substituents are less angled towards the metal center in complex **12** than in the tetrahydropyrimidin-2-ylidene complex due to the shortened NHC ligand backbone. As a result, the steric interference with the benzylidene moiety is less pronounced.[29] This is also reflected in the longer distance between the mesityl *ipso*-carbon atom to the benzylidene carbon atom in complex **12** (3.01 Å *vs.* 2.9 Å). The short distance of the aromatic ring to the carbene moiety was speculated to be responsible for lowered metathesis activity of the tetrahydropyrimidin-2-ylidene complex in comparison to catalyst **2**.[29]

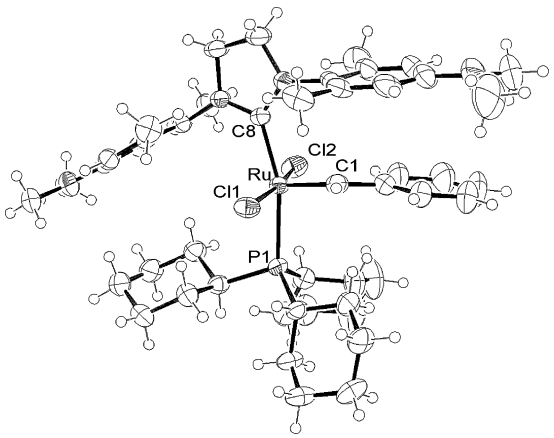


Fig. 1 ORTEP diagram of $H_2ITap(PCy_3)Cl_2Ru$=CHPh **12**.

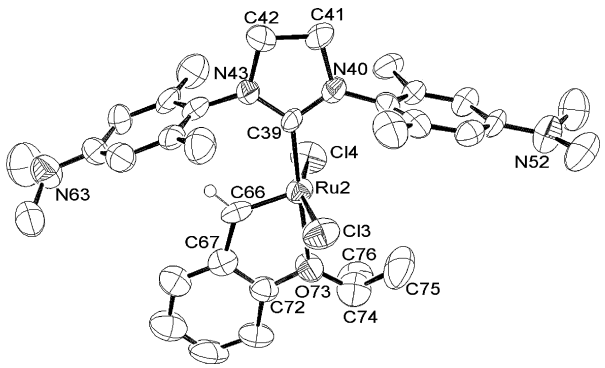


Fig. 2 ORTEP diagram of $H_2ITapCl_2Ru$=CH–(2-*i*PrO)C_6H_4 **13**.

Table 1 Selected bond distances [Å] and bond angles [°] for complexes **12** and **13**

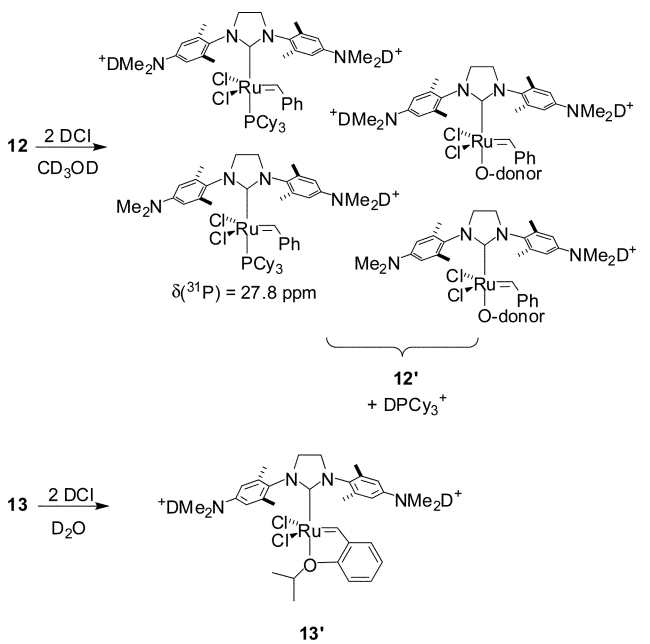
	12	**13**
Ru=C(H)	1.826(2)	1.735(9)
Ru–C_{NHC}	2.0746(19)	1.966(7)
Ru–O	—	2.260(5)
Ru–P	2.4419(6)	—
Ru–Cl	2.4080(6)	2.330(2)
	2.3809(6)	2.339(2)
P–Ru=C(H)	91.45(9)	—
O–Ru=C(H)	—	78.1(3)
C(H)=Ru–C_{NHC}	99.49(9)	103.2(3)
P–Ru–C_{NHC}	179.41(9)	—
O–Ru–C_{NHC}	—	178.5(3)
Cl–Ru–Cl	169.64(4)	159.69(8)

The structure of complex **13** consists of two discrete complexes and one molecule of CH_2Cl_2 in solvation. The averaged bond distances of both complexes are similar to those of H_2IMes complex **3**[4a] (deviations <0.01 Å) with one exception. The distance between the Ru center and the benzylidene carbon atom is extremely short in complex **13** (1.735 Å) and significantly shorter by almost 0.1 Å than in complex **3**. As the only structural difference between the two complexes is the presence of the remote *p*-NMe_2 groups in **13** instead of the *p*-methyl groups in **3**, it is likely that this shortening of the metal–carbene bond is less due to steric reasons than electronic changes. In comparison to complex **3**, the *trans* bond angles at the metal center and the C–Ru–C *cis* angle are slightly larger in complex **13** by approx. 2–3°. However, the C–Ru–O *cis* angle in **13** (78.1°) is smaller by 1.3° than in **3**. This is unexpected due to the shorter Ru–carbene bond which should cause a widening of this angle assuming comparable bond angles in the relatively rigid benzylidene chelate. The small C–Ru–C *cis* angle also causes a large distance between the mesityl *ipso*-carbon atom to the benzylidene carbon atom in complex **13** (3.08 Å) in comparison to PCy_3 ligated complex **12**.

