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Isomerization During Olefin Metathesis: An Assessment of Potential Catalyst Culprits

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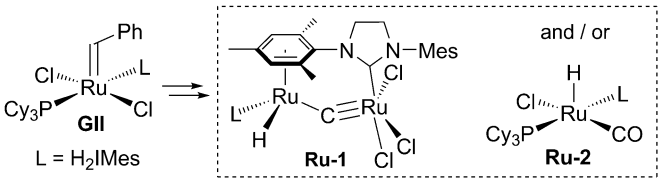
Two ruthenium hydride complexes commonly proposed as agents of unintended isomerization during olefin metathesis are examined for their activity in isomerization of estragole, a representative allylbenzene. Neither proves kinetically competent to account for the levels of isomerization observed during cross-metathesis of estragole by the second-generation Grubbs catalyst. A structure–activity analysis of selected ruthenium hydride complexes indicates that higher isomerization activity correlates with a more electrophilic metal center.

Double-bond isomerization is a common side-reaction in olefin metathesis, even for simple aliphatic olefins.[1–4] Isomerization is particularly problematic for substrates containing allylic amine, ether, or aromatic groups.[5–10] Comparative studies indicate that the problem is most acute for the second-generation Grubbs catalyst [Ru(=CHPh)Cl_2(H_2IMes)(PCy_3)$_2$] (**GII**; H_2IMes = *N*,*N*-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene), Cy = cyclohexyl, as compared to the first-generation catalyst.[11] Isomerization-active species have been proposed to originate in contaminants introduced during catalyst synthesis,[12,13] use,[14] or in intrinsic catalyst deactivation pathways.[15,16] Most commonly cited in recent reports is the potential involvement of two hydride complexes ([Ru_2(μ-C)Cl_3(H)(H_2IMes)$_2$] (**Ru-1**) and [RuCl(CO)H(H_2IMes)(PCy_3)] (**Ru-2**)], accessible by decomposition of **GII** (Scheme 1).[17] Dinuclear **Ru-1** was shown by Hong and Grubbs to form on thermolysis of the resting-state methylidene complex (albeit slowly),[16] whereas several reports describe routes to hydridocarbonyl complexes of type **Ru-2** from **GII**.[18–20] Notably, Percy and co-workers observed **Ru-2** during ring-closing metathesis of 1,7-octadiene by **GII**,[21] and the Grubbs and Mol groups found that closely related carbonyl complexes form on exposure of the Grubbs catalysts to oxygen.[17f,h] The latter findings raised the possibility that incomplete air exclusion could contribute to isomerization.



Scheme 1. Complexes proposed to account for undesired isomerization during metathesis by using **GII**.

Although both **Ru-1**[16] and **Ru-2**[22,23] have been shown to be isomerization-active, it is unclear whether they are kinetically competent to account for the levels of isomerization observed during metathesis reactions. Here, we have examined this point by explicitly comparing their isomerization activity with rates of isomerization observed during self-metathesis of the same substrate under identical conditions. As a further goal, we sought to establish clear-cut structure–activity correlations for a series of selected Ru hydride complexes, which could ultimately aid the identification of plausible culprits.

For both purposes, we chose to study estragole (**1**) as a representative, functionalized allylbenzene of keen interest as a renewable platform chemical.[24] Recent parallel work has pointed out the high-value of products accessible from **1** and isomeric phenylpropenoids through metathesis.[25–27] As noted above, allylbenzene substrates readily undergo isomerization to bring the double bond into conjugation with the phenyl ring, to the extent that they have been used as test substrates to assess potential isomerization inhibitors.[9] In a representative recent study, Bruneau and co-workers reported just 34% cross-metathesis (CM) on treating 2-methoxy-4-allyl-phenol (eugenol) with methyl acrylate, when using **GII** as catalyst.[7] Isomerized species, including secondary metathesis products, accounted for the balance.

Consistent with the Bruneau report, we observed only minor amounts of self-metathesis (SM) on treating **1** with **GII** at 40 °C in toluene (1 mol% **GII**, 0.2 M **1**; Figure 1). The yield of homocoupled estragole (**2**) reached a maximum of 41%, then diminished, owing to competing isomerization, metathesis, or

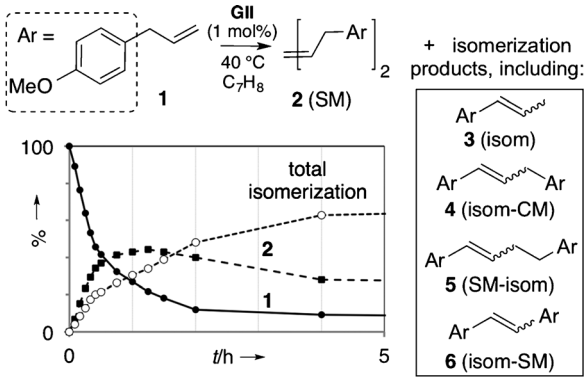


Figure 1. Rates of SM vs. isomerization on treating **1** with **GII** (0.2 M **1**, 1 mol% **GII**); based on replicate runs, ±3%.

