ACS Catalysis

Research Article

pubs.acs.org/acscatalysis

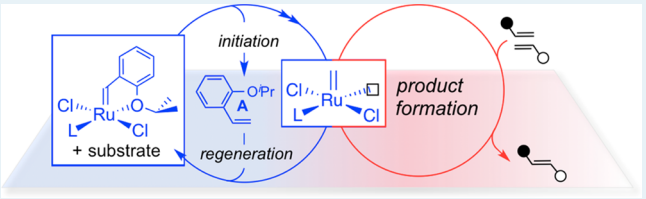
Operation of the Boomerang Mechanism in Olefin Metathesis Reactions Promoted by the Second-Generation Hoveyda Catalyst

Jennifer M. Bates,‡ Justin A. M. Lummiss,‡ Gwendolyn A. Bailey, and Deryn E. Fogg*

Centre for Catalysis Research & Innovation; Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 6N5

Supporting Information

ABSTRACT: A long-standing question in olefin metathesis centers on whether the "release−return" (boomerang) mechanism contributes to the productivity of Hoveyda-class catalysts. According to this mechanism, a molecule of *o*-isopropoxystyrene (**A**) is liberated during catalyst initiation, but recaptures the active catalyst following metathesis. The relevance of this pathway for the second-generation Hoveyda catalyst **HII** was assessed in metathesis of 1,1- and 1,2-disubstituted olefins. Crossover studies with ^{13}C-labeled **A***, as well as competition experiments involving ring-closing or cross metathesis (RCM, CM) in the presence of **A** (equimolar with **HII**) indicated rapid reuptake of styrenyl ether. The crossover studies indicated highly efficient catalyst initiation, with the entire catalyst charge being activated before metathesis was complete. In a comparative study involving CM of anethole with methyl acrylate, sustained activity was shown for **HII**, whereas the second-generation Grubbs catalyst **GII** was rapidly deactivated. These data demonstrate that the release−return mechanism is indeed operative for **HII** in these demanding metathesis reactions, and that facile shuttling from a *protected* recapture cycle into the productive metathesis cycle contributes to the superior performance of **HII** relative to **GII**.

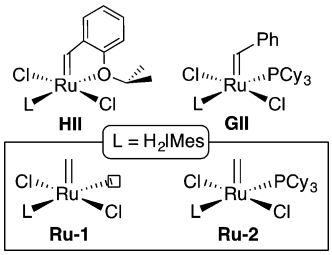


KEYWORDS: *olefin metathesis, boomerang mechanism, Hoveyda catalysts, ^{13}C-labeled crossover, homogeneous catalysis*

INTRODUCTION

Phosphine-free metathesis catalysts, particularly the second-generation Hoveyda catalyst **HII** (Chart 1),[1,2] occupy a position of increasing prominence in olefin metathesis. In the catalytic transformation of seed oils,[3−8] one of the highest-profile topics in sustainable metathesis, **HII** exhibits consistently higher productivity than the important Grubbs catalyst **GII**. This trend is widespread where high concentrations are employed.[9−13] High olefin concentrations favor the associative pathways now known[14,15] to be accessible for **HII**, but precluded for **GII** (which is constrained to react via the rate-determining dissociation of phosphine,[16] and hence four-coordinate **Ru-1**).[17] Even at high dilutions, however, **HII** may exhibit superior performance.[17e,18−24] Of note, reports from pharma indicate that catalysts of the Hoveyda class out-perform **GII** in several demanding ring-closing metathesis (RCM) reactions.[25] Understanding the mechanistic basis of these performance differences takes on added importance as molecular metathesis catalysts enter a new phase of deployment in process chemistry.[26]

Chart 1. Hoveyda and Grubbs Metathesis Catalysts, Active Species Ru-1, and the Off-Cycle Resting-State Species Ru-2 Formed by GII



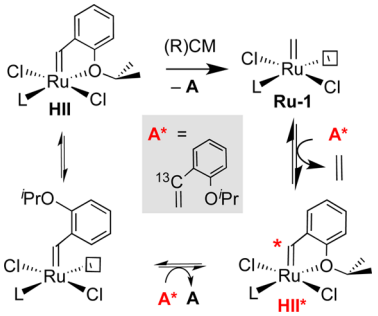
The higher productivity of **HII** has several possible contributors beyond the capacity for associative reaction. The importance of the phosphine-free nature of the catalyst is underscored by comparison with **GII**. Reactions of **GII**, already inhibited by the low lability of the PCy_3 ligand, open the door to two deleterious reactions. Reuptake of phosphine by the active catalyst **Ru-1** generates five-coordinate methylidene **Ru-2** (Chart 1) as an off-cycle resting state. Owing to its very low phosphine lability (drastically lower than that in **GII** itself),[16] **Ru-2** is slow to re-enter the catalytic cycle. Exacerbating the problem, attack by free PCy_3 on **Ru-2** can abstract the methylidene ligand as $[MePCy_3]Cl$. This deactivation pathway has been observed both for isolated **Ru-2**,[27] and during metathesis.[28]

