Highly recoverable pyridinium-tagged Hoveyda–Grubbs pre-catalyst for olefin metathesis. Design of the boomerang ligand toward the optimal compromise between activity and reusability†

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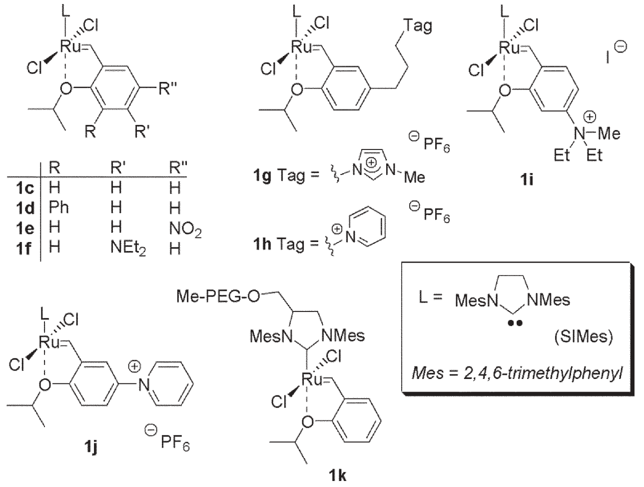
Whereas the boomerang ligand of Hoveyda–Grubbs pre-catalysts can be modified by attachment of a pyridinium tag to its benzylidene moiety, a precise adjustment of the length of the spacer allows the optimum balance to be reached between the activity of the catalyst and its recoverability, exceeding 98% after 6 catalytic runs in the best case.

The tremendous impact of the olefin metathesis reaction in academic[1] and industrial[2] areas led to a continual and exponential effort to improve the performance of the already highly efficient second (**1a**, (SIMes)(PCy$_3$)Cl$_2$Ru=CHPh) and third generation Grubbs catalysts (**1b**, (SIMes)(py)$_2$Cl$_2$Ru=CHPh, Cy = cyclohexyl, py = 3-bromopyridine)[3] and its Hoveyda's recyclable parent **1c**.[4] Further efforts were made toward a decrease in catalyst loadings for obvious economical and environmental reasons.[5] The principal modifications of the Hoveyda catalysts were aimed at providing faster access to the key propagating 14e$^-$ species. This was made by introduction of a bulky phenyl group (Blechert's catalyst **1d**)[6] or an electron-withdrawing substituent (EWG-substituted catalysts, *e.g.* **1e**)[7] on the benzylidene ether fragment.



Recently, we proposed that the introduction of an electron withdrawing group can be used not only to increase the catalyst's activity, but also to alter its physical-chemical properties, such as affinity to silica gel, solubility in polar media or lead to its non-covalent immobilization.[8] Indeed, EWG-activated complexes **1i**[9] and **1j**[10] are more active than the parent Hoveyda catalyst **1c** in traditional solvents and show strong affinity to silica gel,[11] which led to very low Ru-contamination in the final products. In addition, because of the polar ammonium EWGs, these complexes promote metathesis in aqueous media (**1i**, **1j**),[9,10] in neat water (**1i**),[12] and in room-temperature ionic liquids (RTILs, **1j**).[10] Unfortunately, the desired increased activity is counter-balanced by a low re-usability of the complex in RTLs (only two cycles).[10] Similar difficulties to recycle a catalyst were encountered when ionically immobilized salts of **1f** were used in a continous-flow setup (Passflow™).[13] Clearly, the best compromise is to be found between two antinomic properties, such as the activity of the catalyst and its recovery. Ionic-tagged *non-activated* Hoveyda-type precatalysts for applications in RTILs are known.[10,14,15] For example, we have recently described complexes **1g**[14] and **1h**,[10] which are immobilized in ionic liquid phase *via* ionic tags anchored to the benzylidene fragment through a three-carbon spacer (*an insulator*) and obtained high levels of recycling combined with very low levels of Ru-contamination (as low as 1.2 ppm).[14b,c]

In the present work, we have designed a tagged Hoveyda type catalyst representing the best compromise between activity and recyclability by introducing a methylene spacer between the ionic tag and the benzylidene moiety. The required ionic-tagged ligand **5** was synthesized in four steps according to Scheme 1. The exchange with the Grubbs catalyst **1a** in the presence of CuCl[4] afforded the expected air-stable green complex **1l** in excellent yield.‡

The activity of new methylene-pyridinium tagged pre-catalyst **1l** was compared with those of previously identified catalysts **1c** and ionic-tagged pre-catalysts **1g** and **1j** for the ring-closing metathesis (RCM) formation of trisubstituted olefin **7a**. The reactions were carried out at 23 °C with a low catalyst loading (1 mol%) (Fig. 1).