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both.[28] Additional products arose from isomerization of **1** into anethole (**3**), CM-isomerization (**4**), SM-isomerization (**5**), and isomerization-SM (**6**), among other, less obvious pathways.[29]

Having established a baseline for isomerization during metathesis, we turned to the question of whether **Ru-1** and/or **Ru-2** were sufficiently reactive to account for the levels of isomerization observed. These experiments were performed under identical conditions of olefin concentration, temperature, and solvent, using the maximum proportion of hydride complex attainable assuming 100% transformation of the **GII** charge in Figure 1 (i.e., 0.5 mol% for the dimer **Ru-1** or 1 mol% for **Ru-2**). Although clearly much higher than the proportion of any hydride species observed during metathesis, these loadings represented an inarguable upper limit. Nonetheless, both catalysts exhibited marginal isomerization activity (Figure 2).

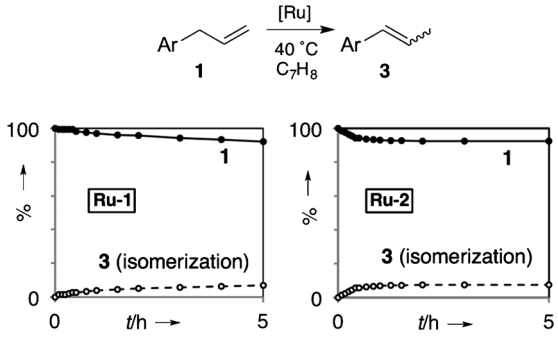

Figure 2. Isomerization of **1** to **3** by using **Ru-1** or **Ru-2** (0.2 M **1**, 1 mol% Ru); based on replicate runs, ±3%.

For **Ru-1**, isomerization reached 6% in 5 h and only 14% after 24 h.[30] The low activity of **Ru-1**, compounded by its slow formation (reported as ≈50% after 3 d at 55 °C in the absence of substrate),[16] was strong evidence against its culpability in the levels of isomerization shown in Figure 1. Similarly feeble activity (maximum 8% isomerization) was seen for **Ru-2**, despite the higher catalyst loading.

Given the implausibility of these catalysts as candidates for the undesired isomerization reactions, we sought to clarify the nature of the ligands associated with higher isomerization activity. To this end, we screened a set of structurally related hydridochloro complexes in the isomerization of **1**. Whereas reviews by the Schmidt and Krompiec groups examine the impact of substrate functional groups on isomerization activity,[20,31] systematic comparisons of ligand effects are more limited. As noted above, however, multiple studies suggest that second-generation [i.e., Ru–*N*-heterocyclic carbene (NHC)] metathesis catalysts trigger more extensive isomerization side-reactions than their first-generation analogues.[11]

To examine this point with well-defined catalysts, we compared the isomerization activity of the complex [RuCl(CO)H-$(PCy_3)_2$] (**Ru-2"**) with that of the NHC derivatives **Ru-2** and [RuCl(CO)H(IMes)(PCy_3)] (**Ru-2′**). Also examined were two complexes with PPh_3 [RuCl(CO)H$(PPh_3)_3$] (**Ru-3**) and [RuClH$(PPh_3)_3$] (**Ru-4**); Figure 3]; this labile ligand was chosen as a proxy for unknown weak donors potentially present during metathesis

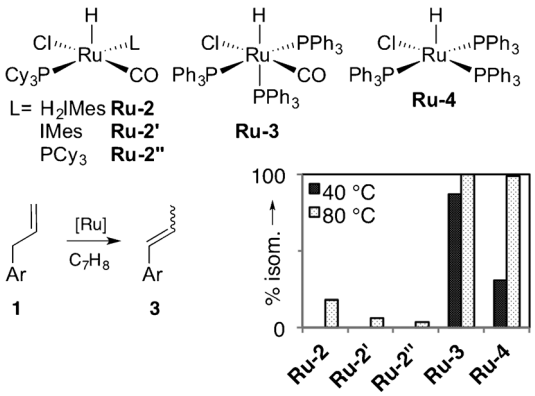

Figure 3. Isomerization of **1** by using various Ru hydrides (0.2 M **1**, 1 mol% Ru; yield of **3** at 0.5 h); based on replicate runs, ±3%.

(e.g., an unsaturated olefin or aryl site within the substrate itself). More fundamentally, the use of PPh_3 allowed us to probe the correlation between isomerization activity and ligand donicity.

Given the low activity observed for **Ru-2** at 40 °C (Figure 2), we evaluated the activity of these five complexes at 80 °C. Consistent with prior reports,[11] levels of isomerization were considerably higher for H_2IMes complex **Ru-2** than its PCy_3 analogue **Ru-2"** or, notably, IMes analogue **Ru-2′**. Dramatically higher activity, however, was seen for the PPh_3 derivatives **Ru-3** and **Ru-4**, suggesting that ligands of weaker donor ability favored isomerization. Decomposed Ru species from which the strong NHC and/or PCy_3 donors had been scavenged may thus have been responsible for the high levels of isomerization activity shown in Figure 1.

