A Good Bargain: An Inexpensive, Air-Stable Ruthenium Metathesis Catalyst Derived from α-Asarone

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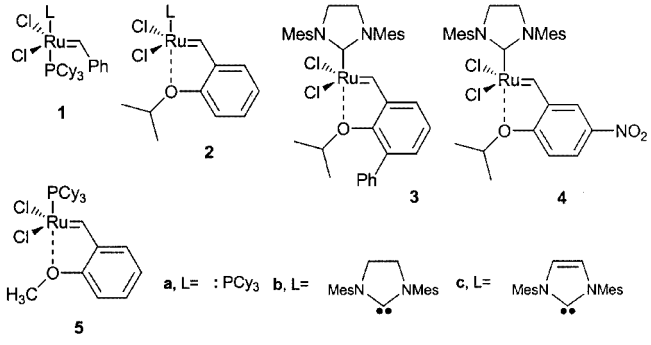
The one-step synthesis of ruthenium carbene precatalyst **7** from inexpensive α-asarone [(*E*)-**6**] is described. This recyclable and easy to obtain complex can be used successfully in various types of metathesis (RCM, CM, enyne) as a cheaper and more potent substitute of the Hoveyda-type precatalyst **2b**.

Introduction

Olefin metathesis has recently become a widely used carbon-carbon bond-forming method in organic synthesis.[1] The rapid progress in recent years was triggered by the discovery of the Grubbs' catalysts **1a** in the mid 1990s.[2] In spite of the general superb application profile of this precatalyst its low activity towards substituted double bonds and thermal instability are major drawbacks.[1]

Follow-up studies focused on improving the catalytic activity of ruthenium-alkylidene complexes have been carried out by several research groups. Exchange of one PCy_3 unit of the classical Grubbs' catalyst **1a** by *N*-heterocyclic carbene (NHC)[3] ligands leads to "second generation" metathesis catalysts of superior reactivity and increased stability.[4] The newly introduced, highly active ruthenium alkylidene complexes **1b**, **1c** were found to efficiently catalyse reactions of previously **1a**-inactive substrates, including α,β-unsaturated olefins (Scheme 1).[4,5]



Scheme 1. The family of ruthenium precatalysts for alkene metathesis; Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl

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Hoveyda has recently established **2** as remarkably robust complexes promoting olefin metathesis by a "release-return" mechanism.[6] The phosphane-free catalyst **2b** was found to possess a greater reactivity toward electron-deficient olefins than **1b**.[7] The fact that the ruthenium carbene **2b** is air-stable, can be easily purified by standard silica-gel chromatography and can be recycled after the reaction are particularly appealing facets of this chemistry.[6]

Blechert and Wakamatsu have shown very recently that replacement of the isopropoxybenzylidene "ligand" in **2b** by BINOL-[8a] or biphenyl-based benzylidene[8b] results in a large improvement in catalyst activity, as, for example, complex **3** is *much more reactive* not only than **2b** but also the "second generation" Grubbs catalyst **1b**.[9]

During our ongoing studies we have shown that the Hoveyda-type catalyst can be significantly improved by changing not only the steric[9] but also the electronic situation in the Ru-chelating isopropoxy fragment: the introduction of the strongly electron-withdrawing NO_2 group to the 2-isopropoxybenzylidene ring of **2b** leads to complex **4** which is just as stable as the parent Hoveyda catalyst **2** but dramatically more reactive.[10] This observation suggests that *decreasing the electron density* on the oxygen atom of the isopropoxy fragment of the Hoveyda-type ruthenium carbene **2b** results in an increase of its catalytic activity.[10]

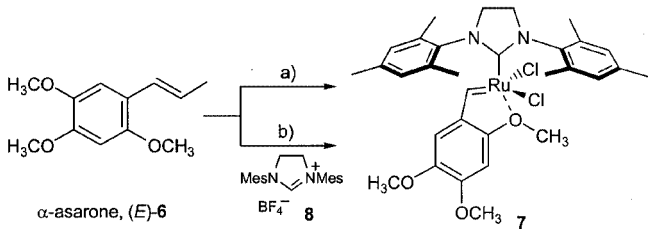
Results and Discussion

Intrigued by the above-described results we decided to test further if the increase of electron density in the benzylidene part of **2** results in any change of catalyst stability and reactivity.

Since neither 2-isopropoxystyrene nor 2-isopropoxybenzaldehyde derivatives are commercially available, we opted to check if any 2-alkoxystyrenes having electron-donating substituents could be easily accessed, and focused on naturally occurring α-asarone [(*E*)-**6**]. This stable, crystalline

compound is a major component of the essential oil from European ginger (*Asarum europeum*), an evergreen herbaceous plant widely cultivated in many gardens.