The new complex **1l** exhibits the same rapid initiation rate as the activated precatalyst **1j**. However, after 2 hours, a slower conversion rate is obtained for **1l**, reflecting a mild insulating effect of the methylene spacer. Next, we attemped to compare the new "fine-tuned" catalyst **1l** and the previously designed **1i** and **1j** in a set of model reactions, including RCM, enyne cycloisomerisation and CM transformation in various solvents *in air* (Table 1). We were pleased to see that **1l** is fully comparable with or even a better catalyst than **1j** and **1i** in classical (CH$_2$Cl$_2$) and aqueous solvents (Table 1, entries b–f). These results, which can be attributed to the

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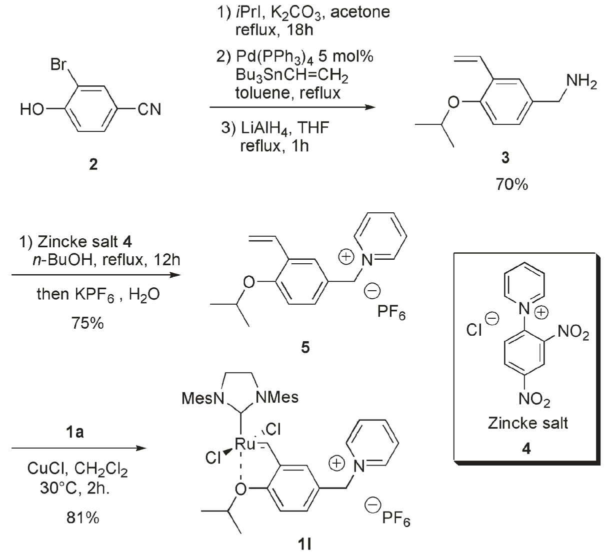


Scheme 1 Five-step synthesis of the methylene-pyridinium tagged catalyst **1l**.

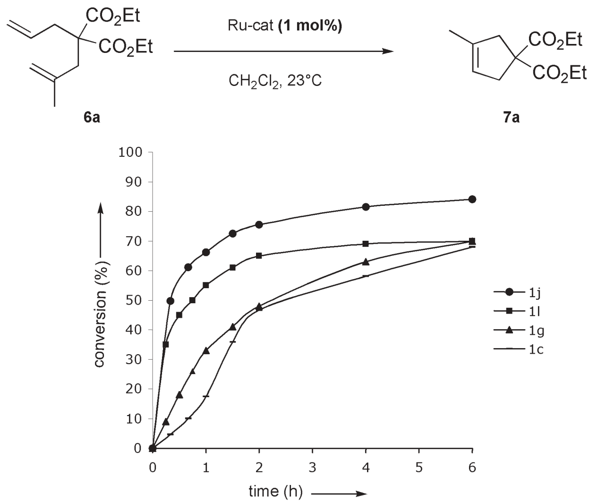
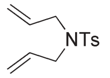
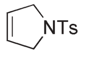
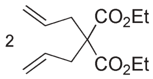
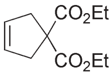
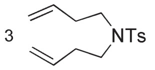
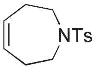
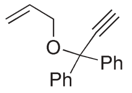
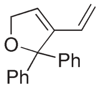
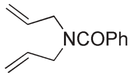
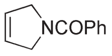
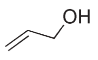
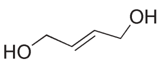


Fig. 1 Relative conversion rates for RCM of **6a** by **1c**, **1g** [Ref. 14*b*], **1h**[Ref. 10] and **1l** (this work) using 1 mol% of catalyst loading at 23 °C.