Catalyst reactions with HCl

Catalysts **12** and **13** are soluble in organic media such as toluene, benzene, CH_2Cl_2 and ethyl acetate. Upon addition of DCl (2 equiv.) both complexes precipitated from organic solution. The precipitate of complex **12** did not exhibit good water solubility. The ^{31}P NMR spectrum of the dried residue in D_2O only indicates the presence of the $DPCy_3^+$ salt at $\delta = 30.8$ ppm (t, $^1J(^{31}P^1H) = 71$ Hz), whereas in d_4-methanol the spectrum also indicated the presence of a $(PCy_3)Ru$ species at $\delta = 28.2$ ppm (s), alongside the $DPCy_3^+$ salt. Both signals for the Ru species and the $DPCy_3^+$ cation are present in approx. 1 : 2 ratio. Very likely, the second equiv. DCl did not afford the complete second protonation of the NHC ligand but instead affords the partial protonation of the PCy_3 ligand. The presence of two ruthenium carbene species was observed in the ^1H NMR spectrum where two signals are present at $\delta = 19.13$ ppm and 18.99 ppm (the typical benzylidene-H region) also in approx.

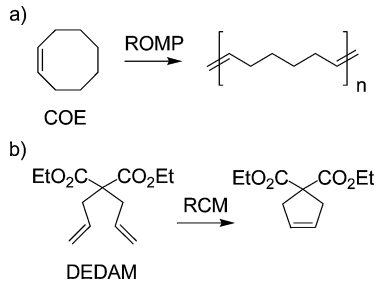
1 : 2 ratio which correlates to the degree of the protonation of the PCy_3 ligand. Therefore, the protonation should afford a dynamic mixture of Ru complexes **12′** of mono or diprotonated species coordinated by a molecule of CD_3OD or PCy_3 (Scheme 3). Similar ruthenium carbene complexes coordinated by weak O-donor ligands have been formulated as they were also obtained *via* the protonation of one phosphine ligand with DCl.[31,32] After several hours, the ^{31}P NMR signal for the Ru species and the ^{1}H NMR signal for the benzylidene-H atoms disappeared indicating the decomposition of the complexes **12′** in this time period. The low thermal stability of phosphine deficient Ru–carbene species has been observed previously.[31] Double protonation of complex **13**, in contrast, affords complex **13′** which is water soluble and stable in 0.1 M DCl in D_2O solution in air for more than 6 h (Scheme 3). After 30 h, the ^{1}H NMR spectrum of **13′** in D_2O exhibited a new set of signals (4% relative intensity) due to the formation of the double protonated NHC ligand precursor **11′** as a result of hydrolytic decomposition of the complex. The hydrolysis of hydrophilic NHC ligands had been observed previously for water-soluble Hoveyda–Grubbs-type catalysts **4** and **5**.[10a,20] Over the course of 7 d at room temperature, 45% of complex **13′** was decomposed. It should be mentioned that the same experiment under inert gas atmosphere exhibited a similar rate of hydrolytic degradation.



Scheme 3 Reaction of catalysts **12** and **13** with DCl (2 equiv.).

ROMP and RCM activities

The metathesis activity of complexes **12** and **13** was tested in ring opening metathesis polymerization (ROMP) reactions of cyclooctene (COE) and ring closing metathesis (RCM) reactions of diethyldiallylmalonate (DEDAM) in benzene solution at room temperature (Scheme 4, Fig. 3 and 4).[32,33] The conversion was monitored *via* ^{1}H NMR spectroscopy and the results were compared to catalyst **2** and **3** under identical conditions. As the steric demands of the H_2IMes and the H_2ITap ligands are very



Scheme 4 Olefin metathesis reactions with catalysts **2**, **3**, **12**, **13** in benzene (20 °C). (a) ROMP of COE ([Ru] = 0.5 mM, 0.5% loading); (b) RCM of DEDAM ([Ru] = 1.0 mM, 1.0% loading).

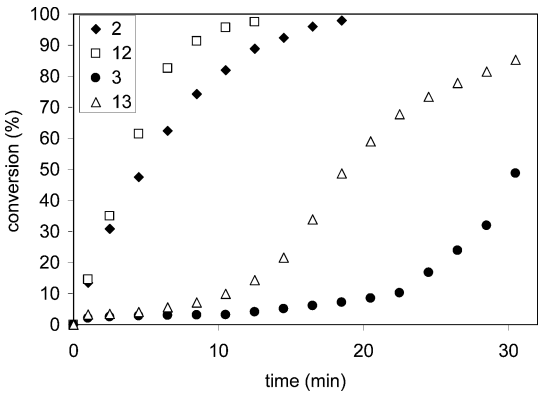


Fig. 3 ROMP of COE with catalysts **2**, **3**, **12**, **13** ([Ru] = 0.5 mM, 0.5% catalyst loading).

