



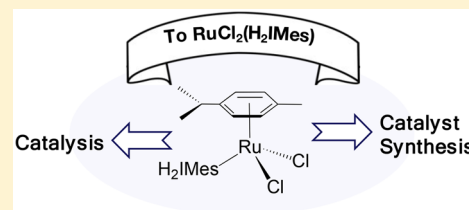
High-Yield Synthesis of a Long-Sought, Labile Ru-NHC Complex and Its Application to the Concise Synthesis of Second-Generation Olefin Metathesis Catalysts

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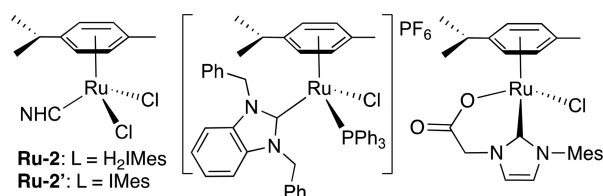
Supporting Information

ABSTRACT: The controlled reaction of $[\text{RuCl}_2(p\text{-cymene})]_2$ with H_2IMes generates the previously challenging precatalyst and Ru synthon $\text{RuCl}_2(p\text{-cymene})(\text{H}_2\text{IMes})$ (**Ru-2**) in 96% isolated yield. Critical to success is inhibiting premature *p*-cymene displacement. This is achieved by carrying out the synthesis at ambient temperatures, protected from light, and at sufficient dilutions (25 mM in THF) to enable stoichiometric control and inhibit bimolecular decomposition. The ease with which *p*-cymene loss can be deliberately induced, however, is key to the utility of **Ru-2** in both catalysis and catalyst synthesis. The transformation of **Ru-2** into two second-generation olefin metathesis catalysts is described. $\text{RuCl}_2(\text{H}_2\text{IMes})(=\text{CH}(o\text{-C}_6\text{H}_4\text{-O}^i\text{Pr}))$ (**HII**) and $\text{RuCl}_2(\text{H}_2\text{IMes})(\text{PPh}_3)(=\text{CHPh})$ (**GII'**) (a desirable, faster-initiating analogue of **GII**) are accessible in ca. 80% yield over two steps from commercially available $[\text{RuCl}_2(p\text{-cymene})]_2$. Synthesis from $\text{RuCl}_2(\text{PPh}_3)_3$, in comparison, requires three or four steps for **HII** or **GII'**, respectively, and proceeds in lower yields.



Piano-stool complexes of the group 8 metals are privileged structures in catalysis, and in bioinorganic and medicinal chemistry.^{1–7} *p*-Cymene complexes of ruthenium dominate, owing to their ease of access from commercially available $[\text{RuCl}_2(p\text{-cymene})]_2$ (**Ru-1**), although expanding roles for iron complexes⁸ and functionalized arene derivatives⁹ have been documented in recent reviews. In particular, attention has focused on catalysis via *N*-heterocyclic carbene (NHC) derivatives of **Ru-1** (Chart 1).^{1–6}

Chart 1. Exemplary *p*-Cymene/NHC Catalysts^{10–15}



Notably sparse, however, are reports of high-performing *p*-cymene catalysts containing *N,N'*-diarylimidazolidin-2-ylidenes, of which the H_2IMes complex **Ru-2** (Chart 1) may be regarded as an exemplar. This is particularly striking given early advances establishing a convenient in situ synthesis of **Ru-2**,¹³ for use in olefin metathesis and atom-transfer radical polymerization.^{13,16–18} Ledoux and co-workers subsequently described **Ru-2** as too unstable to isolate.¹⁹ The Jensen group recently succeeded in isolating the complex,^{10,20} albeit in yields (26%) that support this view. The *N*-*o*-phenol analogue of **Ru-2** also decomposes rapidly.¹⁹ In contrast, IMes analogue **Ru-2'** is stable, and indeed isolable in ca. 80–90% yield.^{11,12}

The behavioral difference between these complexes is critical to their informed deployment. In some cases (e.g., outer-sphere transfer hydrogenation),²¹ retention of the arene ligand is required. In other contexts (e.g., metathesis, arylation, alkylation or hydrogen-borrowing catalysis, or synthesis of new catalysts by elaboration of the $\text{RuCl}_2(\text{H}_2\text{IMes})$ core), *p*-cymene loss is necessary, and its facile, controlled displacement represents a key potential asset. In the present work, we sought to clarify and control the instability of **Ru-2**, as an essential step toward harnessing the potential of this and related *p*-cymene complexes in synthesis and catalysis. Here we identify key factors that promote loss of the *p*-cymene ring; we report the successful development of a high-yield route to **Ru-2**, and we demonstrate the exceptional utility of this complex in enabling a concise, efficient route to high-performing second-generation Ru metathesis catalysts.