More controversial is the potential role of the styrenyl ether ligand **A** in extending the lifetime of **HII**. The "boomerang" or "release−return" mechanism (illustrated with **HII** and ^{13}C-labeled **A*** in Scheme 1) posits reuptake of released **A** by the active catalyst **Ru-1**: that is, regeneration of **HII** post-metathesis. The concept originated in a study of the first-

Received: April 22, 2014
Revised: June 7, 2014

   dx.doi.org/10.1021/cs500539m | ACS Catal. 2014, 4, 2387−2394

Scheme 1. Pathways for Uptake of Styrenyl Ether A* during Metathesis: Uptake by Ru-1 or (Background Reaction) by HII

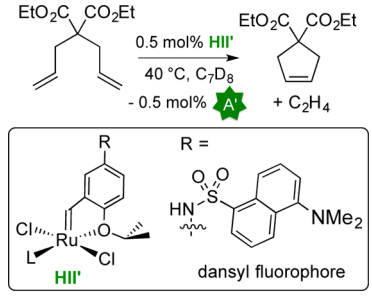


generation catalyst **HI** (L = PCy_3) by Hoveyda and co-workers, who observed up to 98% chromatographic recovery of **HI** after RCM for up to 3 h at 55 °C.[29] If only 2% of the original catalyst charge were active (i.e., 0.1 mol % **HI**), this would imply a remarkably high turnover number of 1000. Regarding this level of activity as implausible—especially given the implied stability of the active species over hours at elevated temperature—the authors suggested that a much higher proportion of the catalyst charge actually initiated, but that **HI** was regenerated by CM with **A** once substrate was depleted. The boomerang mechanism was thus proposed to prolong catalyst lifetime by recapturing the active catalyst.

A key consequence of the boomerang mechanism is thus the potential for higher catalyst productivity. It also opens the door to catalyst recovery (an indirect means of increasing productivity). A number of other reports likewise describe >90% recovery of **HII**,[1,17b,e] although this decreases for challenging targets,[30] presumably reflecting catalyst decomposition prior to recapture.

No consensus has yet emerged from studies designed to probe the validity of the boomerang mechanism.[17e,31−33] Most convincing of the counter-evidence is an experiment by Plenio and co-workers utilizing **HII′**, from which fluorophore-tagged styrenyl ether **A′** is released in the first cycle of metathesis (Scheme 2).[32,34] No decline in fluorescence was observed after

Scheme 2. Fluorometry Study Controverting the Boomerang Mechanism



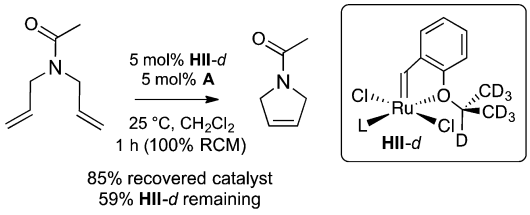
metathesis was complete, leading the authors to conclude that reuptake of **A′** (regeneration of **HII′**) is minimal. The relevance of this conclusion to **HII** is weakened, however, by perturbations arising from the sulfonamide tether in **HII′**. Such electron-withdrawing substituents (especially where para to the ether oxygen, as seen here) promote fast initiation, and significantly retard reuptake of the styrenyl ether.[17b,35−38] This point was explicitly considered and rejected in the Plenio study, which found comparable rates in RCM of DeDAM using tagged and nontagged catalysts. The rapidity of metathesis under the conditions used (0.5 mol % Ru, 40 °C; complete in ∼30 min) has the effect of minimizing rate differences, however.

A further limitation arises from the presence of trapped ethylene in the fluorometry cuvette. Preferential reaction of **Ru-1** with released ethylene, which is both more abundant and more sterically accessible than **A′**, would also limit fluorescence quenching: cycling with ethylene would retard reuptake of **A′**, while ethylene-induced decomposition[27,39−43] would prevent reuptake altogether. Although Plenio's team sought to promote ethylene removal via a syringe needle/balloon assembly, the small gas−liquid interface in the cuvette and the constriction of the needle would severely restrict mass transfer. (Such limitations are explicitly demonstrated in related NMR experiments discussed below.) Consistent with retention of ethylene is the sustained increase in fluorescence intensity (that is, sustained release of **A′**) long after complete consumption of substrate (2 h, vs 30 min). This study should therefore be regarded as offering important insights into the behavior of **HII** derivatives bearing an *electron-deficient* styrenyl ether, especially under mass transfer-limited conditions.