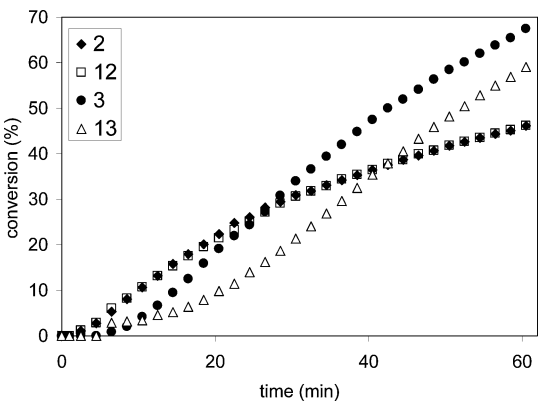


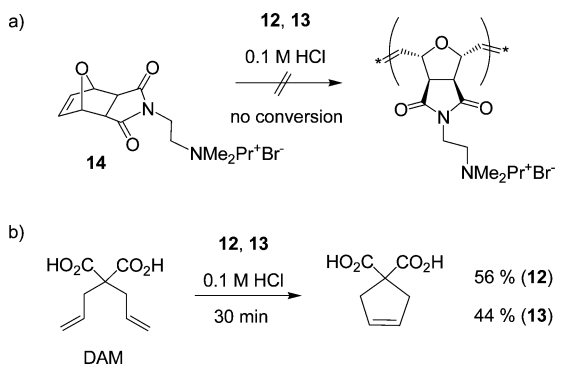
Fig. 4 RCM of DEDAM with catalysts **2**, **3**, **12**, **13** ([Ru] = 0.5 mM, 0.5% catalyst loading).

similar, differences in catalytic activity should be mostly due to electronic effects. Both H_2ITap catalysts **12** and **13** were very active in olefin metathesis and performed the ROMP of COE faster than their H_2IMes ligated counterparts **2** and **3**. The evaluation of the kinetic profiles suggests particularly for catalyst **13** that this is mainly due to a faster rate of initiation as complex **3** exhibited a significantly longer induction period before the dramatic rate acceleration was observed. Such long induction times are typical for slow-initiating but fast-propagating olefin metathesis catalysts and thus strongly affect the overall reaction rates.[3f,g] The PCy_3-ligated complexes **2** and **12** initiated significantly faster under those conditions and afforded >80% conversion in less than 7 min

(**12**) and 11 min (**2**) respectively in comparison to 38 min (**3**) and 28 min (**13**).

In the RCM reactions, catalysts **2** and **12** performed at near-identical rates. Similar to the ROMP reaction, both catalysts exhibited a faster rate of initiation as the initial conversion rates were higher than for catalysts **3** and **13** which exhibited an induction period of 10–15 min. However, the conversion with Hoveyda–Grubbs-type catalysts **3** and **11** accelerated and performed at faster propagation rates. The overall conversions after 60 min therefore were significantly higher (**3**: 67%; **13**: 59%; **2**, **12**: 45%). Interestingly, catalyst **3** marginally outperformed catalyst **13** in the RCM reaction, which is in contrast to the performances observed for the ROMP reaction.

The metathesis activity of complexes **12** and **13** was tested in ring opening metathesis polymerization (ROMP) reactions of cationic *exo*-7-oxanorbornene derivative **14** and ring closing metathesis (RCM) reactions of diallylmalonic acid (DAM) in acidic protic solution (Scheme 5). Catalyst **12** was used in 1 M HCl_{aq}–2-propanol (1 : 9 v/v) solution and catalyst **13** was used in 0.1 M HCl_{aq} solution. The catalyst loadings were 4% in all experiments at [Ru] = 2.0 mM, and a reaction temperature of 50 °C. Generally, the catalytic performance was disappointingly low for both catalysts. The ROMP of derivative **14** has been demonstrated to be sufficiently fast with generally less active first-generation $(PCy_3)_2Ru{=}CHPh$ catalysts in organic–alcoholic[34] and alcoholic–aqueous media[17] at lower catalyst loadings, temperature and reaction times. Under the described conditions, neither catalyst **12** or **13** produced noticeable amounts of polymer in 60 min. Furthermore, the RCM of DAM reached only 56% (**12**) and 44% (**13**) in 30 min and the reactions did not afford further conversion after this time. These low conversion rates are somewhat surprising, in particular as acidic conditions are known to accelerate the initiation rates of the metathesis reaction.[19,31c] Although the donating character of the H_2ITap ligand is certainly influenced by the conversion of the π-donating amino group into the σ-withdrawing ammonium group at the aryl substituents, the variations between withdrawing and donating aryl substituents have not been observed before to play an important role in the catalyst activity.[35] A more detailed investigation of the influence of the pH on the rates of initiation and propagation for these catalysts is currently ongoing.



Scheme 5 Olefin metathesis reactions with catalysts **12** and **13** in protic acidic media. (a) ROMP of **14** ([Ru] = 2 mM [in 2-PrOH : 1 M HCl_{aq}, 9 : 1 v/v for **12**; in 0.1 M HCl_{aq} for **13**], 4% loading); (b) RCM of DAM ([Ru] = 2 mM [in 2-PrOH : 1 M HCl_{aq}, 9 : 1 v/v for **12**; in 0.1 M HCl_{aq} for **13**], 4% loading).

Catalyst separation studies

We utilized the pH-dependent solubility profile to separate catalyst **13** from RCM reaction mixtures. Upon protonation, the Ru complexes are converted into the dicationic species which should exhibit low solubility in the organic reaction medium. We conducted studies with DEDAM and 3,3-diallyl-2,4-pentanedione (DAP). The reactions ([Ru] = 3.3 mM, 2% catalyst loading) were carried out in toluene or ethyl acetate at 50 °C for 30 min, then quenched with ethyl vinyl ether for 10 min, and finally conc. HCl_{aq} or H_2SO_4 (approx. 10 equiv. with respect to catalyst) was added *via* microlitre syringe. The Ru species precipitated within seconds. The slurry was filtered through a plug of Na_2SO_4, and the solvent was removed under reduced pressure. The conversion was determined *via* ^{1}H NMR spectroscopy and aliquots of 20–22 mg were taken and digested with conc. HNO_3. The residual product was extracted as *t*-butyl methyl ether solution with water, dried and aliquots of 20–22 mg again were digested with conc. HNO_3. The ruthenium content of the digested samples was determined *via* ICP (inductively coupled plasma) mass spectrometry.