Table 1 Study of **1i–l** in different solvents[a,b]

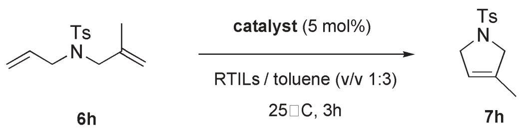
Entry[a]	Substrate	Product	Solvent	Cat. **1** (mol%) time (min)	Yield, %[b]
1	 **6b**	 **7b**	CH_2Cl_2	**1l** (5), 45 **1i** (5), 30 **1j** (5), 30	97 99[c] 99[d]
			EtOH/ H_2O	**1l** (5), 120 **1j** (5), 1440	75 50[d]
2	 **6c**	 **7c**	CH_2Cl_2	**1l** (5), 30 **1l** (5), 60 **1i** (5), 60 **1j** (5), 120	88 99 99[c] 78[d]
3	 **6d**	 **7d**	CH_2Cl_2	**1l** (5), 30 **1l** (1), 120 **1i** (5), 60 **1j** (5), 30	98 99 97[c] 99[d]
4	 **6e**	 **7e**	CH_2Cl_2	**1l** (5), 15 **1l** (1), 30 **1i** (5), 30 **1j** (5), 30	99 99 98[c] 99[d]
			EtOH/ H_2O	**1l** (5), 15 **1i** (5), 30 **1j** (5), 30	97 99[c] 99[d]
5	 **6f**	 **7f**	CH_2Cl_2	**1l** (2.5), 30 **1i** (2.5), 30 **1j** (2.5), 30	99 99[c] 99[d]
6	 **6g**	 **7h**	D_2O[e]	**1l** (1), 480 **1l** (1), 480 **1i** (1), 480 **1i** (2.5), 210 **1j** (1), 480 **1k** (5), 720 **1a** or **1c** or **1e** (1 mol%), 480	19 39[f] 66 99 14 95[g] 0[h]

[a] **Conditions**: 1-5 mol% of catalyst, CH_2Cl_2 or EtOH/H_2O v/v 5:2; c = 0.02 mol L^{-1}, 25 °C, in air. [b] Conversions were determined by GC analysis of the crude reaction mixture. For the methodology used, see [Ref. 13]. [c] [Ref. 9]. [d] [Ref. 10]. [e] Conditions: 1-5 mol% of catalyst, D_2O; $c_{[6g]}$ = 0.02 mol L^{-1}, 25 °C, in air. Conversions were determined by ^1H NMR analysis of the crude reaction mixture. [f] Reaction in presence of 450 eq. of NH_4Cl. [g] Conditions: 5 mol% **1k**, 45 °C, 12 h [Ref. 16]. [h] Catalyst not soluble in D_2O

high level of activity of **1l** *combined with* its increased stability, provide convincing evidence for a better control of the activity enhancement of the pre-catalyst which should allow for increased reusability. In neat water, however the quaternary ammonium iodide species **1i** was found to be the most active catalyst, exceeding the performances of the PEG-tagged **1k**[16] and other catalysts tested (Table 1, entry 6). The lower activity of all the PF_6 salts (**1j–1l**) can be attributed to their lower hydrophilicity as compared with iodide catalyst **1i** and the PEG-tagged catalyst **1k**. To prove this we have repeated the reaction of **1l** in the presence of large excess of Cl^- ions (in aq. solution of NH_4Cl), observing a significant increase of activity (39% instead of 19%, Table 1, entry 6).[17]

Aiming to validate our approach, we next focused on the possibility of recycling **1l** in ionic solvents. Because of their ability to solubilise organometallic species combined with non-miscibility with usual organic solvents, these new solvents represent an attractive media for reusing ionic-tagged catalysts, especially for the olefin metathesis reaction.[14,15] We chose the ring-closing metathesis of 2-allyl-2-methallyltosylamine **6h** as a model reaction and used two different ionic solvents (BMI·PF_6 and BMPy·BF_4) in the presence of toluene as a co-organic solvent (Table 2). In comparison with the excellent recyclability of the *non*-activated ionic pre-catalysts **1g** and **1h** (entries 1–3), and the poor results obtained with the directly-activated complexes **1i** and **1j** where a significant loss of activity is observed after the second cycle (entries 4–5),[18] the new moderately activated pre-catalyst **1l** shows a remarkable activity in *up to 6 runs* (>98%, entry 6). The crude

Table 2 Activity and recyclability of **1f–j** and **1l** in model metathesis reaction in ionic solvents



			Cycle (% conv.)[a]					
Entry	Catalyst	RTILs	1	2	3	4	5	6
1	**1g**[b]	BMI·PF_6	**>98**	**>98**	**>98**	**>98**	**>98**	**>98**
2	**1h**[c]	BMI·PF_6	>98	>98	>98	>98	93	91
3	**1h**[c]	BMPy·BF4[d]	>98	>98	97	92	88	74
4	**1i**	BMI·PF_6	98	33	2	—	—	—
5	**1j**[c]	BMI·PF_6	>98	95	65	6	—	—
6	**1j**[c]	BMPy·BF_4	>98	89	26	—	—	—
7	**1f**	BMI·PF_6	98	38	1	—	—	—
8	**1l**	BMI·PF_6	**>98**	**>98**	**>98**	**>98**	**>98**	**>98**

