

## Grubbs' Catalyst in Paraffin: An Air-Stable Preparation for Alkene Metathesis

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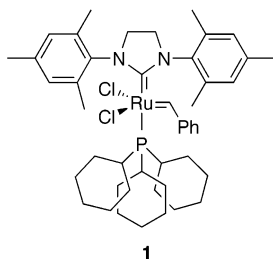
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Received January 6, 2003

**Abstract:** A homogeneous mixture of Grubbs' catalyst in paraffin wax was shown to catalyze three important types of metathesis reactions: ring-closing metathesis, alkene dimerization, and alkene cross-metathesis (e.g., **11** → **13**). This catalyst preparation demonstrated no loss in catalytic activity after 22 months of storage open to the air.

The ruthenium 4,5-dihydroimidazo-2-ylidene complex **1** developed by Grubbs is widely known for its applications in organic and polymer synthesis.<sup>1,2</sup> Despite the obvious utility of Grubbs' catalyst, its routine use is hindered by special storage requirements. Prolonged exposure to air and moisture deactivates the complex, and it is typically stored under inert atmosphere. Recently, it has been shown that attaching the active ruthenium complex to a polymer support improves the stability of the catalyst while retaining full activity.<sup>3</sup> Here, we report that Grubbs' catalyst dispersed in paraffin<sup>4</sup> is easily handled and retains its activity indefinitely with no special storage precautions.



The Grubbs catalyst, complex **1**, was weighed in a nitrogen atmosphere drybox and dispersed (11 wt %) in molten paraffin wax to give a homogeneous purple liquid. This mixture was allowed to cool before removal from the drybox. The ruthenium complex–paraffin mixture was cut into useful pieces and stored without protection from

**TABLE 1. Examples of Metathesis Reaction Using Grubbs' Catalyst in Paraffin**

Entry	Substrate	Product	Percent Yield <sup>a</sup>
1			80
2			84
3			94
4			91 <sup>b</sup>
5			86

<sup>a</sup> Isolated yield based on recovered starting material. <sup>b</sup> Trans/cis ratio 20:1 by integration of the <sup>1</sup>H NMR spectrum.

laboratory air. This makes it convenient to weigh out small quantities of the otherwise easily dispersed ruthenium complex. The mixture can be stored under normal laboratory conditions for many months without concern over the loss of catalytic activity. A sample stored for 22 months with no special storage precautions showed no loss of activity.

Entries 1 and 2 in Table 1 illustrate ring-closing metathesis (RCM) reactions using this catalyst preparation. The diene was dissolved in distilled CH<sub>2</sub>Cl<sub>2</sub>, the paraffin–catalyst mixture was added, and the reaction mixture was stirred for 10 h. Flash chromatography then separated the paraffin from the cyclized product. Reactions with the paraffin–catalyst mixture appear to run at the same rate as the same reactions with pure catalyst. Entry 3 illustrates the homo-dimerization metathesis of a terminal alkene by an analogous procedure. Entry 4 demonstrates the cross-metathesis reaction between diethyl malonate and methyl acrylate.<sup>5</sup>

(1) For recent reviews of olefin metathesis, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(2) (a) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

(3) (a) Dowden, J.; Savovic, J. *Chem. Commun.* **2001**, 37. (b) Jafarpour, L.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 4075. (c) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657. (d) Ahmed, M.; Arnault, T.; Barrett, A. M. G.; Braddock, D. C.; Procopiou, P. A. *Synlett* **2000**, 1007.

(4) The coating of air-sensitive catalysts with paraffin is a common industrial practice, with many references in the patent literature. For a recent example, see: Fang, Y.; Liu, Y.; Ke, Y.; Guo, C.; Zhu, N.; Mi, X.; Ma, Z.; Hu, Y. *Applied Catalysis, A: General* **2002**, *235*, 33.

Entry 5 is an example of olefin cross-methathesis using the inexpensive *cis*-1,4-butanediol to yield the allylic alcohol **13**.<sup>6</sup> Such trans allylic alcohols are important as, inter alia, substrates for Sharpless asymmetric epoxidation. This is also the first synthesis of **13**, a natural product isolated from the rhizomes of *Zingiber cassumunar*, a medicinal plant from Southeast Asia possessing antioxidant and antiinflammatory properties.<sup>7</sup>

We believe that these examples demonstrate that Grubbs' catalyst in paraffin is a useful reagent for routine organic synthesis. This easily handled preparation will facilitate the use of the Grubbs' catalyst in trial metathesis reactions and small-scale synthesis. There are many catalysts in common usage in the organic synthesis laboratory that are much more air and moisture sensitive than the Grubbs catalyst. It is remarkable that dispersion in paraffin to protect them has not been more widely employed.