Generally, all reactions under the described conditions afforded >99% conversion. With one exception, the Ru contamination could be reduced by up to 68% (entries 9 and 10, Table 2) for the samples washed with water in comparison to those just obtained after filtratrion. However, the overall product yield was also reduced significantly by washing as a result of the small amounts of RCM product. In one case (entries 5 and 6, Table 2), the Ru content was higher after the wash, which may be due to an experimental error. With respect to the substrate, products obtained with DEDAM contained significantly lower amounts ruthenium (prewash: 24–140 ppm; after wash: 11–48 ppm) than the products obtained with DAP (prewash: 149–498 ppm; after wash: 80–160 ppm). It is conceivable that the diketone product functions as a reasonably good ligand for the metal and as a consequence, the Ru removal becomes much less efficient. With respect to acid and solvent, no clear trend is apparent. The lowest

Table 2 Efficiency of Ru removal for the RCM reactions of DEDAM and DAP with catalyst **13** in toluene and ethyl acetate ([Ru] = 2 mM, 2% loading) with addition of excess acid (conc. HCl_{aq} and H_2SO_4 [96%]) and filtration (F) or filtration and subsequent extraction with H_2O (W)

Entry	Substrate	Acid	Solvent	Method	Yield (%)[a, b]	ppm Ru[c]
1	DEDAM	HCl	Toluene	F	86.5	82
2	DEDAM	HCl	Toluene	W	58.8	48
3	DEDAM	H_2SO_4	Toluene	F	72.0	24
4	DEDAM	H_2SO_4	Toluene	W	60.3	11
5	DEDAM	HCl	AcOEt	F	76.9	34
6	DEDAM	HCl	AcOEt	W	52.9	45
7	DEDAM	H_2SO_4	AcOEt	F	85.7	140
8	DEDAM	H_2SO_4	AcOEt	W	45.7	48
9	DAP	HCl	Toluene	F	43.2	498
10	DAP	HCl	Toluene	W	68.9	160
11	DAP	H_2SO_4	Toluene	F	79.1	213
12	DAP	H_2SO_4	Toluene	W	44.5	80
13	DAP	HCl	AcOEt	F	78.2	335
14	DAP	HCl	AcOEt	W	63.3	144
15	DAP	H_2SO_4	AcOEt	F	68.1	149
16	DAP	H_2SO_4	AcOEt	W	44.3	90

[a] All conversions of the substrates were determined to be >99%. [b] The yields for method W are given with respect to the extraction only. [c] Estimated determination limit <0.1 ppm.

Ru contents in the RCM product were accomplished after filtration and extraction with water when the reaction solution of DEDAM in toluene was treated with H_2SO_4 (entries 3 and 4, Table 2). The residual Ru levels of 24 ppm and 11 ppm are already very close to the pharmaceutical standard of <10 ppm.

Conclusions

The first Grubbs-type (**12**) and Hoveyda–Grubbs-type (**13**) olefin metathesis catalysts bearing a pH-responsive NHC ligand were synthesized by introducing a *p*-NMe_2 group to the benzene rings of the ligand. Under neutral solvent conditions, the catalysts are neutrally charged, soluble in organic solvents and have similar activity in RCM and ROMP reactions as their non-functionalized, commercially available counterparts. The NMe_2 groups could be protonated with HCl and the complexes become dicationic. In complex **12**, the addition of 2 equiv. HCl in methanol resulted in the formation of an only moderately stable mixture of Ru species only partially ligated by the PCy_3 ligand. The residual ligand was protonated and observed as $DPCy_3^+$ Cl^- salt *via* ^{31}P NMR spectroscopy. The phosphine-ligated Ru species decomposes within several hours at room temperature. Complex **13** was dissolved in dilute HCl_{aq} (0.1 M) where it formed the diprotonated complex **13′**. The complex remained stable for several hours under non-inert conditions. Slow hydrolysis afforded 45% decomposition after 7 d. Both catalysts are active during the RCM of diallylmalonic acid in protic media at 50 °C, however, the reactions proceeded at low rates and did not afford complete conversions. The ROMP of cationic oxanorbornene derivative **14** did not afford noticeable conversions at 50 °C. It is likely that the NHC ligand in its protonated form is significantly less σ-donating and thus, the activity is dramatically reduced. A protocol was developed to remove the ruthenium from RCM reaction mixtures by acid addition and subsequent filtration. The residual Ru contents in the isolated RCM products were as low as 24 ppm after simple filtration, and as low as 11 ppm when the isolated organic materials after filtration were additionally extracted three times with water. These values are very close to the pharmaceutical standard of <10 ppm Ru without applying cost-intensive chromatography or chemical adsorption methods. Further investigations are ongoing.

Experimental

General procedures

All experiments with organometallic compounds were performed under a dry nitrogen atmosphere using standard Schlenck techniques or in an MBraun dry-box (O_2 <2 ppm). NMR spectra were recorded on a Varian Inova instrument (300.1 MHz for ^1H, 75.9 MHz for ^{13}C, and 121.4 MHz for ^{31}P). ^1H and ^{13}C NMR spectra were referenced to the residual solvent, ^{31}P NMR spectra were referenced using H_3PO_4 ($\delta = 0$ ppm) as external standard. For sonication a Fischer Scientific Ultrasonic Cleaner FS 30 was used. The bath temperature was set to 30 °C.