Literature reports describe the use of thermal and photolytic triggers to displace the *p*-cymene ligand from phosphine²² and NHC derivatives of **Ru-1**.^{12,13} In the case of **Ru-2**, we suspected that steric pressure exerted by the H_2IMes mesityl groups could add to the lability of the η^6 -arene ligand. While rotation about the Ru– H_2IMes bond is restricted^{23–25} (a consequence of the π -acceptor character of the saturated NHC),^{26,27} *N*–Mes bond rotation is facile. In contrast, the IMes ligand has a higher barrier to *N*–Mes rotation,^{28,29} as well as a lower buried volume.³⁰ These factors could account for the improved stability of **Ru-2'**. NOE experiments on isolated **Ru-2** (Figure S2; generated as described below)

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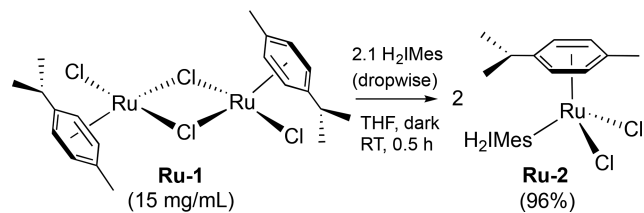


confirm the presence of steric interactions between the mesityl *o*-Me groups and the *p*-cymene ligand in solution.

We bore these points in mind in seeking to synthesize **Ru-2** for direct study. The thermal lability of the *p*-cymene ring rules out, for example, in situ production of H₂IMes from its imidazolium salt,¹⁹ which typically requires high temperatures as well as strong base. Instead, **Ru-2** was prepared by adding free H₂IMes to dimeric **Ru-1**, under conditions designed to minimize exposure of the product to light and heat: that is, at 22 °C in a foil-wrapped vessel, with the glovebox light switched off.

The stoichiometry of the reaction—and hence the solubility of **Ru-1**—emerged as a key additional criterion. Synthesis of **Ru-2** in CH₂Cl₂, in which **Ru-1** is fully soluble, is precluded by the rapid reaction of H₂IMes with CH₂Cl₂.³¹ THF was therefore employed, despite only partial solubility of **Ru-1** in this solvent even at millimolar concentrations. An important insight was offered by the observation of negligible yields of **Ru-2** when solid H₂IMes was added to the **Ru-1** suspension, but greatly improved yields when THF solutions of H₂IMes were added. We infer that a local excess of H₂IMes is able to displace the *p*-cymene ligand from **Ru-2**. In an optimized synthetic protocol (Scheme 1), we therefore slowly infused a

Scheme 1. High-Yield Synthesis of **Ru-2**



solution of the free carbene (1 mL/min; 25 mM) into a THF suspension of **Ru-1** (ca. 15 mg/mL). Addition was complete after 30 min, at which point a clear deep red solution was present. Evaporation of the solvent and reprecipitation of the residue from CH₂Cl₂–hexanes afforded **Ru-2** as a dark red powder, in 96% yield.

With clean **Ru-2** in hand, we examined its stability. As anticipated from the experiments above, adding H₂IMes to **Ru-2** caused extensive loss of the *p*-cymene ring (minutes at room temperature; Figure 1a). Exposing C₆D₆ solutions of **Ru-2** to fluorescent laboratory light at room temperature caused nearly 70% decomposition over 5 h, vs 10% for a foil-wrapped sample over the same period (Figure 1b,c). Of note, the photolytic reaction showed a first-order rate dependence on [**Ru-2**], while decomposition in the dark was second order, albeit slower (Figure 1d). The latter, bimolecular reaction underscores the importance of maintaining low concentrations during the synthesis of **Ru-2**. Irradiating CH₂Cl₂ solutions of **Ru-2** at 465 or 365 nm led to broadening of the absorption bands (Figure S7) and formation of a black suspension, suggesting nanoparticle formation.³²

The historical difficulties in isolating **Ru-2** noted above are unsurprising, given the need to inhibit loss of *p*-cymene by protecting from (i) light and heat, (ii) uptake of a second H₂IMes ligand, and (iii) bimolecular decomposition. Once recognized, however, these conditions are readily met, as indicated by near-quantitative isolation of **Ru-2** on a nearly 1 g scale via the protocol of Scheme 1.

