A simple and practical phase-separation approach to the recycling of a homogeneous metathesis catalyst†
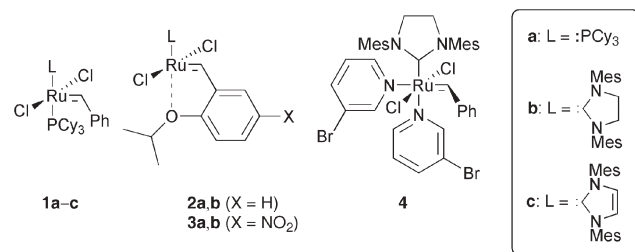
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The air stable asarone-derived Ru carbene 16, a robust olefin metathesis catalyst, can be easily separated after reaction by deposition on silica gel and reused up to nine times. This procedure provides products of excellent purity with low Ru content.

Despite the general superiority offered by modern *homogeneous* Grubbs and Hoveyda–Grubbs catalysts **1–4** (Scheme 1),[1] they share some disadvantages. Since olefin metathesis reaction is expected to be used in pharmaceutical processes, the most undesirable feature of these complexes is that during the reaction they form ruthenium byproducts, which are difficult to remove from the reaction products.[2] In many cases, ruthenium levels of > 2000 ppm remain after chromatography of products prepared by RCM with 5 mol% of Grubbs catalysts.[3]

Several protocols to remove toxic ruthenium impurities have been proposed.[3] Use of biphasic extraction,[4] various scavengers, such as lead tetraacetate,[5] DMSO or phosphine additives[6] (including supported phosphines)[7] were reported to reduce the ruthenium content to 200–1200 ppm. Alternatively, two cycles of chromatography, followed by 12 h incubation with activated charcoal, resulted in < 100 ppm.[8] From an economic point of view, in the whole chemical process the catalyst's cost is another important attribute. Therefore the development of improved strategies for recovering homogeneous catalyst and for removal of ruthenium decomposition by-products is of great importance.

One particularly innovative method involves the use of tagged catalysts, which can be easily separated from untagged products by a phase-transfer event (precipitation or liquid–liquid partition).[9] Recently, numerous Hoveyda type[11] catalysts bearing various 'phase-tags' for application in dendrimer-supported organic synthesis,[10] soluble polymer-supported organic synthesis (SPSOS),[12] fluorous synthesis[13] and ionic liquids[14] have been developed (Scheme 2).

We have recently reported on a new metathesis catalyst **16**.[15] Catalyst **16**, very stable and easy to prepare from inexpensive α-asarone, shows activity comparable to the parent Hoveyda carbene **2b**.[15] Interestingly, complex **16** exhibits a high affinity for silica gel when CH_2Cl_2 is used as eluent (TLC: R_f = 0.00 in CH_2Cl_2) which can potentially enable its efficient recovery. In the present investigation we decided to scrutinize this observation.[16] The model RCM reaction of *N*,*N*-diallyl-*p*-toluenesulfonamide using 5 mol% of **16**, followed by simple silica gel filtration (10 × weight of the product), affords *N*-*p*-tosyl-2,5-dihydro-1*H*-pyrrole as a colorless solid (Scheme 3 and Fig. 1). Inductively coupled plasma mass spectrometry (ICP-MS) analysis of the crude product sample indicated only 83 ppm Ru (0.0083 wt.%), which is substantially lower than contamination levels obtained with catalyst **2b** (up to 22600 ppm Ru; 2.26 wt.%), where all of the