Materials and methods

All solvents for manipulations under inert gas (heptane, thf, CH_2Cl_2) were dried by passage through solvent purification (MBraun-Auto-SPS). All NMR solvents used in combination with complexes **12** and **13** (D_2O, DCl–D_2O, CD_2Cl_2, $CDCl_3$) were degassed prior to use. Other solvents were used as purchased. Reagents were purchased from commercial sources, were degassed and stored in the dry-box when directly used in combination with organometallic complexes, and otherwise were used without further purification. 2-*i*-Propoxystyrene,[36] diethyldiallylmalonate (DEDAM),[37] diallylmalonic acid (DAM),[38] 3,3-diallylpentane-2,4-dione (DAP),[39] and monomer **14**[34a] were synthesized according to literature procedures. Grubbs' catalyst **1** was purchased from Aldrich, degassed and stored in the dry-box.

N,*N*-3,5-Tetramethyl-1,4-phenylenediamine (8)[28]

A solution of $NaNO_2$ (9.922 g, 143.8 mmol) in water (20 mL) was added slowly to a solution of *N*,*N*-3,5-tetramethylaniline **7** (20.032 g, 134.4 mmol) in conc. HCl_{aq} (50 mL) under vigorous stirring *via* a capillary which was immersed in the reaction solution at −5 °C over a period of 60 min. During the addition, a yellow precipitate (4-nitroso-*N*,*N*-3,5-tetramethylaniline·HCl) was formed. After the addition, the slurry was stirred for another 60 min at 0 °C and then filtered cold through a Buchner funnel. The yellow residue (4-nitroso-*N*,*N*-3,5-tetramethylaniline·HCl) was washed with ethanol (3 × 50 mL) and suction-dried for 60 min. Then the powdered residue was added in small portions to a slurry of powdered tin (7.360 g, 61.8 mmol) in conc. HCl_{aq} (50 mL) at 70 °C. While adding the nitrosoaniline the solution turned intensely yellow in color and reverted back to colorless within a few seconds. Once all tin was consumed, the yellow color persisted. The residual nitrosoaniline salt not used in the conversion was stored for a later transformation. It should be noted that this procedure avoids the addition of excess tin. Otherwise an insoluble precipitate is formed during the basic work-up, and this causes a significant reduction of the yield. The resulting slightly yellow solution was slowly added to ice-cold 3 M aqueous NaOH (300 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the organic phases were combined and dried over $NaSO_4$. The solvent was removed to give compound **8** (9.770 g, 60.3 mmol, 45%) in over 98% purity (^1H NMR) as a golden-colored viscous liquid.

Glyoxalbis(4-dimethylamino-2,6-dimethylphenyl)imine (9)

Compound **8** (6.373 g, 39.4 mmol) was added to a solution of 40% aqueous glyoxal (3.852 g, 26.6 mmol) in methanol (100 mL) and one drop of conc. HCl_{aq} (approx. 20 µL) and stirred for 24 h at room temperature. During the reaction, a deep-yellow colored precipitate was formed. The slurry was filtered, the residue was washed with methanol (3 × 20 mL), sucked dry and the dried in the vacuum oven at 60 °C for 3 h to give compound **9** (5.874 g, 16.8 mmol, 85%) in >99% purity (^1H NMR) as a golden-yellow powder. ^1H NMR (300.1 MHz, 20 °C, $CDCl_3$) δ 8.11 (s, 2 H, N=C*H*), 6.50 (s, 4 H, C_6H_2), 2.94 (s, 12 H, $N(CH_3)_2$), 2.24 (C_6H_2–CH_3); ^{13}C NMR (75.9 MHz, 20 °C, $CDCl_3$) δ 162.5 (N=*C*H), 148.1, 140.6, 128.9, 112.8 (C_6H_2), 40.8 ($N(CH_3)_2$), 19.2 (C_6H_2–CH_3).

N,*N*′-Bis(4-dimethylamino-2,6-dimethylphenyl)ethylene-1,2-diamine (10)

A solution of compound **9** (3.380 g, 9.66 mmol) in thf (100 mL) containing $NaBH_4$ (0.821 g, 21.6 mmol) and boric acid (1.781 g,

28.8 mmol) was stirred at 30 °C over a period of 60 min. In this time period the solution turned colorless. The solution was cooled to room temperature and water (40 mL) was added carefully and then conc. HCl_{aq} (10 mL) was added dropwise until the solution stopped developing gas. The solution was warmed to 50 °C under stirring for 10 min and then cooled to room temperature. The thf was removed under reduced pressure and the aqueous solution was neutralized with Na_2CO_3. The aqueous phase was extracted with *t*BuOMe (60 mL), and the organic layer was washed with brine (3 × 40 mL). The organic phase then was dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure with a rotary evaporator, and the residue was dried in the vacuum oven at 60 °C for 2 h to give compound **10** (3.00 g, 8.47 mmol, 88%) as a colorless, viscous liquid in >98% purity (^{1}H NMR) which solidified at room temperature over 12 h. ^{1}H NMR (300.1 MHz, 20 °C, $CDCl_3$) δ 6.51 (s, 4 H, C_6H_2), 3.11 (s, 4 H, NH–CH_2), 2.89 (s, 12 H, N(CH_3)$_2$), 2.34 (s, 12 H, C_6H_2–CH_3); ^{13}C NMR (75.9 MHz, 20 °C, $CDCl_3$) δ 146.7, 136.7, 131.5, 113.9 (C_6H_2), 49.7 (NH–CH_2), 41.3 (N(CH_3)$_2$), 18.8 (C_6H_2–CH_3).

