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 alkylidyne complexes with sterically demanding N-heterocyclic carbene (NHC) ligands have dramatically alleviated this limitation.[3] 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]

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 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.[6] 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 the preparation of the corresponding ruthenium carbene 9. The green microcrystalline complex 9 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

![Scheme 1](https://example.com/scheme1.png)

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

![Scheme 2](https://example.com/scheme2.png)

Scheme 2. Synthesis of catalyst 9. a) PCy3, K2CO3, Cs2CO3 (cat.), DMF, 2 days, room temperature, 86%; b) Ph3P = CH3, THF, –78°C→RT, 1 h, 57%; c) 1b, CuCl, CH2Cl2, 30°C, 1 h, 83%.

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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-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

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).

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Table 1. Comparative investigation of 9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 10</th>
<th>Product 11</th>
<th>Yield using 9 [%][a]</th>
<th>Yield using ref. catalyst [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>11a</td>
<td>99%[b] (1 mol%, RT, 2 h)</td>
<td>2: 50%[b] (2.5 mol%, RT, 18 h)</td>
</tr>
<tr>
<td>2</td>
<td>10b</td>
<td>11b</td>
<td>98% (1 mol%, 80°C, 2 h)</td>
<td>1c: 85%[b] (1 mol%, 80°C, 1 h)</td>
</tr>
<tr>
<td>3</td>
<td>10c</td>
<td>11c</td>
<td>99% (1 mol%, 80°C, 1 h)</td>
<td>1b: 99%[b] (1 mol%, RT, 1 h)</td>
</tr>
<tr>
<td>4</td>
<td>10d</td>
<td>11d</td>
<td>78% (2.5 mol%, 80°C, 8 h)</td>
<td>1b: 99%[b] (1 mol%, RT, 1.5 h)</td>
</tr>
<tr>
<td>5</td>
<td>10e</td>
<td>11e</td>
<td>99%[b] (2.5 mol%, 80°C, 1 h)</td>
<td>1b: 99%[b] (1 mol%, RT, 1 h)</td>
</tr>
<tr>
<td>6</td>
<td>10f</td>
<td>11f</td>
<td>82% (2.5 mol%, RT, 30 min)</td>
<td>5: 90%[b] (1 mol%, RT, 40 min)</td>
</tr>
<tr>
<td>7</td>
<td>10f</td>
<td>11f</td>
<td>95% (1 mol%, RT, 30 min)</td>
<td>5: 91%[b] (2.5 mol%, RT, 20 min)</td>
</tr>
<tr>
<td>8</td>
<td>10f</td>
<td>11f</td>
<td>90% (2.5 mol%, RT, 16 h)</td>
<td>1b: 85%[b] (5 mol%, 40°C, 16 h)</td>
</tr>
<tr>
<td>9</td>
<td>10f</td>
<td>11f</td>
<td>87%[b] (5 mol%, RT, 30 min)</td>
<td>2: 79%[b] (8 mol%, 40°C, 6 h)</td>
</tr>
<tr>
<td>10</td>
<td>10f</td>
<td>11f</td>
<td>58% (5 mol%, 40°C, 16 h)</td>
<td>1b: 0%[b] (5 mol%, 80°C, 24 h)</td>
</tr>
</tbody>
</table>


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%), CH2Cl2, room temperature, x = conversion.
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 washed with n-pentane and dried under vacuum to afford 9 as a green crystalline solid (100 mg, 83%). Rᵋ = 0.30 (cyclohexane/EtOAc 8:2);

¹H NMR (500 MHz, CD₂Cl₂): δ = 16.42 (s, 1 H; 1-H), 8.46 (dd, J = 9.1, 2.5 Hz, 1H; 2-H), 7.38 (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, 12-H), 2.47 (2 × s, 18H; 12-H, 13-H), 1.00 ppm (d, J = 9.1, 6.1 Hz, 6H; 9-H, 9'-H); ¹³C NMR (125 MHz, CD₂Cl₂): 3 = 289.1 (C1), 208.2 (C10), 156.8 (C7), 150.3, 145.0 (C2), 134.5 (C4), 139.6 (C15), 139.3, 129.8 (C16), 124.5 (C5), 117.2 (C3), 113.3 (C6), 78.2 (C8) 52.0 (C11), 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):  ν = 2924, 2850, 1606, 1521, 1480, 1262, 1093, 918, 745 cm⁻¹; HRMS (IE): m/z: calcd for C₃₉H₉₃N₂O₂₆Cl₁₁Ru: [M⁺]⁺ 671.1255, found 671.1229; elemental analysis (% calcd for C₃₉H₉₃N₂O₂₆Cl₁₁Ru: 55.44, H 5.55, N 6.26; found: C 55.35; H 5.70, N 6.09.

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[6] For a comparative study of the performance of precatalysts 1b and 2 in the RCM reaction of diallylsilane, see: ref. [9a].


[8] Catalysts 1a, 1b, and 2 are available from Aldrich Chemical Co.


[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 Barbusiewicz for carrying out some preliminary AM1 calculations.