Scheme 1 Selected ruthenium precatalysts for alkene metathesis. Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.
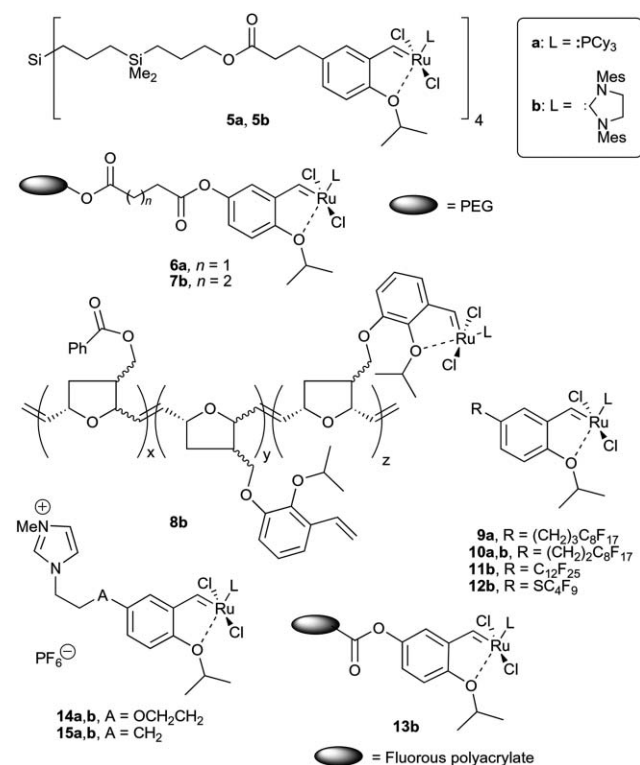
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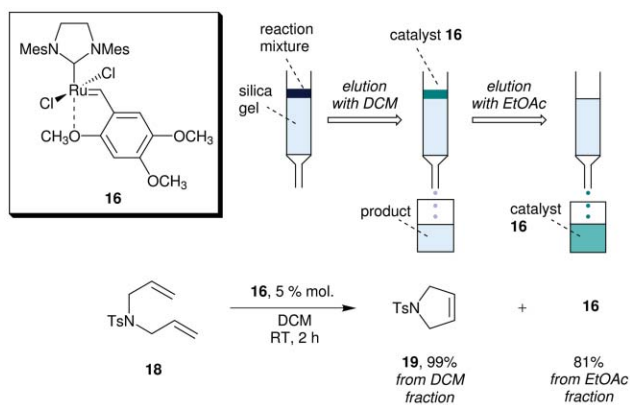† Electronic supplementary information (ESI) available: experimental section. See DOI: 10.1039/b517088e

Scheme 2 Selected ruthenium precatalysts for phase-separation applications (refs. [10–14]).

Scheme 3 Phase-separation and catalyst **16** recovery experiment (5 mol% Ru) using ordinary silica gel.
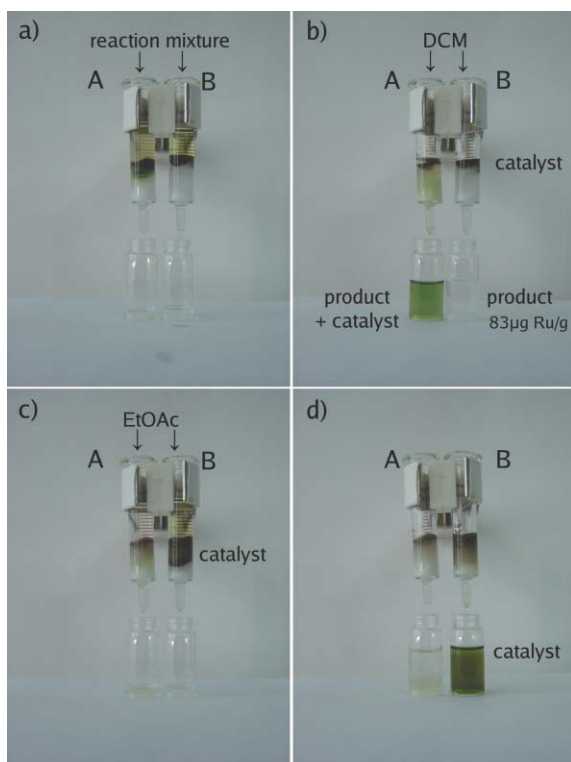

Fig. 1 Purification of RCM product **19** (0.3 mmol scale, 5 mol% Ru) on silica gel cartridges, using: A = Hoveyda–Grubbs catalyst **2b**; B = asarone-derived catalyst **16**. Legend: a)–b) Crude reaction mixture loaded on silica gel cartridge and washed with 5.0 mL of DCM; c)–d) the same cartridge washed further with EtOAc (5 mL).

catalyst remains in the product (Fig. 1).[17] Complex **16** can be eluted in a next chromatographic pass by washing with ethyl acetate, allowing 81% catalyst recovery (Scheme 3).[18]

Regenerated **16** contains 3–6 wt.% of 2,4,5-trimethoxybenzaldehyde **17** and other compounds,[10] but can be used similarly to the pristine catalyst, and this process can be continued through nine cycles (Table 1). In those recycling experiments the reaction mixtures were loaded onto a silica gel containing glass cartridge (shown in Fig. 1) and eluted with CH_2Cl_2 and EtOAc, allowing isolation of 56–90% of **16**. The lower recovery at larger scale (120–160 mg of **16**) can be explained by incomplete removal

