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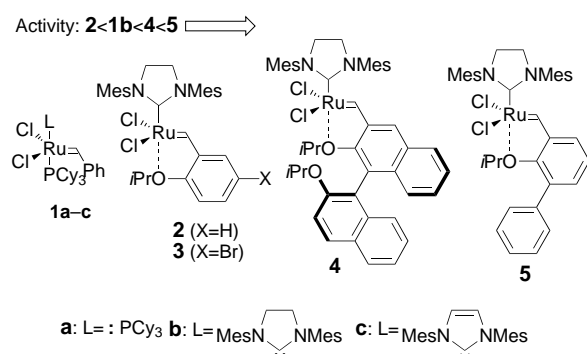
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A Highly Efficient Ruthenium Catalyst for Metathesis Reactions**

Karol Grela,* Syuzanna Harutyunyan, and Anna Michrowska

The development of accessible metathesis catalysts that combine high activity with excellent tolerance to a variety of functional groups has been key to the widespread application of olefin metathesis in organic synthesis. In spite of the general superb application profile of the ruthenium carbene **1a**, its limited thermal stability and the low activity towards substituted double bonds are major drawbacks.^[1]

Specifically, the preparation of substituted olefins with electron-withdrawing functionality (such as α,β -unsaturated carbonyl compounds, nitriles, sulfones, etc.) through cross metathesis (CM) with terminal alkenes remains a difficult task. The newly introduced highly active ruthenium alkylidene complexes with sterically demanding N-heterocyclic carbene (NHC)^[3] ligands have dramatically alleviated this limitation.^[2] Compounds of type **1b** and **1c** were found to be efficient catalysts in the reactions of previously metathesis-inactive substrates, including α,β -unsaturated olefins (Scheme 1).^[2,4]



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

Hoveyda and co-workers have recently established **2** as a remarkably robust complex, which promotes olefin metathesis by a “release–return” mechanism.^[5] Despite the fact that phosphane-free catalyst **2** was found to be more sluggish than **1b**,^[6] it has a superior general reactivity toward electron-deficient olefins.^[7] The fact that the ruthenium carbene **2** is air-stable and can be easily purified by standard silica-gel chromatography and recycled after the reaction is a particularly appealing facet of this chemistry.^[5,8]

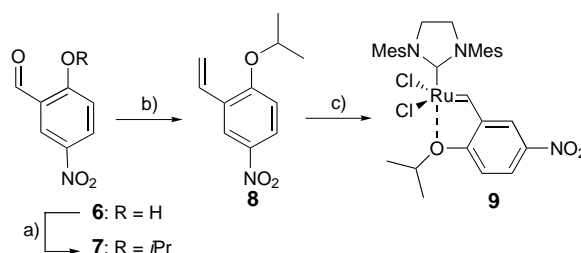
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Blechert and Wakamatsu have shown recently that the replacement of the isopropoxystyrene “ligand” in **2** by binol- or biphenyl-based styrene results in a large improvement in the activity of the catalyst, as complexes **4** and **5** are much more reactive than both **2** and the “second-generation” Grubbs catalyst **1b**.^[9]

During our project aimed at the preparation of the immobilized metathesis catalyst, we prepared the bromo analogue **3** of Hoveyda’s catalyst **2**.^[10] Although the reactivity patterns of complexes **2** and **3** were in general similar, the latter system was visibly less reactive in some model reactions.^[4b] This result once again shows that even a small variation in the isopropoxystyrene “ligand” can result in a change in the activity of the catalyst. Impressed by results published recently by Blechert and Wakamatsu,^[9] we decided to investigate the electronic effects in the isopropoxystyrene “ligand” sphere of complex **2** which are not fully understood.^[11] At first, we decided to test whether a decrease in the electron density of the styrene part of **2** would result in increased catalyst reactivity.

As illustrated in Scheme 2, we used commercially available **6** as a starting material for preparation of the corresponding ruthenium carbene **9**. The green microcrystalline complex **9**



Scheme 2. Synthesis of catalyst **9**. a) *i*PrI, K₂CO₃, Cs₂CO₃ (cat.), DMF, 2 days, room temperature, 86%; b) Ph₃P=CH₂, THF, –78°C→RT, 1 h, 57%; c) **1b**, CuCl, CH₂Cl₂, 30°C, 1 h, 83%.

was easily obtained in good yield (83%) by the reaction of **1b** (1 equiv) and CuCl (1 equiv) with styrene **8** (1 equiv), followed by routine flash chromatography. Having secured an efficient method for the preparation of complex **9**, we tested its catalytic activity. As the reactions of standard model substrates diallyltosylamide or diallylmalonate are too fast for an accurate measurement of their conversions,^[12] we decided to use more challenging ring-closing metathesis of **10a**. This model reaction showed that precatalyst **9** is significantly more reactive than **2** and **3** in the formation of trisubstituted double bonds (Figure 1). Notably, **9** is not only highly active but also stable, as it can be stored in air (+4°C) for more than four weeks without decomposition or loss of activity.