A recent computational analysis by Solans-Monfort and co-workers also disputes the boomerang mechanism.[33] A higher barrier was found for initiation of **HII** than for reaction of **Ru-1** with olefin, and the calculated barriers to olefin binding were lower for cyclopentene than for **A**.[44] From this and a TD-DFT analysis, it was inferred that the **HII** recovered by chromatography is probably unreacted virgin catalyst, not regenerated **HII**. Only dissociative reaction of **HII** was considered, however. As noted above, an emerging consensus holds that associative pathways are favored,[14,15] where not prohibited by bulk or high dilution.

The most convincing evidence to date supporting the release−return mechanism was presented in a study by Grela and co-workers, in which RCM was carried out with the deuteroisopropoxy catalyst **HII-*d*** in the presence of unlabeled **A** (Scheme 3).[17e] The catalyst residues were isolated (85% yield) following complete RCM, and subjected to ^{1}H NMR analysis. A methine septet was observed for the isopropoxy group, which is consistent with uptake of **A** by four-coordinate **Ru-1**. Although this experiment is persuasive, some possibility exists that the deuterated methine in **HII-*d*** could be washed out by H−D scrambling mediated by the Ru center. C−H activation processes are commonplace for ruthenium complexes, and are well-documented for both PCy_3 and NHC derivatives.[45] Crossover could also be amplified by accelerated metathesis during concentration for work-up, an issue highlighted in reports from pharma,[46] and confirmed below.

Scheme 3. Deuterium-Labeling Study Supporting the Boomerang Mechanism



dx.doi.org/10.1021/cs500539m | ACS Catal. 2014, 4, 2387−2394

The present study was undertaken to resolve this long-standing debate, while addressing the potential deficiencies outlined above. To establish whether the boomerang mechanism operates within the relatively demanding contexts in which **HII** is arguably most valuable, we chose 1,1- and 1,2-disubstituted olefins for study. Here we report that competition experiments involving metathesis in the presence of added **A** demonstrate reuptake of **A** in both early and late stages of catalysis. Crossover experiments with ^{13}C-labeled **A*** reveal fast, efficient initiation of **HII**, even with these sterically deactivated olefins. These observations constitute strong evidence that the much-debated "boomerang" pathway is operative in these reactions. Finally, we show that shuttling of **HII** between its protected resting state and the metathesis cycle is disrupted by addition of PCy_3.

RESULTS AND DISCUSSION

Assessing Inhibition of Metathesis by Added Styrenyl Ether A. The Plenio and Solans-Monfort studies concluded that released **A** does not recapture four-coordinate **Ru-1** to any significant extent. However, an earlier study by the Blechert group demonstrated that RCM of *N*-tosyldiallylamine via the first-generation catalyst **HI** was inhibited by added **A**,[35] implying reuptake. We therefore began with experiments aimed at clarifying whether metathesis via **HII** is inhibited by equimolar added **A**. This offers a clear-cut preliminary screen: if **A** is able to compete with a large excess of substrate, the efficiency of reuptake of **A** by **Ru-1** is unequivocal. Secondary questions relating to initiation efficiency (or re-entry into the catalytic cycle), catalyst lifetime, and productivity can then be asked.

We chose two reactions of very different demand to bracket the possibilities. RCM of diene **1** to afford trisubstituted **2** (Figure 1a) is a stringent challenge to uptake of **A** because this substrate is very rapidly cyclized by **HII**, even at ambient temperatures.[1] Inhibition by added **A** would thus indicate high competence of **A** in reuptake. (An added challenge, uncovered in the course of this work, is unexpectedly aggressive catalyst decomposition by **1**; see below.) The second test reaction (Figure 1b) is the CM of anethole **3**, containing a 1,2-trans-disubstituted olefin, with the electron-deficient acrylate **4**. If **A** is unable to compete with the deactivated substrates **3** and **4**, this would support the contention of Plenio and Solans-Monfort that release of **A** is not followed to any significant extent by its return. This test reaction is of added interest given the importance of **HII** in enabling access to **5** and related high-value antioxidants from renewable arylpropenes.[47]

These RCM experiments revealed 99% consumption of diene **1** within 10 min, even at ambient temperature. The rate curves of Figure 1a indicate that **A** inhibits consumption of **1** even at early stages of reaction: that is, a single equivalent of **A** competes with a significant excess of **1**. This is particularly striking given the mildly deactivated nature of **A** in metathesis, even relative to styrene.[48] It reflects the fact that consumption of **1** requires not only initial metathesis at the accessible vinylic olefin, but also subsequent cyclization onto the sterically encumbered 2,2-disubstituted olefin.