Table 1 Reuse of catalyst **16** in the metathesis of **18** to **19**[a]

	Product **19**[a]		Catalyst **16**[b]	
Cycle no	Yield % (mg) [Ru ppm]		Yield % (mg)	**17** (wt.%)
1	96 (742.0)		56 (60.0)	3.1
2	85 (321.1) [110]		68 (32.1)	—
3	84 (199.1)		65 (18.3)	3.2
4	83 (99.5) [130]		71 (10.2)	5.7
5	79 (68.5)		74 (7.4)	5.7
6	73 (51.1) [130]		77 (5.6)	5.8
7	77 (39.0)		71 (4.0)	—
8	71 (30.6)		89 (3.6)	6.4
9	73 (27.0)		90 (3.1)[c]	—

[a] Conditions: 5 mol% catalyst **16**, 0.02 M in CH_2Cl_2, 22 °C, 2 h. Conversions determined by GC. Level of Ru impurity determined by ICP-MS and shown as percent by mass. [b] The amount of **17** determined by analysis of 200 MHz ^{1}H NMR spectrum of recovered unpurified **16** after removal of EtOAc *in vacuo*. [c] No benzylidene proton signal present in the ^{1}H NMR spectrum.
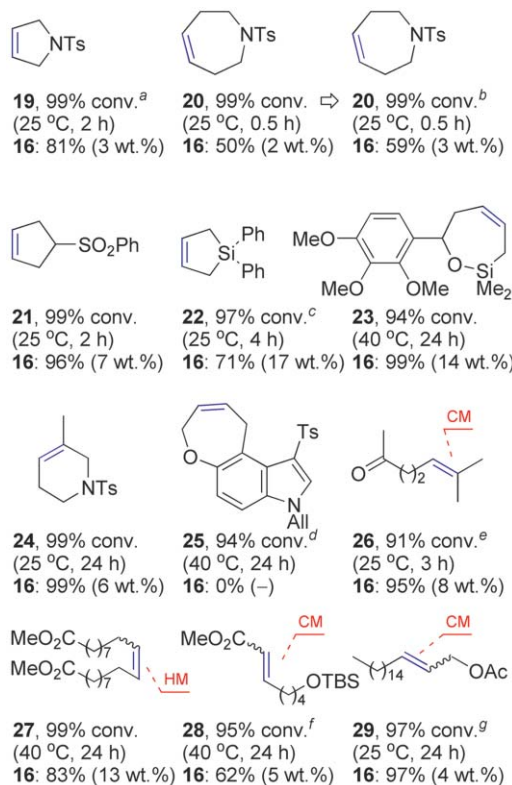
of catalyst from the cartridge. The conversion of the substrate, measured after 2 h of reaction, decreased from 96% (first run) to 73% (ninth run). All operations, including passing the reaction mixture through silica gel, washing with reagent-grade CH_2Cl_2 and ethyl acetate and concentration of the filtrate, can be carried out in air. It should be noted, however, that no recovery of **16** was possible after reactions at higher temperatures (50 °C).

The scope of this separation protocol was tested by conducting several ring closing metathesis reactions under standard conditions (0.3 mmol scale, 5 mol% of **16**, 25–45 °C, 0.5–24 h), and the results of these experiments are summarized in Scheme 4. All model substrates cyclized smoothly to form various hetero- and carbocycles, including polar 2,3,4-trimethoxybenzene-oxasilepine (**23**) and 7,10-dihydro-3*H*-oxepino[3,2-*e*]indole (**25**) derivatives. Conversions were good (99–79%), and the catalyst was recovered in 76–92% yields in all but one case. After metathesis reaction leading to **25** no catalyst **16** was recovered, probably due to its sequestering by a free *N*-allyl substituent still present in the product.

Next, the reactivity of **16** in some representative cross-metathesis reactions with methyl acrylate, 2-methyl-2-butene and (*Z*)-4-(acetyloxy)-2-butenyl acetate was tested under the standard conditions, to obtain valuable products, such as **29**, a pheromone of the Leopard moth (*Zeuzera pyrina*) (Scheme 4).[19]

In our standard procedure, the crude reaction mixtures were loaded onto ordinary silica gel glass cartridges (10–30 × weight of the substrate), which were eluted with CH_2Cl_2 to provide a fraction containing organic products and with EtOAc to recover catalyst **16**. Representative ^{1}H NMR and GC/MS and ICP-MS analyses show that the products **19–29** are of high purity and the level of Ru contamination is typically below 400 ppm (Scheme 4).[20]

We have thus designed an efficient new strategy for homogeneous Ru-catalyst phase-separation and recovery which provides products of excellent purity before silica gel chromatography or distillation. Complex **16**, a convenient and practical olefin metathesis catalyst, exhibits high reactivity and can be easily recycled without the need to use expensive fluorous solvents or special silica gel. This process can be automated and has been successfully applied to very small scale reactions. It therefore may be found useful for preparing small quantities of pure compound for biological screening.