The metathesis of selected benchmark substrates was then examined. The results compiled in Table 1 illustrate the remarkably wide scope of this catalyst: 1) The RCM and enyne variant of the metathesis reaction can be performed efficiently at 0°C (Table 1, entries 2–4); 2) Various degrees of substitution of the double bond are tolerated, and even trisubstituted olefins can be synthesized in good yields at ambient temperature (Table 1, entries 1 and 5); 3) The CM reaction of terminal alkenes and α,β -unsaturated compounds

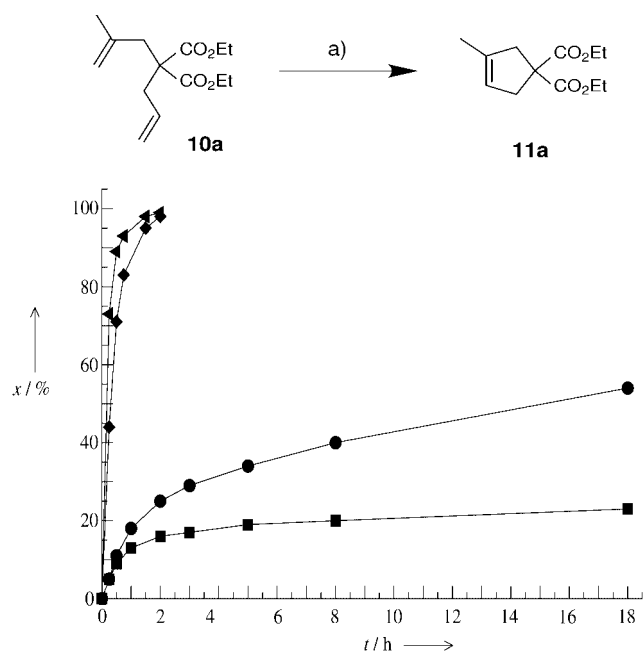


Figure 1. RCM of **10a** with pre-catalysts **1b** (▲, 1 mol %), **2** (●, 2.5 mol %), **3** (■, 2.5 mol %), and **9** (◆, 1 mol %). a) cat. (1–2.5 mol %), CH₂Cl₂, room temperature, x = conversion.

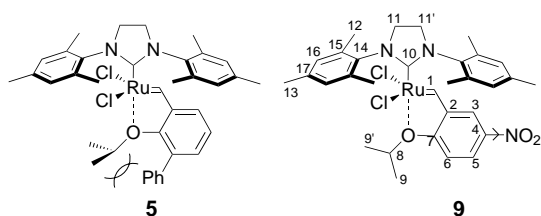
can be also performed at room temperature (Table 1, entries 6–9). The more demanding CM reactions of phenyl vinyl sulfone^[4] (Table 1, entry 8) and acrylonitrile^[7a] (Table 1, entry 9) show that also in this particular case complex **9** is superior to **1b** and **2**. Most remarkably, the new pre-catalyst **9** can be used for CM of methacrylonitrile; the transformation is *beyond the scope* of the “second generation” Grubbs' carbene **1b** (Table 1, entry 10).

In conclusion, we have shown that the catalysts related to that of Hoveyda can be significantly improved by changing not only the steric^[11] but also the electronic character of the Ru-chelating isopropoxy fragment. For example, introduction of a strong electron-withdrawing group at the 2-isopropoxy-styrene ring of **2** leads to complex **9**, which is equally stable but dramatically more reactive than the parent catalyst **2**. We assume that the decrease in the electron density^[13] of the oxygen atom of the isopropoxy fragment reduces its chelating ability, thus facilitating formation of the catalytically active 14-electron Ru–carbene species, and suppressing repeated reassociation to the metal center. Therefore, this mode of catalyst activation is, in fact, similar to that of **4** and **5**, in which the increase in steric bulk improves the leaving-group ability of the styrene “ligand” (Scheme 3).^[9] Complex **9** is attractive

Table 1. Comparative investigation of **9**.