Added **A** is even more strongly inhibiting in CM of *trans*-anethole **3** with methyl acrylate (Figure 1b). Inhibition was maintained, even when the proportion of **A** relative to **3** was reduced from 1:100 to 1:2000. In the latter experiment, higher temperatures were used to compensate for the lower catalyst loading (0.05 mol %), and catalyst deactivation resulted in

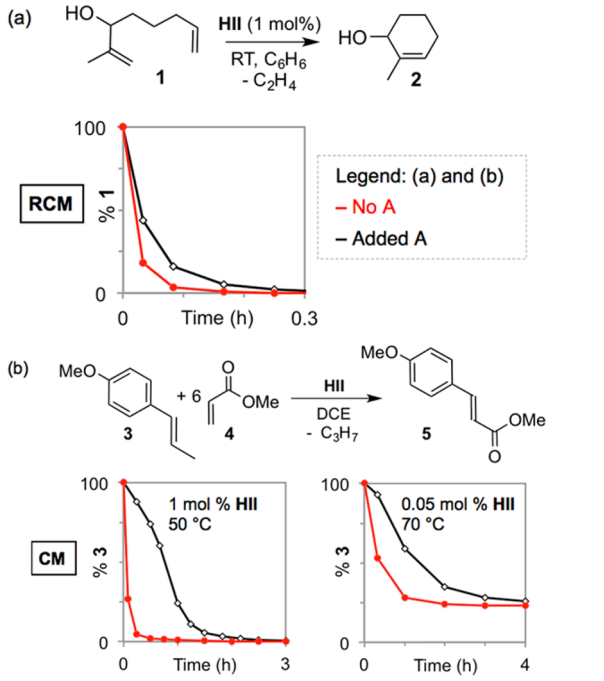


Figure 1. Assessing inhibition of **HII** in the presence of 1 equiv **A** (a) in RCM of **1** (100 mM) and (b) in CM of **3** (200 mM, using 1 mol % or 0.05 mol % **HII**). Reactions were stirred open to N_2; olefin consumption assessed by GC/FID.

incomplete consumption of **3**. Notably, however, the total turnover number (TON) was unaffected by added **A**. The mechanistic implications of this observation will be discussed in the final section.

These data indicate that in both test reactions, **A** was able to compete with olefin, even at early stages of metathesis. This indicates efficient uptake of **A** by the active species **Ru-1**, a prerequisite for operation of the release–return mechanism.

Reaction Conditions and C_2H_4 Removal. The fact that RCM was inhibited by 1 mol % added **A** implies that ethylene, given its greater abundance and reduced steric bulk, may well suppress reaction of **Ru-1** with **A**. This has potentially critical implications for the validity of probe studies carried out in vessels with limited headspace (see the Introduction), in which mass transfer is necessarily retarded. To evaluate the impact on catalyst lifetime and productivity, we carried out RCM of **1** in C_6D_6 under the conditions of Figure 1 (i.e., open, stirred), and in a sealed J. Young NMR tube. The proportion of catalyst present was assessed by integrating the ^{1}H NMR signal for the alkylidene proton against an internal standard.

The rigor of this assessment is aided by the unexpectedly destructive nature of substrate **1**. Extensive catalyst decomposition was observed even where ethylene was efficiently removed, with 33% loss of **HII** at quantitative conversion (see Table 1, entry 1). (Notably, no decomposition was seen in the corresponding reaction of DeDAM, perhaps pointing toward a role for the allylic alcohol functionality in catalyst deactivation.) On carrying out the RCM of **1** in a sealed J. Young NMR tube, decomposition was nearly doubled, and conversions dropped to 88% (entry 2). RCM of **1** is clearly an instance when styrenyl ether reuptake competes with decomposition, but does not completely inhibit it.