19, 99% conv.[a]
(25 °C, 2 h)
16: 81% (3 wt.%)

20, 99% conv.
(25 °C, 0.5 h)
16: 50% (2 wt.%)

20, 99% conv.[b]
(25 °C, 0.5 h)
16: 59% (3 wt.%)

21, 99% conv.
(25 °C, 2 h)
16: 96% (7 wt.%)

22, 97% conv.[c]
(25 °C, 4 h)
16: 71% (17 wt.%)

23, 94% conv.
(40 °C, 24 h)
16: 99% (14 wt.%)

24, 99% conv.
(25 °C, 24 h)
16: 99% (6 wt.%)

25, 94% conv.[d]
(40 °C, 24 h)
16: 0% (−)

26, 91% conv.[e]
(25 °C, 3 h)
16: 95% (8 wt.%)

27, 99% conv.
(40 °C, 24 h)
16: 83% (13 wt.%)

28, 95% conv.[f]
(40 °C, 24 h)
16: 62% (5 wt.%)

29, 97% conv.[g]
(25 °C, 24 h)
16: 97% (4 wt.%)

Scheme 4 Library of ring-closing and cross-metathesis reactions catalyzed by **16** (products shown only; 0.3 mmol scale, 5 mol% Ru). For a description of the equipment used, see ref. [19]. Conversions were determined by analysis of ^{1}H NMR or GC/MS of the reaction mixture. The amount of aldehyde **17** in recovered catalyst **16** is given in parentheses. [a]Ru impurity 83 ppm. [b]Catalyst recovered from previous experiment. [c]Ru impurity 420 ppm. [d]All = allyl. See discussion in text. [e]CM reaction of 5-hexen-2-one with 10 equiv. of 2-methyl-2-butene. [f]CM reaction of *tert*-butyl(5-hexenyloxy)dimethylsilane with 2 equiv. of methyl acrylate. [g]CM reaction of 1-heptadecene with 2 equiv. of (*Z*)-4-(acetyloxy)-2-butenyl acetate. Ru impurity 320 ppm.

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16b
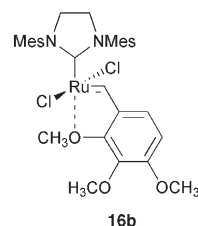
16 This investigation was in part inspired by recent elegant work of Fogg *et al.* on new aryloxide Ru complexes, which show also a high affinity for silica gel. See ref. [3].

17 We thank Ms. Zuzanna Kaczmarska and Mr Michal Barbasiewicz for the photographic documentation of this experiment.

18 Representative procedure of metathesis and catalyst recovery: A reaction flask equipped with a magnetic stirring bar was charged under argon with CH₂Cl₂ (30 mL), catalyst **16** (20.2 mg, 0.031 mmol) and diene **18** (155 mg, 0.61 mmol). The reaction mixture was stirred for 2 h at RT. After complete conversion (TLC), the reaction mixture was passed through a cartridge containing silica gel (1.4 g). The cartridge was washed with an additional portion of CH₂Cl₂ (10 mL) and then with EtOAc (20 mL). The CH₂Cl₂ fraction was concentrated under reduced pressure to yield *N-p*-tosyl-2,5-dihydro-1*H*-pyrrole (**19**) as a colorless solid (137 mg, 99% yield, > 95% purity (GC), 83 ppm Ru). After evaporation of the EtOAc fraction catalyst **16** was obtained as an olive green microcrystalline solid (16.5 mg, 81% yield, 96% purity (NMR)).

19 The product library presented in Scheme 4 was obtained using the "Radleys Heated Carousel Reaction Station" parallel reactor (www.radleys.com). We suppose that the catalyst recovery step can also be automated, *e.g.* by using the "Radleys Carousel Work-Up Station" or similar equipment.

20 In the case of fluorous solid-phase separation of **9a** and **10a**, **10b** the remaining ruthenium levels were in the range 1000–4000 ppm, see ref. [13].