As illustrated in Scheme 2, we used this inexpensive styrene as a starting material for preparation of the corresponding ruthenium carbene **7**. The olive-green microcrystalline complex **7** could be easily obtained in almost quantitative yield (91−96%, four runs) by the reaction of **1b** (1 equiv.) and CuCl (1 equiv.) with α-asarone (1 equiv.), followed by flash chromatography (route a).[11]



Scheme 2. Synthesis of catalyst **7**; a) **1b**, CuCl, CH_2Cl_2, 40 °C, 91−96%; b) i) **8**, $tC_5H_{11}OK$, *n*-hexane, room temp., 1 h, then **1a**, 80 °C, 30 min, ii) (*E*)-**6**, CuCl, CH_2Cl_2, 40 °C, 82−89%

As synthesis of **7** from relatively expensive **1b**[12] would be economically unfavourable on a larger scale, we developed a two-step, one-pot process using the cheaper "first generation" carbene **1a** as a Ru source (route b).[13] In this procedure solid **1a** (1 equiv.) was stirred with the commercially available 4,5-dihydroimidazolium salt **8** in the presence of potassium *tert*-pentanolate[13] in *n*-hexane. The in-situ generated **1b** was then treated in the same flask with a CH_2Cl_2 solution of α-asarone (1.1 equiv.) providing, after flash chromatography, complex **7** in high yield (82−89%, five runs).

Having secured an efficient method for the preparation of complex **7**, we tested its catalytic activity. A ring-closing

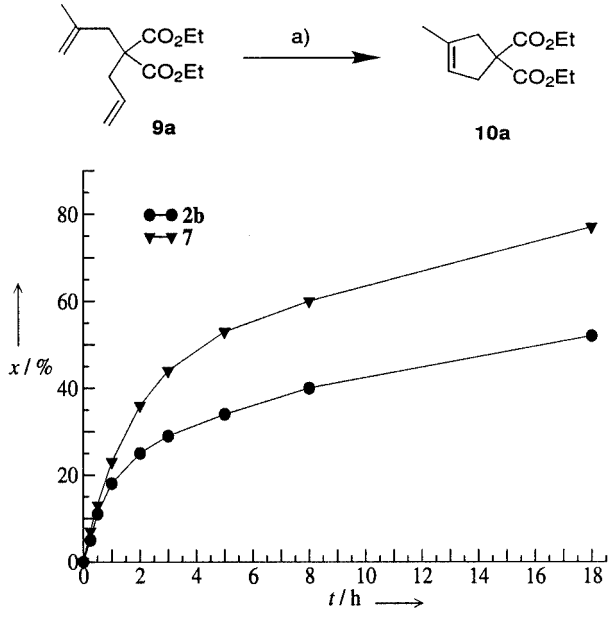
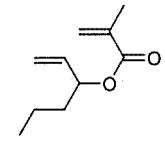
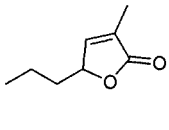
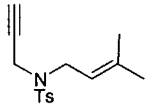
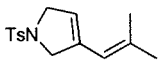
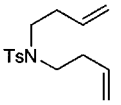
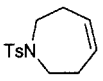
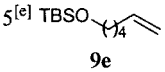
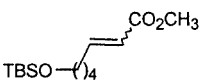
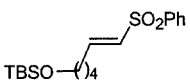
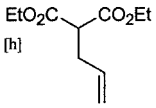
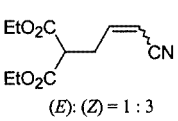


Figure 1. RCM of **9a** using precatalysts **2b** and **7**: a) cat. (2.5 mol %); CH_2Cl_2, room temp.; x = conversion

metathesis (RCM) reaction of the model diene **9a** showed that complex **7** effectively promotes formation of the trisubstituted double bond. Interestingly, the ginger-derived precatalyst **7** was slightly more reactive in this transformation than the parent Hoveyda carbene **2b** (Figure 1). It has been reported by Hoveyda that the variation from an isopropoxy to a methoxy chelating group has a dramatic impact on the catalyst performance, as the 2-methoxy analogue **5** (Scheme 1) was significantly *less stable* and *less reactive* than **2a**.[6a] In the light of this observation it is worthwhile to note that the ruthenium carbene **7** is not only highly active but also very stable, as it can be stored in air for several months without decomposition or loss of activity.[14]

The metathesis of selected benchmark substrates was then examined. As illustrated in Table 1, complex **7** (1−5 mol %, room temp. to 40 °C) serves as an effective catalyst for formation of carbo- and heterocycles bearing a di- or trisubstituted double bond (entries 1−4).

Table 1. Comparative investigation of **7**

Entry	Substrate **9**	Product **10**	Yield using **7** [%] [a]	Yield using ref. catalyst [%] [a]
1	**9a**	**10a**	75 % [b] (2.5 mol.%, r.t., 18h)	**2b**: 50% [b] (2.5 mol.%, r.t., 18h)
2			85 % (2.5 mol.%, 40°C, 8h)	
3			91% (5 mol.%, 40°C, 30min)	**1c**: 89% [c] (5 mol.%, 80°C, 30min)
4			96% (1 mol.%, r.t., 10min)	**1b**: 18% [d] (1 mol.%, r.t., 10min)
5 [e]	 **9e**	 (*E*): (*Z*) = 98 : 2	89% (2.5 mol.%, 40°C, 60min)	
6 [f]	**9e**	 (*E*)-**8f**	80% (5 mol.%, 40°C, 16h	**1b**: 85% [g] (5 mol.%, 40°C, 16h)
7 [h]		 (*E*): (*Z*) = 1 : 3	79% (5 mol.%, 40°C, 6h)	**2b**: 79% [i] (8 mol.%, 40°C, 6h)