The loss of **HII** tracks with the 20-fold higher proportion of ethylene in the NMR-tube reaction. We infer that retention of

dx.doi.org/10.1021/cs500539m | ACS Catal. 2014, 4, 2387–2394

Table 1. Examining the Impact of Mass-Transfer-Limited (NMR tube) Conditions on Conversions and Lifetime of HII[a]

entry	conditions	conv. (%)	loss of **HII** (%)	equiv C_2H_4
1	open, stirred	>99	33 ± 1	1.1 ± 0.1
2	NMR-tube, sealed	88	55 ± 2	20.1 ± 0.5
3	NMR-tube, balloon	88	58 ± 2	22.3 ± 0.5

[a]Measured by ^{1}H NMR analysis, by integration of the alkylidene and ethylene signals vs 1,3,5-trimethoxybenzene (TMB) as internal standard; normalized to initial proportion of **HII**. Conditions: 100 mM **1**, 1 mol % **HII**, C_6D_6, RT, 10 min. Reactions in duplicate; conversions ±1%.

ethylene perturbs operation (or indeed, investigation) of the boomerang mechanism in two ways: it impedes reuptake of **A**, and it promotes competing decomposition to metathesis-inactive species that are unable to regenerate **HII**. Faster initiation is also plausible, but if operative, it is countered by faster decomposition.

Attempts to vent C_2H_4 from a septum-sealed Rotaflo NMR tube by connecting it via a needle to an N_2-filled balloon were completely ineffective. Removal of ethylene was inefficient, even when the tube was shaken by hand: indeed, the proportion *increased* slightly (see entry 3) relative to the sealed-tube experiments, which could be shaken more vigorously. To promote efficient removal of C_2H_4 from solution, subsequent experiments were therefore carried out in open vessels with stirring, with a single exception (see below).

Crossover Experiments. We next turned to quantifying the rate and extent of styrenyl ether uptake under conditions of catalysis. These experiments were enabled by Marciniec's 2011 report of straightforward routes to styrenyl ether **A*** and complex **HII***,[49] bearing a ^{13}C label at the styrene β-carbon or at the benzylidene carbon, respectively (Figure 2). These

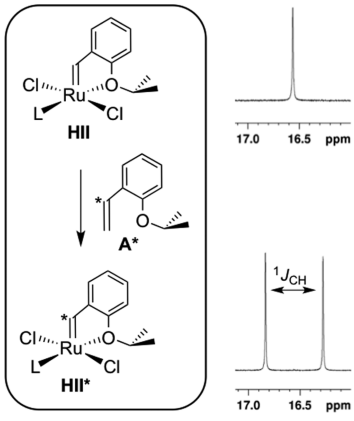


Figure 2. Uptake of ^{13}C-labeled **A*** by **HII** and accompanying changes in the alkylidene region of the ^{1}H NMR spectrum (C_6D_6).

compounds offer a unique opportunity to unambiguously assess both release and reuptake of the styrenyl ether via experiments that address the potential limitations in Grela's important deuterium-labeling study (see the Introduction). Specifically, we envisaged using the $^1J_{CH}$ splitting of the alkylidene proton as a powerful spectroscopic handle to distinguish **HII** from **HII*** in crossover NMR experiments. Use of ^{13}C-labeled **A*** eliminates perturbations arising from substituents on the styrenyl ether, while ensuring that the label is immune to non-metathetical scrambling.

For metathesis using **HII** in the presence of styrenyl ether **A*** (or **HII*** in the presence of **A**), internal standards were used to quantify both catalyst initiation and regeneration. Uptake of **A*** was measured without work-up, to eliminate the possibility of accelerated catalyst regeneration at high concentrations of **A***. Finally, these reactions were performed in the glovebox so that aliquots could be withdrawn without risk of introducing air and hence decomposition of four-coordinate **Ru-1**, which would limit uptake of **A*** (see above).

Uptake of A* During CM. Initiation efficiency ultimately controls the proportion of the active species **Ru-1** available for reaction with **A** and hence the extent of crossover. ROMP studies (including experiments measuring the rate constants for initiation vs propagation) led to the early inference that the bidentate Hoveyda catalysts initiate with low efficiency.[29,50−53] This could well reflect faster propagation, however, rather than inherently slow initiation. The Plenio and Percy groups have demonstrated rapid initiation of **HII** in metathesis of vinyl olefins. We suspected that the steric encumbrance of trans-disubstituted **3** might constrain dissociative initiation of **HII**, unless initial reaction could occur at the electron-deficient acrylate olefin.