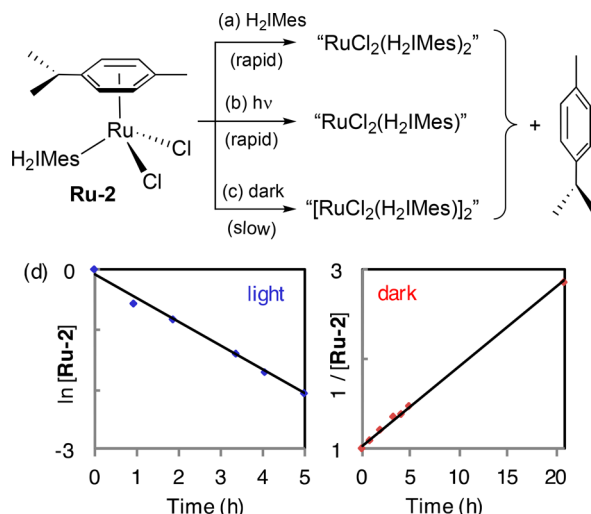
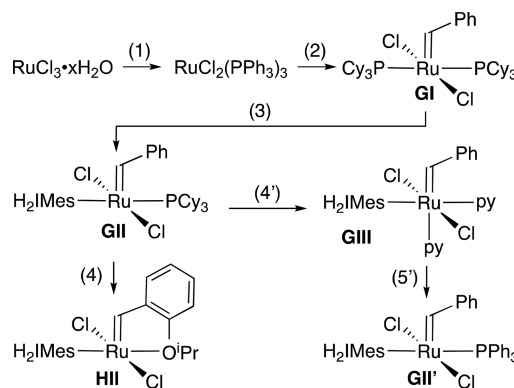


Figure 1. (a–c) Decomposition of **Ru-2** (20 mM; C₆D₆, room temperature), showing plausible initial products, and (d) first-order dependence of decomposition on [**Ru**] in the light, vs second-order dependence in the dark.

From a complementary perspective, the ease with which the *p*-cymene ring can be displaced is a core asset that enables use of **Ru-2** as a clean source of “RuCl₂(H₂IMes)” in catalysis or catalyst synthesis. A final aspect of this work focused on the latter opportunity: specifically, use of **Ru-2** as an entry point to olefin metathesis catalysts. The important “second-generation” metathesis catalysts are typically accessed via multiple steps (Scheme 2),^{33–39} commencing with transformation of

Scheme 2. Dominant Routes to **HII** and **GII'**^{a,b}



^aOverall yields 34–52% for **HII** and 29–33% for **GII'**: see the Supporting Information. ^bConditions: (1) 6 PPh₃, refluxing MeOH;⁴¹ (2) 2 PhCHN₂ + 2.2 PCy₃, CH₂Cl₂, –78 °C to room temperature;^{36a} (3) 1.1 H₂IMes, THF, Merrifield resin;³⁸ (4) 1.1 ArCH=CH₂, 1.3 CuCl, refluxing CH₂Cl₂;³⁷ (4') 1/3 toluene/py;⁴² the product is a mono/bis-py mixture;⁴³ (5') 1.1 PPh₃, C₆H₆.⁴² For further details, see the Supporting Information. Steps 3 and 4 in the synthesis of **HII** can be advantageously reversed.^{38,39}

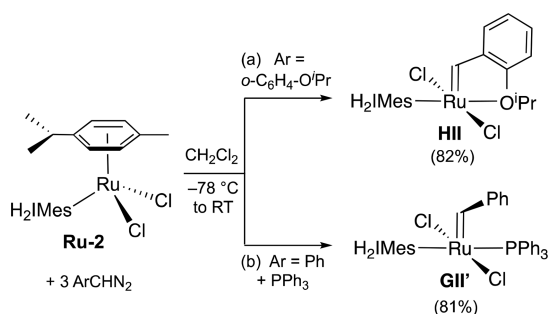
hydrated RuCl₃ into RuCl₂(PPh₃)₃ and then the first-generation Grubbs catalyst **GI**.^{36a} RuCl₂(PPh₃)₃ is attractive relative to many alternative Ru precursors for its ease of handling,^{36b} and because the bulk of the stabilizing phosphine ligands provides leverage for ligand exchange.⁴⁰

A major drawback, however, is the need to first install, and then remove, the PPh₃ ligands and one or more PCy₃ ligands.