Entry	Substrate 10	Product 11	Yield using 9 [%] ^[a]	Yield using ref. catalyst [%] ^[a]
1	10a	11a	99 % ^[b] (1 mol %, RT, 2 h)	2 : 50 % ^[b] (2.5 mol %, RT, 18 h)
2			98 % (1 mol %, 0°C, 1 h)	1c : 85 % ^[c] (1 mol %, 80°C, 1 h)
3			99 % (1 mol %, 0°C, 1 h)	1b : 99 % ^[d] (1 mol %, RT, 1 h)
4			78 % (2.5 mol %, 0°C, 8 h)	1b : 99 % ^[d] (1 mol %, RT, 1.5 h)
5			99 % ^[b] (2.5 mol %, RT, 4 h)	
6 ^[e]	10f TBSO-(CH ₂) ₄ -CH=CH-CH=CH-C(=O)R		82 % (2.5 mol %, RT, 30 min)	5 : 90 % ^[d] (1 mol %, RT, 40 min)
		<i>E</i> : <i>Z</i> = 99 : 1		
7 ^[f]	10f TBSO-(CH ₂) ₄ -CH=CH-CH=CH-CO ₂ CH ₃		95 % (1 mol %, RT, 30 min)	5 : 91 % ^[d] (2.5 mol %, RT, 20 min)
		<i>E</i> : <i>Z</i> = 95 : 5		
8 ^[g]	10f TBSO-(CH ₂) ₄ -CH=CH-CH=CH-SO ₂ Ph		90 % (2.5 mol %, RT, 16 h)	1b : 85 % ^[b] (5 mol %, 40°C, 16 h)
		(<i>E</i>)- 11h		
9 ^[h]			87 % ^[b] (5 mol %, RT, 30 min)	2 : 79 % ^[i] (8 mol %, 40°C, 6 h)
		<i>E</i> : <i>Z</i> = 1 : 2		
10 ^[k]	10f TBSO-(CH ₂) ₄ -CH=CH-CH=CH-CN		58 % (5 mol %, 40°, 16 h)	1b : 0 % ^[b] (5 mol %, 80°C, 24 h)
		<i>E</i> : <i>Z</i> = 1 : 2		

[a] Yield of isolated product, unless stated otherwise. [b] Yield determined by GC. [c] Ref. [2g]. [d] Ref. [9b]. [e] Reaction with methyl vinyl ketone (2 equiv). [f] Reaction with methyl acrylate (2 equiv). [g] Reaction with phenyl vinyl sulfone (2 equiv). [h] Ref. [4]. [i] Reaction with acrylonitrile (2 equiv). [j] *E/Z* = 1:3, ref. [7a]. [k] Reaction with methacrylonitrile (4 equiv).



Scheme 3.

from a practical point of view as it is active and easy to obtain in a three-step synthesis. This catalyst operates under very mild conditions (0°C to room temperature) and can be successfully applied in various types of metathesis reactions (RCM, CM, enyne). Further investigations to determine the full scope and limitations of **9** and similar systems are under way.

Experimental Section

9: Carbene complex **1b** (153 mg, 0.18 mmol), CuCl (18 mg, 0.18 mmol), and CH₂Cl₂ (10 mL) were placed in a Schlenk tube. A solution of **8** (38 mg, 0.18 mmol) in CH₂Cl₂ (4 mL) was then added and the resulting solution was stirred under argon at 30°C for 1 h. After this step, all manipulations were carried out in air with reagent-grade solvents. The reaction mixture was concentrated in vacuo, and the resulting material was purified by column chromatography on silica. Elution with cyclohexane/EtOAc (5:2) led to the isolation of **9** as a green band. The solvent was evaporated, the residue was washed with *n*-pentane and dried under vacuum to afford **9** as a green microcrystalline solid (100 mg, 83%). *R*_f = 0.30 (cyclohexane/EtOAc 8:2); ¹H NMR (500 MHz, CD₂Cl₂): δ = 16.42 (s, 1H; 1-H), 8.46 (dd, *J* = 9.1, 2.5 Hz, 1H; 5-H), 7.80 (d, *J* = 2.5 Hz, 1H; 3-H), 7.10 (s, 4H; 16-H), 6.94 (d, *J* = 9.1 Hz, 1H; 6-H), 5.01 (sept, *J* = 6.1 Hz, 1H; 8-H), 4.22 (s, 4H; 11-H, 11'-H), 2.47 (2 × s, 18H; 12-H, 13-H), 1.30 ppm (d, *J* = 6.1 Hz, 6H; 9-H, 9'-H); ¹³C NMR (125 MHz, CD₂Cl₂): δ = 289.1 (C1), 208.2 (C10), 156.8 (C7), 150.3, 145.0 (C2), 143.5 (C4), 139.6 (C15), 139.3, 129.8 (C16), 124.5 (C5), 117.2 (C3), 113.3 (C6), 78.2 (C8) 52.0 (C11, C11'), 21.3 (C9, C9'), 21.2 (C12), 19.4 ppm (C13) (where assignments of the NMR signals are given (based on 2D ¹H, ¹³C-chemical shift correlated spectra: GHSQC, GHMBC), they are unambiguous and refer to the arbitrary numbering shown in Scheme 3); IR (KBr): $\bar{\nu}$ = 2924, 2850, 1606, 1521, 1480, 1262, 1093, 918, 745 cm⁻¹; HRMS (IE): *m/z* calcd for C₃₁H₃₇N₃O₃³⁵Cl₂Ru: [*M*⁺] 671.1255, found 671.1229; elemental analysis (%) calcd for C₃₁H₃₇N₃O₃Cl₂Ru (671.63): C 55.44, H 5.55, N 6.26; found: C 55.35; H 5.70, N 6.09.

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- [12] For example, see footnote 32 in ref. [2g].
- [13] We thank Mr. Michal Barbasiewicz for carrying out some preliminary AM1 calculations.