Surprisingly efficient initiation, however, was observed in crossover experiments using 1 equiv of **A***. Thus, near-equilibrium proportions of **HII*** (43%) were reached after 2 h, prior to complete consumption of anethole **3** (92% conversion; Figure 3a). To ensure that the added **A*** was not accelerating

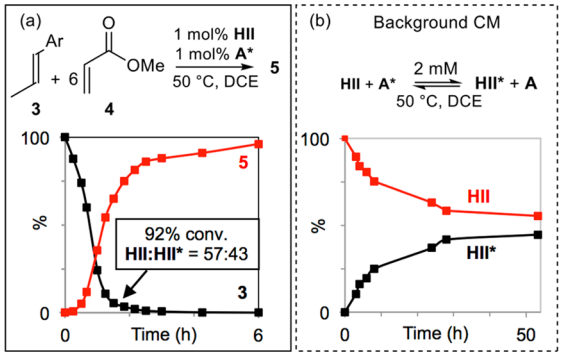


Figure 3. (a) CM of **3** with methyl acrylate by **HII** in the presence of **A***. (b) Time scale for equilibration of **A*** in the absence of substrate; conditions as in part a. Ar = 4-methoxybenzene.

initiation, control experiments were carried out, in which the time scale for equilibration of **HII** with **A*** was assessed in the absence of **3**/**4** (Figure 3b). Under these conditions, the proportion of **HII*** was just 6% at 2 h, and full equilibration required days. Similarly slow exchange was reported by Blechert and co-workers in 1:1 reactions of **HII** with deuterated **A**.[54] (The expected 50:50 ratio was not reached either in the Blechert study or in any of the reactions studied herein: this is due to a competing side-reaction of **A***, as discussed below.) We infer that the background reaction of **HII** with **A*** makes a negligible contribution to the proportion of **HII***. That is, the crossover in the CM reaction of Figure 3a reflects the amount of **Ru-1** generated by reaction of the catalyst with **3**/**4**. This confirms efficient initiation, as well as efficient uptake of **A*** by **Ru-1**.

dx.doi.org/10.1021/cs500539m | ACS Catal. 2014, 4, 2387−2394

Uptake of A* during RCM. The rapidity with which **1** is cyclized severely tests both the initiation efficiency of **HII** and uptake of labeled **A*** (i.e., crossover). As shown in Figure 4a,

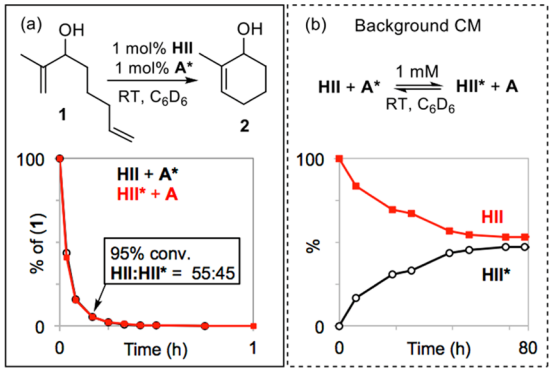


Figure 4. (a) Time scale for RCM of **1** vs equilibration of **HII**/**HII***. (b) Time scale for equilibration of **A*** in the absence of substrate; conditions as in part a.

conversions of **1** in the presence of 1 mol % of **HII** and **A*** reached 95% within 10 min. We measured the **HII**/**HII*** ratio at this point (that is, just prior to complete consumption of **1**) to assess the extent of catalyst conscription on the time scale of the RCM reaction. Unexpectedly, equilibration was close to complete after just 10 min (45% **HII***), indicating that both initiation of **HII** and uptake of **A*** are rapid. As with the CM study above, a control experiment in the absence of substrate indicated that background equilibration of **A*** with **HII** contributes minimally to exchange (Figure 4b; 1 mM Ru). Thus, <1% **HII*** was observed at the 10 min mark, and equilibration occurred only over days. Again, we conclude that the crossover observed under conditions of catalysis reflects the amount of **Ru-1** generated by reaction of the catalyst with **1**.

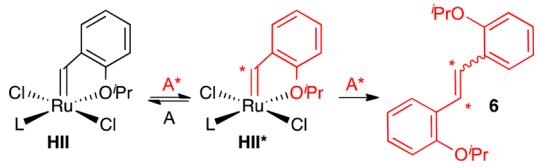
To assess whether recapture is maintained at synthetically relevant catalyst loadings, the crossover RCM experiment was repeated at 0.2 mol % **HII** (0.2 mM). Both initiation of **HII** and reuptake of **A*** remained efficient, even at these low loadings, with an equilibrium level of 47% **HII*** being measured after RCM was complete.[55] Background uptake of **A*** is negligible under these conditions, as judged from the ∼5% CM seen at 3 h for experiments using 1 mM Ru (i.e., a 5-fold higher catalyst concentration).