The correlations above have important mechanistic implications. Whereas the higher activity of **Ru-3** versus **Ru-2** could reflect the greater lability of PPh_3 than PCy_3, comparison of **Ru-3** and **Ru-4** tells a different story. In experiments performed at 40 °C to maximize discrimination, the carbonyl complex **Ru-3** is observed to be nearly three times more active than **Ru-4**, despite the fact that the π-acid ligand attenuates PPh_3 lability. Higher activity thus appears to be associated with a more electron-deficient Ru center (a factor that could contribute to the impressive activity of a cationic Ru complex reported by Grotjahn and co-workers).[27,32] This, in turn, suggests that olefin binding occurs during or before the rate-determining step. Although early work on dihydride catalysts related to **3** also suggested an associative pathway,[33] isomerization by catalysts of type **2** has been presumed to proceed through a dissociative mechanism.[21]

To clarify this point, we evaluated rates of isomerization at a range of concentrations of **1** (20 mM, 0.20 M, or 1.0 M) with **Ru-2** as catalyst. An approximately first-order dependence on olefin concentration was observed, with the onset of saturation kinetics near 1 M. This indicated a mechanism that is associative in olefin, despite the bulk associated with the PCy_3 and H_2IMes groups already present on the catalyst. Added PCy_3 inhibited the reaction, however, consistent with a subsequent step involving the rate-determining loss of PCy_3 (as also demonstrated in prior studies).[21,33]

Two lead candidates have been favored in the recent literature as probable triggers for unintended double-bond isomerization during olefin metathesis. We have provided strong evidence against their involvement. Indeed, the correlation between weaker donor ligands and higher isomerization activity tends to suggest that the isomerization-active species may arise from more extensive decomposition of the metathesis catalyst, in which the PCy_3 and/or NHC ligands have been scavenged. One intriguing possibility is that the observable hydride species play no active role, with the true culprits instead being species that operate via a π-allyl mechanism. Finally, an associative pathway has been uncovered in the isomerization mechanism, even with rather bulky ligands on the metal. This corroborates earlier work showing similar behavior for Ru-PPh_3 complexes. If this pathway is general, isomerization may be most problematic for metathesis reactions performed at high olefin concentrations, including neat olefin.

Experimental Section

General

Reactions were performed under an inert atmosphere by using standard Schlenk and glove-box techniques. Toluene was dried by using a solvent purification system (Anhydrous Engineering) and stored over 4 Å molecular sieves (Linde) under N_2. **1** (Sigma–Aldrich, 98%) was degassed by consecutive freeze–pump–thaw cycles and filtered through neutral alumina under N_2. Decane (Sigma–Aldrich, anhydrous, 99%) and potassium trispyrazolylborate (TCI Chemicals, 97%) were used as received. Complexes **GII**,[34] **Ru-1**,[16] **Ru-2**,[35] **Ru-2′**,[35] **Ru-2″**,[35] **Ru-3**,[36] and **Ru-4**[37] were prepared according to literature methods. Yields in catalytic runs were measured on an GC (Agilent 7890A) equipped with a flame ionization detector (FID) and polysiloxane column (Agilent HP-5) at an inlet split ratio of 10:1 and inlet temperature of 250 °C. Retention times for **1**, **3**, and **2** were confirmed by comparison with pure samples. Yields were determined from integrated peak areas vs. decane, and corrected for the response factors for decane and analyte. Calibration curves (peak areas vs. concentration) were constructed in the relevant concentration regime to account for the dependence on detector response for all analytes.

Representative procedure for cross-metathesis

A Schlenk tube was loaded with **1** (270 mg, 1.8 mmol), decane (internal standard; 259 mg, 1.8 mmol) and toluene (9.4 mL). An aliquot was removed and assessed by using GC-FID to establish the starting ratio of **1**/decane. Catalyst **GII** (15.5 mg, 0.018 mmol, 1 mol%) was then added. The Schlenk tube was removed immediately from the glovebox and attached to the Schlenk line. The cap was replaced with a septum for sampling with a syringe. The Schlenk tube was then submerged in a thermostatted oil bath at 40 °C. Aliquots were taken at specific time intervals, quenched with potassium trispyrazolylborate (solution in THF, 10 mg/1 mL, 10 equiv), diluted with CH_2Cl_2, and analyzed by using GC-FID.

Representative procedure for isomerization

A Schlenk tube was charged with **1**, decane, and toluene (quantities as above), after which an aliquot was removed to establish initial GC-FID integrations. Catalyst **Ru-2** was then added (14.1 mg, 0.018 mmol, 1 mol%) and the reaction heated at 80 °C. Aliquots removed at specific time intervals were quenched by exposure to air, diluted with CH_2Cl_2, and analyzed by GC-FID.

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