1,3-Bis(2,6-dimethyl-4-dimethylaminophenyl)-4,5-dihydroimidazolium chloride, H_2ITap·HCl (11)

A solution of diamine **10** (2.567 g, 7.25 mmol) and ammonium chloride (380 mg, 7.22 mmol) in triethyl-*ortho*-formiate (30 mL) was heated under stirring at 130 °C for 16 h. The excess triethyl-*ortho*-formiate was distilled under reduced pressure (0.1 Torr) and collected to be reused. Cyclohexane (30 mL) was added to the solid residue and sonicated for 30 min at 30 °C. The slurry was filtered, washed with cyclohexane (3 × 20 mL), sucked dry on the filter for 10 min and dried in the vacuum oven at 60 °C for 3 h to give compound **11** (2.499 g, 6.31 mmol, 87%) as a slightly off-white powder in >99% purity. ^{1}H NMR (300.1 MHz, 20 °C, d_6-DMSO) δ 8.97 (s, 1 H, N–C*H*=N), 6.55 (s, 4 H, C_6H_2), 4.37 (s, 4 H, N–CH_2), 2.92 (s, 12 H, N(CH_3)$_2$), 2.32 (s, 12 H, aryl-CH_3); ^{13}C NMR (75.9 MHz, 20 °C, d_6-DMSO) δ 160.8 (N-CH=N), 150.8, 135.9, 122.2, 111.7 (C_6H_2), 51.3 (N–CH_2), 40.0 (N(CH_3)$_2$), 17.8 (C_6H_2–CH_3).

NMR studies of H_2ITap·(HCl)(DCl)$_2$ (11′)

Complex **11** (4.0 mg, mmol) was dissolved in 0.1 M DCl/D_2O (0.60 mL) and NMR spectra were recorded. ^{1}H NMR (300.1 MHz, 20 °C, D_2O) δ 8.57 (s, 1 H, N–C*H*=N), 7.25 (s, 4 H, C_6H_2), 4.31 (s, 4 H, N–CH_2), 3.00 (s, 12 H, N(CH_3)$_2$), 2.19 (s, 12 H, aryl-CH_3); ^{13}C NMR (75.9 MHz, 20 °C, $CDCl_3$) δ 160.0 (N–*C*H=N), 142.7, 139.1, 134.1, 121.0 (C_6H_2), 51.1 (N–CH_2), 46.3 (N(CH_3)$_2$), 17.3 (C_6H_2–CH_3).

H_2ITap(PCy$_3$)Cl$_2$Ru=CH–Ph (12)

Ligand precursor **11** (637 mg, 1.61 mmol) and KO*t*Bu (178 mg, 1.60 mmol) were heated under stirring to 60 °C in n-heptane for 60 min under inert gas conditions. After cooling to room temperature, Grubbs' catalyst **1** (1.003 g, 1.22 mmol) was added and the slurry was heated to 65 °C for 24 h also under inert gas conditions. In this time period an orange-brownish precipitate was formed. The solution then was cooled to room temperature, the solvent was removed under reduced pressure and methanol was added under non-inert conditions. The resulting slurry was sonicated for 30 min in air and then filtered. The filter residue was washed with water (10 mL) and methanol (3 × 10 mL). The resulting light brown powder was dried in the vacuum oven at 60 °C for 60 min to give catalyst **12** (794 mg, 0.86 mmol, 70%) in >98% purity (^{1}H and ^{31}P NMR). Crystals suitable for X-ray analysis were obtained from slow vapor diffusion of pentane into a saturated solution of complex **12** in CH_2Cl_2 at –20 °C. ^{1}H NMR (300.1 MHz, 20 °C, CD_2Cl_2) δ 19.02 (s, 1 H, Ru=C*H*), 8.95 (br, 2 H), 7.07 (br, 3 H, C_6H_5), 6.49 (s, 4 H, C_6H_2), 3.91 (br, 4 H, N–CH_2), 2.96 (s, 12 H, N(CH_3)$_2$), 2.72 (s, 12 H, C_6H_2–CH_3), 2.42–2.60 (br m, 3 H), 2.12–2.37 (br m, 3 H), 1.92–2.05 (br m, 3 H), 1.29–1.55 (br m, 12 H), 0.92–1.12 (br m, 12 H, PCy_3); ^{13}C NMR (75.9 MHz, 20 °C, CD_2Cl_2) δ 294.1 (br, Ru=*C*), 221.4 (d, ^2J[^{31}P^{13}C] = 80.1 Hz, NHC-*C*), 164.4, 129.7, 128.0, 127.5 (s, =CH–C_6H_5), 152.1, 150.5, 150.1, 140.0 (br), 137.6 (br), 128.3, 112.3, 111.7 (s, NHC-Ph-*C*H), 53.1 (d, ^4J[^{31}P^{13}C] = 3.3 Hz), 52.1 (s, N–CH_2), 40.5, 40.4 (s, N(CH_3)$_2$), 20.9 (s), 19.3 (br, C_6H_2), 31.7 (d, ^1J[^{31}P^{13}C] = 16.5 Hz), 29.6 (br), 28.3 (d, ^3J[^{31}P^{13}C] = 10.2 Hz), 26.8 (s, PCy_3-*C*); ^{31}P{^{1}H} NMR (121.4 MHz, 20 °C, CD_2Cl_2) δ 30.2 (s).