A final experiment in this series was aimed at exploring the extent of crossover prior to depletion of **1**. To intercept the reaction at lower conversions, when the proportion of **1** is high, RCM was carried out at 10 °C in a Rotaflo NMR tube. As noted above, volatilization of ethylene is limited under these conditions, and the rate and extent of crossover are therefore under-reported. Even so, the **HII**/**HII*** ratio had already reached 65:35 by 50% conversion. The rapidity of uptake is consistent with the inhibition studies of Figure 1a.

Collectively, these data offer convincing evidence for reuptake of **A***; they also indicate that reuptake occurs throughout the catalytic reaction, rather than being limited to late stages when substrate is depleted, as originally believed.[1,29] Also notable is the high efficiency of catalyst conscription for **HII** in all of these reactions, even the particularly challenging CM reaction of Figure 3a. This has important practical implications. It indicates that **HII** is rapidly engaged in catalysis, even for rather recalcitrant substrates, and that the whole catalyst charge contributes to the observed metathesis activity. In both reactions studied, any recovered **HII** would not be virgin, unreacted catalyst, but rather regenerated **HII** formed by reaction of **Ru-1** with **A**. More fundamentally, the ease of initiation *and* regeneration of **HII** means that this robust "precatalyst" should be viewed as a reactive resting-state species, which readily re-enters the catalytic cycle.

Incomplete Crossover: Stilbene Formation. As noted above, the anticipated 50:50 ratio of **HII** to **HII*** was not achieved in any of the crossover experiments described. Instead, a ∼3% bias toward **HII** was observed for experiments involving **HII** and **A***. A similar observation by Blechert and co-workers[54] in experiments with deuterium-labeled **A** was noted above. We attribute the discrepancy to a minor side-reaction involving self-metathesis of **A*** to afford the doubly labeled stilbene derivative **6** (Scheme 4). Stilbenes are challenging substrates for

Scheme 4. Loss of ^{13}C Label via Stilbene Formation



metathesis owing to 1,2-disubstitution of the olefin with aromatic groups over which the electron density of the double bond is delocalized. We recently highlighted the resistance to metathesis of the stilbenes derived from **3**, even for reactions at 70 °C.[47] Loss of the ^{13}C label is thus expected whenever emerging **HII*** reacts with **A*** (the latter of which remains the statistically dominant form of the styrenyl ether until equilibrium is reached). Consistent with this, the **HII**/**HII*** ratio is reversed (47:53) when the reaction is performed with **HII*** and **A**. Formation of the stilbenoid was confirmed by GC/MS analysis for the corresponding reaction of **HII** with **A**.

Impact of Styrenyl Ether Reuptake. Given the evidence for operation of the boomerang mechanism above, a key question is its impact on productivity. We examined this point within the context of acrylate CM, in which **HII** consistently and dramatically out-performs **GII** (see Introduction). In the CM of anethole with methyl acrylate, a turnover number (TON) of 1500 was obtained for **HII**, as compared with just 120 for the second-generation Grubbs catalyst **GII**. We attribute the difference to faster decomposition of the Grubbs catalyst system by the PCy_3 present, which causes conversions to plateau at a very early stage of reaction (Figure 5a). Consistent with this, the superior performance of **HII** was completely erased when PCy_3 was deliberately added to the catalytic reaction mediated by **HII** (1 equiv relative to **HII**; see Figure 5b).

As established above, however (see Figure 1), added styrenyl ether inhibits metathesis. That is, the co-ligands present in *both* **GII** and **HII** impede metathesis. The advantage of the Hoveyda catalyst, relative to **GII**, thus lies not in recapture of **A**, which only serves to take the catalyst out of the metathesis cycle, but in the absence of phosphine. The penalty for recapture of **Ru-1** by **A** is relatively small: while this slows turnover, the regenerated **HII** is sterically protected against nucleophilic attack and can re-enter the catalytic cycle with comparative ease. Efficient initiation and regeneration of **HII** thus shuttles the catalyst between the productive metathesis cycle and a protected recapture cycle. Added **A** therefore reduces turnover

dx.doi.org/10.1021/cs500539m | ACS Catal. 2014, 4, 2387−2394

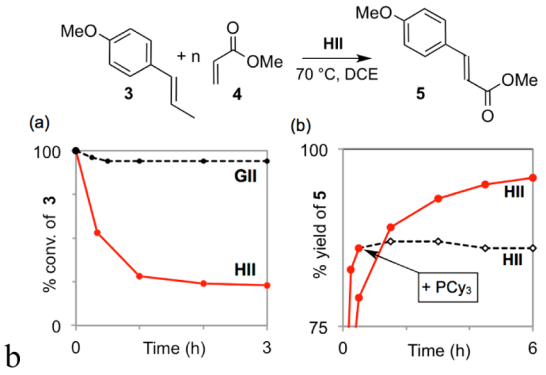


Figure 5. (a) Comparative activity of **HII** and **GII** in CM of anethole with methyl acrylate (n = 6; 0.05 mol % Ru). (b) Poisoning of **HII**-mediated CM by adding PCy_3 at 15 min (0.5 mol % **HII**; 1 equiv PCy_3; n = 4).

frequencies, with no significant impact on turnover numbers (i.e., productivity).