[a] Conversions were determined by ^{1}H NMR analysis. [b] [Ref. 14*b,c*]. [c] [Ref. 10]. [d] Reaction performed at 45 °C.

colourless product **7h** isolated by the evaporation of the toluene phase was >95% pure by NMR and its inductive coupled plasma mass spectroscopy (ICP-MS) analysis revealed extremely low levels of Ru-wastes (cycle 1: 11.5 ppm; cycle 3: 1.6 ppm and cycle 6: 9.5 ppm). These levels are similar to those observed with the imidazolium catalyst **1g** (ranged between 1.2 to 22 ppm).[14b] An additional charcoal treatment of the cyclised product **7h** (in refluxed CH_2Cl_2 over 24 h) before the ICP-MS analyses did not decrease significantly the Ru-contamination (cycle 1: 10.7 ppm; cycle 3: 5.5 ppm; cycle 6: 0.8 ppm).

In a summary, the results presented here indicate that the introduction of a methylene spacer between the tag and the benzylidene fragment allows an optimum recovery of the pre-catalyst in the ionic phase. In addition, it also enhances the recyclability while considerably limiting the undesirable extraction of the active 14e$^-$ species along with the organic phase during the isolation of the RCM product. The "fine-tuned" **1l** can find applications as a more universal catalyst for metathesis reactions in traditional solvents as well as in aqueous media and RTILs.

Notes and references

‡ **Synthesis of ionic catalyst 1l**: The 1-(4-isopropoxy-3-vinylbenzyl)pyridinium hexafluorophophate **5** (10 mg, 0.025 mmol), the Grubbs II precatalyst **1a** (21 mg, 0.025 mmol, 1 eq.) and the copper(I) chloride (2.5 mg, 0.025 mmol, 1 eq.) was introduced in a Schlenk flask under argon. Then dichloromethane (3 mL) was introduced and the solution was degased three times (vacuum/argon). The reaction mixture was stirred for 2 h at 30 °C under argon and the dichloromethane was removed under vacuum. The residue was dissolved with acetone (5 mL) and the insoluble salt was filtered off through a Celite plug. The filtrate was concentrated to dryness and the residue was purified by silica gel chromatography using dichloromethane/acetone (4 : 1) as eluent to afford the desired complex **1l** as a green solid (18 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.24 (d, J = 6.1 Hz, 6H, $(CH_3)_2$), 2.38 (s, 6H, CH_3), 2.44 (s, 18H, $(CH_3)_4$), 5.00 (sept, J = 6.1 Hz, 1H, CH), 6.09 (s, 2H, CH_2), 7.01 (d, J = 2.1 Hz,1H, CH_{Ar}), 7.04 (s, 4H,$(CH_2)_2$), 7.16 (d, J = 8.6 Hz,1H, CH_{Ar}), 7.81 (dd, J = 8.5 Hz and J = 2.1 Hz,1H, CH_{Ar}), 8,33 (t, J = 7.2 Hz, 2H, CH_{pyr}), 8.81 (t, J = 7.80 Hz, 1H, CH_{pyr}), 9.23 (d, J = 5.91 Hz, 2H, CH_{pyr}), 16.50 (s, 1H, CH_{Ru}); ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −73.0 (d, J = 707 Hz, 6F, F_6); ^{31}P NMR (162 MHz, $CDCl_3$, δ ppm): −143.0 (sept., J = 708 Hz, 1P, P); HRMS ESI+, [M$^+$] ion, *m/z* 718: $C_{37}H_{44}N_3O^{35}Cl_2{}^{102}Ru^+$, *m/z* calcd. 718.1909, *m/z* found 718.1890.

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18 The high activity of **1f** in RTILs can be explained by the formation of some amounts of an ammonium salt by (partial) ionization caused by the solvent. Catalyst **1f** as a free base is practically inactive in CH_2Cl_2, while its salts with various Brønsted acids are of high activity: see Ref. 13 and Ł. Gułajski, A. Michrowska, R. Bujok and K. Grela, *J. Mol. Catal. A: Chem.*, 2006, **254**, 118–123.