## Experimental Section

**Grubbs' Catalyst 1 in Paraffin.** In a nitrogen atmosphere (grade 4.8) drybox, Grubbs' catalyst **1** (1.27 g, 1.50 mmol) was combined in a 25 mL beaker with paraffin wax (paraffin wax for canning, mp = 48–50 °C, 8.73 g). The mixture was warmed to melting in a heating mantle and stirred with a glass rod to apparent homogeneity (one min). After cooling, the solid was removed from the drybox, broken into useful-sized pieces, and stored in a brown glass bottle without further protection.

**3,3-Dimethyl-2,4-dioxaspiro[5.5]undec-8-ene 3.** Starting diene **2** (177 mg, 0.892 mmol) was dissolved in 4 mL of CH<sub>2</sub>Cl<sub>2</sub>, and Grubbs' catalyst in paraffin was added (0.15 mmol/g catalyst, 300 mg, 0.045 mmol, 5 mol %). The mixture was stirred for 7 h, during which time it changed in color from purple to brown. The reaction mixture was adsorbed directly onto silica gel and chromatographed<sup>8</sup> to yield **3** as a clear oil (121 mg, 0.709 mmol, 79% yield): TLC *R<sub>f</sub>* = 0.32 (5% MTBE (methyl *tert*-butyl ether)/PE (petroleum ether)); <sup>1</sup>H NMR δ 1.42 (s, 6 H), 1.57 (t, *J* = 6.25 Hz, 2 H), 1.96 (s, 2 H), 2.03 (m, 2 H), 3.59 (s, 4 H), 5.63 (m, 2 H); <sup>13</sup>C NMR δ d 23.7, 24.3, 124.7, 126.4; u 21.6, 27.3, 31.4, 68.6, 98.3 (<sup>13</sup>C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u"); IR 1736, 1652, 1453 cm<sup>-1</sup>; MS *m/z* 181 (100), 169 (85), 167 (17). Anal. Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>: C, 72.49; H, 9.95. Found: C, 72.33; H, 9.91.

**Cyclopent-3-ene-1,1-dicarboxylic Acid Diethyl Ester 5.** Diethyl diallyl malonate (321 mg, 1.34 mmol) was dissolved in 4 mL of CH<sub>2</sub>Cl<sub>2</sub>, and Grubbs' catalyst in paraffin was added (5% catalyst by wt, 273 mg, 0.016 mmol, 1.2 mol %). The reaction was stirred for 11 h, during which time it changed in color from dark pink to brown. The reaction mixture was adsorbed directly onto silica gel and chromatographed to yield **5** as a clear oil (239 mg, 1.12 mmol, 84% yield): TLC *R<sub>f</sub>* = 0.23 (8.5% MTBE/PE); <sup>1</sup>H NMR δ 1.25 (t, *J* = 7.5 Hz, 6 H), 3.02 (s, 4 H), 4.202 (q, *J* = 6.5 Hz, 4 H), 5.61 (s, 2 H); <sup>13</sup>C NMR δ d 14.1, 128.1; u 41.0,

58.9, 61.7, 172.5; IR 1733, 1448 cm<sup>-1</sup>. These data are congruent with those previously reported.<sup>9</sup>

**1,10-Bis-(3-methoxyphenyl)dec-5-ene-1,10-dione 7.** 1-(3-Methoxyphenyl)hex-5-en-1-one<sup>10</sup> (237 mg, 1.16 mmol) was dissolved in 3 mL of CH<sub>2</sub>Cl<sub>2</sub>, and Grubbs' catalyst in paraffin was added (5 wt % catalyst, 249 mg, 0.015 mmol, 1.3 mol %). The reaction was stirred for 12 h, adsorbed directly onto silica gel, and chromatographed to yield **7** as a white solid (204 mg, 0.536 mmol, 46% yield): TLC *R<sub>f</sub>* = 0.36 (24% MTBE/PE); mp = 93.5–95.0 °C; <sup>1</sup>H NMR δ 1.80 (m, 4 H), 2.01 (m, 4 H), 2.94 (t, *J* = 7.5 Hz, 4 H), 3.85 (s, 6 H), 5.44 (m, 2 H), 7.09 (d, *J* = 8.5 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.43 (tt, *J* = 7.5, 2.5 Hz, 4 H); <sup>13</sup>C NMR δ d 112.4, 119.5, 120.8, 129.6, 130.7; u 24.1, 32.1, 38.0, 138.7, 159.8, 200.4; IR 2096, 1640 cm<sup>-1</sup>; HRMS calcd for C<sub>24</sub>H<sub>28</sub>O<sub>4</sub> 381.2066, obsd 381.2063. Anal. Calcd for C<sub>24</sub>H<sub>28</sub>O<sub>4</sub>: C, 75.76; H, 7.42. Found: C, 75.42; H, 7.55.