[a] Isolated yield unless stated otherwise. [b] Yield determined by GC. [c] Ref.[4g] [d] Ref.[8a] However, after longer reaction times this cyclisation proceeds quantitatively (99% after 1 h; cf. ref.[8b]). [e] Reaction with 2 equiv. of methyl acrylate. [f] Reaction with 2 equiv. of phenyl vinyl sulfone. [g] Ref.[5] [h] Reaction with 2 equiv. of acrylonitrile. [i] Ref.[7a]

Furthermore, the potential of catalyst **7** for more challenging cross-metathesis has been proved (entries 5−7). In all reported cases complex **7** exhibits similar or even higher activity than the reference systems **1b**,**c** and **2b**. Moreover, this catalyst is easily recyclable, as it was possible to regenerate after the reaction 80−86% of complex **7** by flash chromatography (runs 3−4).

In conclusion, we have shown again[10] that substitution exerts a strong influence on the reactivity pattern of the Hoveyda-type ruthenium carbene complexes which is far from being comprehensively studied. The replacement of 2-isopropoxybenzylidene by 2,4,5-trimethoxybenzylidene leads to a recyclable catalyst which is not only very stable but also more reactive than **2b**. Therefore, this catalyst can be successfully used in various types of metathesis (RCM, CM, enyne) as a cheaper[15] and more potent substitute of **2b**. The ginger-derived catalyst **7** is also superior to the Grubbs catalyst **1b** in the cases when application of **1b** is known to be difficult.[7]

Although the activity of **7** does not reach the level outlined very recently by the extremely active **3**[8] and **4**,[10] this inexpensive and easy to prepare catalyst is very attractive from a practical point of view. Experiments to learn in more detail the substitution effects on the structure and catalytic activity of Hoveyda-type ruthenium carbene complexes are under way.

Experimental Section

Catalyst 7. Procedure a: Carbene complex **1b** (102 mg, 0.12 mmol), CuCl (13 mg, 0.132 mmol) and CH_2Cl_2 (8 mL) were placed in a Schlenk flask equipped with a condenser. A solution of (*E*)-**6**, (28 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) was then added and the resulted solution was stirred under argon at 40 °C for 1 h. From this point forth, all manipulations were carried out in air with reagent-grade solvents. The reaction mixture was concentrated in vacuo and the resultant material was purified by column chromatography on silica. Elution with CH_2Cl_2/EtOAc (5:1) removed **7** as a khaki band. Removal of the solvent, washing with a minimal amount of cold *n*-pentane and drying under vacuum afforded **7** as an olive-green microcrystalline solid (79 mg, 96% of yield). R_f = 0.05 (CH_2Cl_2); 0.20 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 16.03 (br. s, 1 H), 7.37 (s, 1 H), 7.08 (s, 4 H), 6.43 (s, 1 H), 6.36 (s, 1 H), 4.15 (s, 4 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.46 (s, 12 H), 2.41 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 294.7, 211.9, 150.7, 149.3, 144.6, 138.8, 138.6, 137.7, 129.7, 128.3, 105.4, 96.9, 58.9, 56.3, 56.2, 51.6, 21.1, 19.2 ppm. MS (ESI): *m*/*z* = 623 $[M - Cl]^+$. $C_{31}H_{38}Cl_2N_2O_3Ru$ (658.64): calcd. C 56.53, H 5.82, N 4.25; found C 56.41, H 6.01, N 4.18.

Procedure b: A solution potassium *tert*-amylate (0.2 mL, 0.3 mmol, 1.7 M in toluene, Fluka) was added under argon to a suspension of **8** (123 mg, 0.3125 mmol, Strem) in *n*-hexane (6 mL) and the resultant slightly turbid, yellow solution was stirred at room temperature for 1 h. Catalyst **1a** (206 mg, 0.25 mmol) was then added to the flask as a solid and the reaction mixture was heated to reflux for 30 min. After that time TLC indicated complete conversion of the Grubbs catalyst **1a**. A solution of (*E*)-**6** (57 mg, 0.275 mmol) in CH_2Cl_2 (10 mL) and CuCl (27 mg, 0.275 mmol) were added to the resultant brown-pink suspension at room temp. After 1 h at 40 °C the product was purified as before to afford **7** as olive-green crystals (163 mg, 89%).

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2002, *114*, 4210−4212; *Angew. Chem. Int. Ed.* **2002**, *41*, 4038−4040.
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[14] The electronic/steric effects in the alkoxy-chelating fragment of **2** must also be seen in the light of a recent publication from Fürstner's group which demonstrates that stronger donors at that site (-CO_2*i*Pr instead of -O*i*Pr) reduce the catalytic activity of the corresponding complex: A. Fürstner, O. R. Thiel, C. W. Lehmann, *Organometallics* **2002**, *21*, 331−335.
[15] Phoshane-free complex **2b** is now available from Aldrich Chemical Co.

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