H_2ITapCl$_2$Ru=CH–(C$_6$H$_4$–O–*i*Pr) (13)

Catalyst **12** (303 mg, 0.33 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature under inert gas conditions with CuCl (36 mg, 0.40 mmol) and 2-*i*-propoxystyrene (54 mg, 0.33 mmol) for 2 h. The solution turned from brown to green in this time period. Then the solvent was removed under reduced pressure and the residue was taken up in 10 mL of a mixture of CH_2Cl_2–heptane 1 : 1 v/v in air. The solution was filtered, and then was loaded onto a flash column with silica gel. The column was washed with a mixture of CH_2Cl_2–ethanol 95 : 5 v/v until all green color was removed from the stationary phase. The solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (10 mL). Heptane (30 mL) was added and the residual CH_2Cl_2 was removed under reduced pressure. The product precipitated and the slurry was filtered. The filter residue was washed with n-heptane (3 × 10 mL), sucked dry for 5 min and dried in the vacuum oven at 60 °C for 60 min to give catalyst **13** (162 mg, 0.23 mmol, 70%) as a green powder in >98% purity (^{1}H NMR). Crystals suitable for X-ray analysis were obtained from slow layer diffusion of n-heptane into a saturated solution of complex **13** in CH_2Cl_2 at room temperature. ^{1}H NMR (300.1 MHz, 20 °C, $CDCl_3$) δ 16.80 (s, 1 H, Ru=C*H*), 7.47 (m, 1 H), 7.01 (m, 1 H), 6.85 (m, 1 H), 6.78 (m, 1 H, C_6H_4), 6.58 (s, 4 H, NHC-C_6H_2), 4.15 (s, 4 H, N–CH_2), 3.00 (s, 12 H, N(CH_3)$_2$), 2.44 (br, 12 H, NHC-Ph–CH_3), 4.89 (sept., ^3J[^{1}H^{1}H] = 6.0 Hz, 1 H, $CH(CH_3)_2$), 1.28 (d, ^3J[^{1}H^{1}H] = 6.0 Hz, 6 H, CH(CH_3)$_2$); ^{13}C NMR (75.9 MHz, 20 °C, $CDCl_3$) δ 299.0 (Ru=*C*), 211.7 (N=*C*–N), 161.0, 150.8, 122.8, 122.2, 112.9, 112.2 (s, =CH–C_6H_4), 152.2, 145.5, 129.3, 112.2 (s, C_6H_2), 74.8 ($CH(CH_3)_2$), 26.9 ($CH(CH_3)_2$), 40.8 (s, N(CH_3)$_2$), 21.1 (C_6H_2–CH_3).

^{1}H NMR investigation of the hydrolytic stability of H_2ITapCl$_2$Ru=CH–(C$_6$H$_4$–O–*i*Pr)·(HCl)(DCl)$_2$ (13′)

Complex **13** (2.0 mg, 3 μmol) was dissolved in 0.1 M DCl/D_2O in air and kept at room temperature in an NMR tube. ^{1}H NMR spectra were recorded in certain time intervals and the intensities were monitored for the corresponding NMR signals for complex **13′** and the hydrolysis product H_2ITap·(HCl)(DCl)$_2$ (**11′**). **13′** ^{1}H

NMR (300.1 MHz, 20 °C, 0.1 M DCl/D_2O) δ 16.29 (s, 1 H, Ru=C*H*), 7.04 (s, 4 H, C_6H_2), 7.11 (m, 1 H), 6.49 (m, 1 H), 6.43 (m, 2 H, C_6H_4), 4.46 (m, 1H, C*H*(CH_3)$_2$), 3.64 (s, 4 H, N–CH_2), 2.81 (s, 12 H, N(CH_3)$_2$), 1.91 (s, 12 H, aryl-CH_3), 0.58 (m, 6 H, CH(CH_3)$_2$; ^{13}C NMR (75.9 MHz, 20 °C, 0.1 M DCl/D_2O) δ (Ru=*C*, n.o.), 207.2 (N=*C*–N), 139.2, 132.1, 122.6, 122.0, 113.7 (1 signal n.o., =CH–C_6H_4), 152.0, 145.0, 142.3, 120.4 (s, C_6H_2), 74.8 (*C*H(CH_3)$_2$), 26.9 (*C*H(CH_3)$_2$), 40.8 (s, N(CH_3)$_2$), 21.1 (C_6H_2–*C*H_3).

General procedure for ROMP of COE with catalysts 2, 3, 12, 13

COE (7.8 µL, 60 µmol) was added to the catalyst solution (0.60 mL, 0.50 mM, 0.30 µmol [**2**, **12** in C_6D_6; **3**, **13** in $CDCl_3$]) under inert conditions *via* a microlitre syringe and the monomer conversion was monitored *via* ^{1}H NMR spectroscopy (300.1 MHz, 20 °C) by integration of the sufficiently separated multiplet signals at δ = 5.51 ppm (COE, =C*H*–) and 5.46 ppm (polymer, C*H*) over a period of 60 min.

General procedure for RCM of DEDAM with catalysts 2, 3, 12, 13

DEDAM (14.4 µL, 60 µmol) was added to the catalyst solution (0.60 mL, 1.00 mM, 0.60 µmol [**2**, **12** in C_6D_6; **3**, **13** in $CDCl_3$]) under inert gas conditions *via* a microlitre syringe and the monomer conversion was monitored *via* ^{1}H NMR spectroscopy (300.1 MHz, 20 °C) by integration of the sufficiently separated multiplet signals at δ = 2.87 ppm (DEDAM, allyl-CH_2) and 3.16 ppm [cyclopentene-3,3-di(ethylcarboxylate), ring-CH_2] over a period of 2 h.