**5-Ethoxycarbonylhex-2-enedioic Acid 6-Ethyl Ester 1-Methyl Ester 10.** Diethyl allyl malonate (206 mg, 1.03 mmol) was dissolved in 3 mL of CH<sub>2</sub>Cl<sub>2</sub>. Benzoic acid (9 mg, 0.075 mmol) was added as a cocatalyst along with Grubbs' catalyst in paraffin (488 mg, 0.073 mmol, 7.1 mol %). The reaction vial was vented to a bubbler via a nitrogen line and stirred for 22.5 h. The reaction mixture was adsorbed directly onto silica gel and chromatographed to yield **10** as a clear oil (0.206 g, 0.798 mmol, 77% yield): TLC *R<sub>f</sub>* = 0.39 (25% 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MTBE-PE); <sup>1</sup>H NMR δ 1.27 (t, *J* = 7.8 Hz, 6 H), 2.80 (dt, *J* = 7.3, 1.5 Hz, 2 H), 3.50 (t, *J* = 7.5 Hz, 1 H), 3.72 (s, 3 H), 4.22 (q, *J* = 6.3 Hz, 4 H), 5.91 (d, *J* = 16.5 Hz, 1 H), 6.90 (td, *J* = 15.8, 7.0 Hz, 1 H); <sup>13</sup>C NMR δ d 14.1, 50.6, 51.6, 123.4, 144.2; u 31.1, 61.7, 166.4, 168.3; IR 3639, 3454, 2984, 1728, 1438 cm<sup>-1</sup>; HRMS calcd for C<sub>12</sub>H<sub>18</sub>O<sub>6</sub> 259.1182, obsd 259.1171.

**4-(4-Hydroxy-3-methoxyphenyl)but-2-en-1-ol 13.** Eugenol (0.224 g, 1.36 mmol) and *cis*-2-butene-1,4-diol (0.761 g, 8.53 mmol, 6.3 equiv) were dissolved in 4 mL of PE, and Grubbs' catalyst in paraffin (5 wt % catalyst, 455 mg, 0.027 mmol, 2 mol %) was added. The reaction was stirred for 23 h, during which time it changed in color from purple to brown. The reaction mixture was adsorbed directly onto silica gel and chromatographed to yield **13** as a colorless solid (210 mg, 1.08 mmol, 80% yield): TLC *R<sub>f</sub>* = 0.15 (50% 1:1 CH<sub>2</sub>Cl<sub>2</sub>/MTBE-PE). This was recrystallized from CHCl<sub>3</sub> to give small colorless needles: mp = 95–96 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.33 (d, *J* = 6.3 Hz, 2 H), 3.88 (s, 3 H), 4.14 (m, 2 H), 5.73 (m, 1H), 5.82 (m, 1H), 6.68 (m, 2 H), 6.85 (d, *J* = 8.5 Hz, 1 H); <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 3.15 (m, 5 H), 3.83 (d, *J* = 4.3 Hz, 2 H), 5.48 (m, 1 H), 5.66 (m, 1 H), 6.45 (d, *J* = 1.8, 1H), 6.60 (dd, *J* = 6.3, 2.0 Hz, 1 H), 7.02 (d, *J* = 8.0 Hz, 1 H); <sup>13</sup>C NMR(CDCl<sub>3</sub>) δ d 56.0, 111.1, 114.4, 121.2, 130.1, 132.1; u 38.4, 63.7, 131.9, 144.1, 146.6; IR 2744, 1591. These data are congruent with those previously reported.<sup>7</sup>

**Acknowledgment.** We thank the NIH (GM60287) for financial support of this work. We thank Professor Robert H. Grubbs of the California Institute of Technology for his advice on acid catalysis of metathesis reactions.

**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>C spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO030005P

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