A Highly Efficient Ruthenium Catalyst for Metathesis Reactions**

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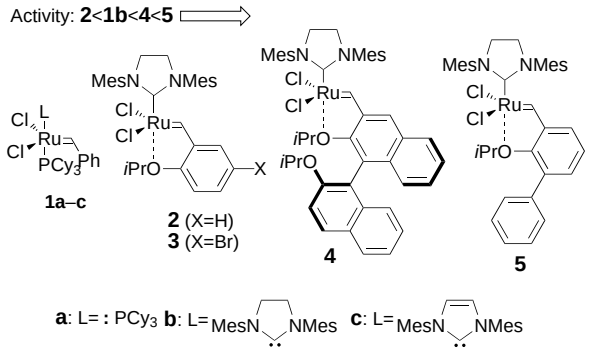
The development of accessible metathesis catalysts that combine high activity with excellent tolerance to a variety of functional groups has been key to the widespread application of olefin metathesis in organic synthesis. In spite of the general superb application profile of the ruthenium carbene **1a**, 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]



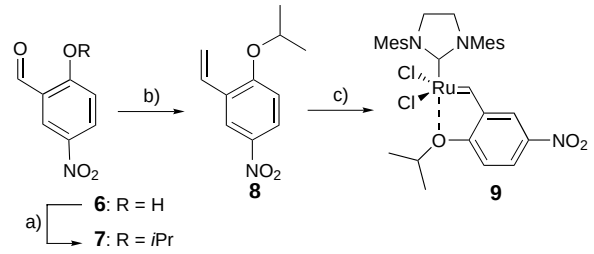
Scheme 1. Evolution of ruthenium precatalysts for alkene metathesis. Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.

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]

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, K_2CO_3, Cs_2CO_3 (cat.), DMF, 2 days, room temperature, 86%; b) $Ph_3P{=}CH_2$, THF, −78°C→RT, 1 h, 57%; c) **1b**, CuCl, CH_2Cl_2, 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

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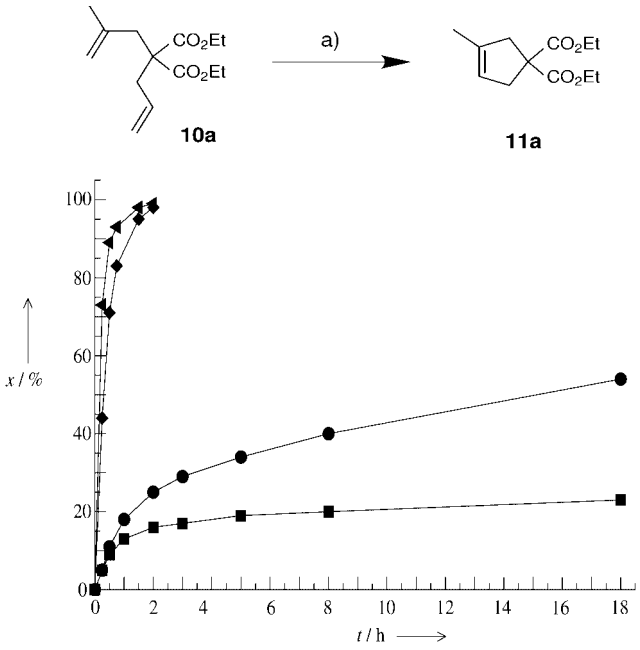
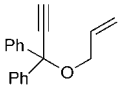
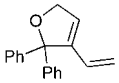
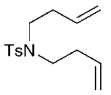
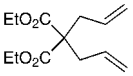
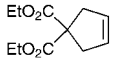
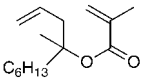
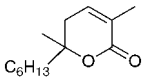
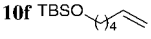
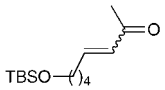
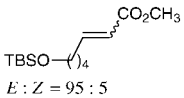
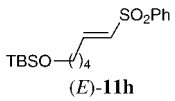
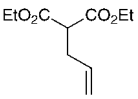
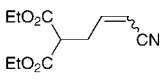
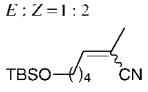


Figure 1. RCM of **10a** with precatalysts **1b** (▲, 1 mol %), **2** (●, 2.5 mol %), **3** (■, 2.5 mol %), and **9** (◆, 1 mol %). a) cat. (1–2.5 mol %), CH_2Cl_2, room temperature, x = conversion.

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 precatalyst **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-isopropoxystyrene 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** 	 $E:Z = 99:1$	82 % (2.5 mol %, RT, 30 min)	**5**: 90 %[d] (1 mol %, RT, 40 min)
7[f]	**10f**	 $E:Z = 95:5$	95 % (1 mol %, RT, 30 min)	**5**: 91 %[d] (2.5 mol %, RT, 20 min)
8[g]	**10f**	 (*E*)-**11h**	90 % (2.5 mol %, RT, 16 h)	**1b**: 85 %[h] (5 mol %, 40 °C, 16 h)
9[i]		 $E:Z = 1:2$	87 %[b] (5 mol %, RT, 30 min)	**2**: 79 %[j] (8 mol %, 40 °C, 6 h)
10[k]	**10f**	 $E:Z = 1:2$	58 % (5 mol %, 40°, 16 h)	**1b**: 0 %[b] (5 mol %, 80 °C, 24 h)

[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).

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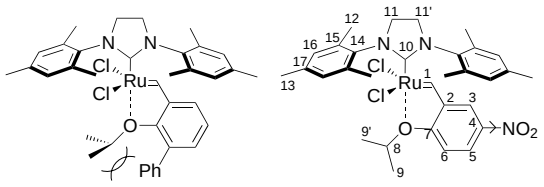

5 **9**

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 CH_2Cl_2 (10 mL) were placed in a Schlenk tube. A solution of **8** (38 mg, 0.18 mmol) in CH_2Cl_2 (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); ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 16.42$ (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); ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 289.1$ (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 ^{1}H,^{13}C-chemical shift correlated spectra: GHSQC, GHMBC), they are unambiguous and refer to the arbitrary numbering shown in Scheme 3); IR (KBr): $\tilde{\nu} = 2924$, 2850, 1606, 1521, 1480, 1262, 1093, 918, 745 cm^{-1}; HRMS (IE): *m*/*z* calcd for $C_{31}H_{37}N_3O_3{}^{35}Cl_2{}^{102}Ru$: [$M^{+\cdot}$] 671.1255, found 671.1229; elemental analysis (%) calcd for $C_{31}H_{37}N_3O_3Cl_2Ru$ (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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[11] Extensive studies described in ref. [9a,b] suggest that a steric bulk adjacent to the chelating isopropoxy moiety of **4** and **5** is the crucial factor required for the unusually high activity of these complexes.

[12] For example, see footnote 32 in ref. [2g].

[13] We thank Mr. Michal Barbasiewicz for carrying out some preliminary AM1 calculations.

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