General procedure for ROMP of monomer 14 with catalysts 12 and 13 in acidic protic media

The catalyst (8 µmol) and monomer **14** (67.8 mg, 0.50 mmol) were dissolved in the protic solvent (**12** in 2-PrOH–1 M HCl_{aq} 9 : 1 v/v; **13** 0.1 M HCl_{aq}, 2.0 mL) under inert gas conditions and the solution was heated to 50 °C under stirring. An aliquot (0.3 mL) was taken after 30 min, quenched with ethylvinyl ether, dried under vacuum, and the monomer conversion was monitored *via* ^{1}H NMR spectroscopy (300.1 MHz, 20 °C, D_2O) by integration of the signals δ 6.49 ppm (m, 2 H, **14**), δ 5.97 ppm (m, 2 *trans*-H, polymer) and δ 5.81 ppm (m, 2 *cis*-H, polymer).

General procedure for RCM of DAM with catalysts 12 and 13 in acidic protic media

The catalyst (8 µmol) and DAM (36.8 mg, 0.20 mmol) were dissolved in the protic solvent (**12** in 2-PrOH–1 M HCl_{aq} 9 : 1 v/v; **13** 0.1 M HCl_{aq}, 2.0 mL) under inert gas conditions and the solution was heated to 50 °C under stirring. An aliquot (0.3 mL) was taken after 30 min and 60 min, quenched with ethylvinyl ether, dried under vacuum, and the monomer conversion was monitored *via* ^{1}H NMR spectroscopy (300.1 MHz, 20 °C, D_2O) by integration of the signals δ 2.58 (DAM-CH_2) and δ 2.98 ppm (cyclopentene-CH_2). The aliquots taken after 60 min indicated the same conversion level as those taken after 30 min.

General procedure for RCM of DEDAM/DAP with catalyst 13 and subsequent Ru removal

The substrate (DEDAM: 96 mg, 0.40 mmol; DAP: 108 mg, 0.60 mmol) was added to a solution of catalyst **13** (DEDAM: 5.4 mg, 8 µmol; DAP: 8.1 mg, 12 µmol) in toluene or ethyl acetate (DEDAM: 2.0 mL; DAP: 3.0 mL) under inert gas conditions and the solution was kept stirring for 60 min at 50 °C. Then the solution was cooled to room temperature and acid (4 µL, conc. HCl_{aq} or H_2SO_4 [96%]) was added under inert gas atmosphere and stirred for another 2 min causing the formation of a precipitate. The solution was filtered through Na_2SO_4, washed with the solvent (3 × 2 mL), and the solvent was removed under reduced pressure. The product was dried in the vacuum (0.1 Torr) for 30 min. Isolated yields were obtained in the range of 72–87% (DEDAM) and 43–79% (DAP). ^{1}H NMR was used to determine the conversion (all >99%) by integration of distinct signals for the starting material and RCM product [δ 2.86 ppm (DEDAM-CH_2) *vs.* δ 3.16 ppm (cyclopentene-CH_2); δ 2.65 ppm (DAP-CH_2) *vs.* δ 2.91 ppm (cyclopentene-CH_2)]. An aliquot of 20–22 mg was taken from each reaction for Ru analysis *via* ICP MS. The residual product was dissolved in *t*-butylmethyl ether (20 mL) and washed with water (3 × 20 mL), the organic phase was dried over Na_2SO_4 and the solvent was removed and the product was dried in the vacuum (0.1 Torr) for 30 min. Product recoveries after the washing steps were between 44–69%. Again aliquots of 20–22 mg were taken for Ru analysis *via* ICP MS.

Crystal structure determination of complexes 12 and 13

Deep brown crystals of **12** are triclinic, a = 9.6949(5) Å, b = 13.969(2) Å, c = 17.5080(7) Å, α = 99.287(7)°, β = 99.451(4)°, γ = 90.001(7)°, volume = 2307.4(4) Å^3, two molecules per cell in space group $P\bar{1}$ (#2); very small green crystals of **13** are monoclinic, a = 19.6502(11) Å, b = 10.9433(5) Å, c = 33.440(2) Å, β = 104.928(7)°, volume = 6948.2(7) Å^3, eight molecules per cell in space group $P2_1/a$ (#14). Data was collected with Mo-Kα radiation (λ = 0.71073 Å) at 295(2) K, and an analytical absorption correction was applied. Structures were solved with SHELXS-86;[40] non-H atoms were modeled with anisotropic vibrational parameters, H atoms were located in difference electron density maps but placed in idealized positions with isotropic vibrational parameters 20% larger than the equivalent isotropic vibrational factor of the adjacent carbon atom. In each structure, aryl methyl hydrogens are disordered over alternate trigonal positions; these were modeled by refining occupancy factors. Structural models were refined to convergence by full-matrix least-squares using SHELXL-97.[41] Final R for **12** was 0.040 for 9628 reflections with $I > 2\sigma(I)$, 513 parameters, goodness-of-fit 1.04; for **13**, final R was 0.086 for 5128 reflections with $I > 2\sigma(I)$, 774 parameters, goodness-of-fit 0.99.

ICP MS analyses

The aliquots of RCM product were digested in hot conc. HNO_3 (1 mL). The solid residue was then dissolved in 0.16 M HNO_3 containing 2 ppb In as an internal standard. The final analytical solution contained about 0.67 mg of product per mL acid. Ru was determined in this solution using a sector-field ICP-MS (ThermoFinnigan Element 2). Equivalent results were obtained from five different Ru isotopes (masses 99, 100, 101, 102, and 104);

likewise, no difference was noted between results obtained in low resolution ($m/\Delta m = 300$) or medium resolution ($m/\Delta m = 4000$), suggesting a lack of interferences. Blank samples of the digested starting materials gave Ru contents of <0.1 ppm (DEDAM) and 0.6 ppm (DAP) Ru content.

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