While phosphine scavengers can significantly improve isolated yields,³⁸ the net process is laborious and wasteful.⁴⁴ More efficient routes to Ru metathesis catalysts, which circumvent reliance on $\text{RuCl}_2(\text{PPh}_3)_3$ as a precursor,^{36b} are highly desirable.

In important early work, metathesis-active allenylidene or indenylidene complexes were generated by treating $[\text{RuCl}(\text{p-cymene})(\text{PCy}_3)](\text{OTf})$ or **Ru-2'** with terminal alkynes,^{11,45,46} while benzylidene species were generated by treating piano-stool Os complexes with phenyldiazomethane.^{47,48} Here we sought to build on these advances by displacing the arene ring from **Ru-2**, while simultaneously introducing a benzylidene ligand and a stabilizing donor. We envisaged that this could offer access to the second-generation Hoveyda catalyst **III** (Scheme 3a),^{33,34} for example, in a single step.

Scheme 3. One-Step Synthesis of High-Performing Metathesis Catalysts from Ru-2



Accordingly, we adapted to **Ru-2** a procedure used by the Hoveyda group to install chelating benzylidene ether ligands on $\text{RuCl}_2(\text{PPh}_3)_3$.³³ Adding ArCHN_2 ($\text{Ar} = o\text{-C}_6\text{H}_4\text{-O}^i\text{Pr}$)⁴⁹ to a CH_2Cl_2 solution of **Ru-2** at -78°C caused evolution of N_2 , accompanied by a color change from red to green over the ca. 20 min time of addition. The solution was then warmed to 0°C and briefly (10 min) irradiated with a standard portable UV lamp mounted 5 cm away. **III** was obtained after flash chromatography in 82% isolated yield, or ca. 70% overall yield from the ultimate precursor RuCl_3 . This compares favorably with the dominant route shown in Scheme 1 (four steps and 3–5 days from RuCl_3 , with a maximum net yield of ca. 50%).

Chelation of the stabilizing ligand is not essential, as demonstrated by the synthesis of **GII'** (Scheme 3b), an analogue of the Grubbs catalyst **GII**. Such PPh_3 derivatives are attractive for the higher lability⁵⁰ and reduced nucleophilicity⁵¹ of the phosphine ligand, which helps inhibit catalyst decomposition.⁵² Owing to their cumbersome synthesis,^{42,53} however, these catalysts see little use.⁵⁴ **GII'** was synthesized as above, but with addition of PPh_3 to the cold solution of **Ru-2** prior to cannula addition of PhCHN_2 . **GII'** was obtained in 81% yield after flash chromatography. In comparison, the literature route^{42a} to **GII'** requires five steps from RuCl_3 and proceeds in overall yields of 29–33%. From the perspective of atom efficiency, the new route represents an improvement of more than 3-fold (see the Supporting Information).

The foregoing describes the successful synthesis and isolation of the long-sought precatalyst and synthon $\text{RuCl}_2(\text{p-cymene})(\text{H}_2\text{IMes})$ (**Ru-2**). This previously intractable complex is readily generated in high yields at room temperature by controlling reaction stoichiometry, limiting exposure to light, and keeping concentrations low to inhibit

bimolecular displacement of the *p*-cymene ring. We anticipate that these precautions may likewise afford access to related *p*-cymene complexes bearing bulky, inflexible imidazolidene or other donors, and hence expand the deployment of such complexes in catalysis.

Importantly, the lability of the η^6 -arene ring represents a major asset in use of **Ru-2** as a precatalyst or a building block. An exceptionally efficient route to high-performing phosphine-free and phosphine-stabilized metathesis catalysts from **Ru-2** is demonstrated. Attractive features are its brevity (just two synthetic steps from commercially available **Ru-1**), time efficiency, and high yields (ca. 70% from RuCl_3). In comparison, existing routes proceed in overall yields of ca. 30–50% over four to five steps and require up to 1 week. These findings are anticipated to open the door to new, efficient transformations based on **Ru-2** as a precatalyst, and to improve the efficiency, economy, and reliability of synthetic routes to leading metathesis catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00745.

Experimental procedures and NMR and UV–vis spectra (PDF)

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Notes

The authors declare no competing financial interest.

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