In comparison, the performance of **GII** is limited by low phosphine lability, and hence feeble initiation. Once formed, **Ru-1** reacts more readily with olefin than with free PCy_3 (a condition for which Chen has coined the term "high-commitment").[56] Recapture by phosphine, however, traps the catalyst as methylidene **Ru-2**, which is both slow to re-enter catalysis, and susceptible to attack by PCy_3[27,28] and related nucleophiles.[28]

CONCLUSIONS

The foregoing provides strong evidence for the operation of the boomerang mechanism in RCM and CM reactions promoted by **HII**. Competition and crossover studies indicated unexpectedly rapid uptake of styrenyl ether even at early stages of reaction, not merely once diene consumption was complete. Competition between substrate and styrenyl ether retards productive metathesis (i.e., turnover frequencies), particularly for challenging substrates and in later stages of reaction, although it helps to conserve the catalyst charge. It should be emphasized, however, that styrenyl ether reuptake impedes decomposition, but does not inhibit decomposition altogether.

Particularly given the facile regeneration of **HII**, a key aspect of the findings above is the ease with which the catalyst initiates, even for sterically encumbered substrates. Slow initiation (i.e., release of **A**) from both **HI** and **HII** would result in catalysis via a small proportion of the original catalyst charge. The foregoing adds to a growing body of evidence that this is not the case. Instead, the entire catalyst charge is rapidly conscripted, even by sterically and electronically deactivated substrates, but a proportion of the vulnerable four-coordinate intermediate is also rapidly recaptured by styrenyl ether. **HII** is thus not merely the precatalyst, but is in fact the resting-state species in catalysis.

These results point toward several factors that contribute to the impressive performance of **HII** relative to **GII**. Notwithstanding its permanent "Hall of Fame" status in olefin metathesis, **GII** is limited by slow initiation, a condition severely exacerbated by the poorer lability of its off-cycle resting state, methylidene **Ru-2**. The latter represents a thermodynamic sink that limits catalyst participation. For **GII**, the recapture cycle is thus destructive: it impairs TOF (by taking the active catalyst out of circulation), while also eroding catalyst productivity via catalyst decomposition. As a net effect, metathesis is carried by a smaller proportion of the starting catalyst charge. The key advantages of **HII**, in comparison, lie in fast, efficient mobilization of the entire catalyst charge, and in the stability of the chelated benzylidene moiety, a protected resting-state structure. Although the latter represents a "holding pattern" that does not contribute to productivity (and indeed retards turnover), the reservoir of catalyst is able to re-enter the catalytic cycle without a major energetic penalty. Facile initiation, the steric protection of the resting state, and relative ease of re-entry into the catalytic cycle are all factors that contribute to the improved performance of **HII** relative to **GII**.

EXPERIMENTAL SECTION

General Procedures. Reactions were carried out in an N_2-filled glovebox using dry, oxygen-free solvents (for details, see the Supporting Information (SI)). Olefin reagents were obtained from commercial sources (*trans*-anethole **3**, methyl acrylate; both 99%, monomethyl ether hydroquinone as inhibitor in the latter) or prepared by literature methods (RCM substrate 1, 2-methylocta-1-7-dien-3-ol,[57] 2-isopropoxystyrene **A** and its ^{13}C-labeled analogue **A*** (^{13}C 99%).[49] NMR and GC standards (1,3,5-trimethoxybenzene (TMB), ≥99%; decane, ≥99%; dimethyl terephthalate) and the quenching agent potassium tris(pyrazolyl)borate (KTp), >97% were used as received. Literature methods were used to prepare the second-generation Hoveyda catalyst **HII**.[58] Labeled **HII*** was prepared similarly using ^{13}C-labeled **A***. Standard solutions were made up for catalyst, substrate, and internal standard, as described in the SI.

^1H NMR spectra were recorded at 298 K and referenced to the residual proton signals of the deuterated solvent. Signals are reported in parts per million (ppm) relative to TMS at 0 ppm. Gas chromatography utilized an Agilent HP-5 polysiloxane column (30 m length, 320 μm diameter). The FID response was maintained between 50 and 2000 ρA using analyte concentrations of ∼5 mM (diluted with CH_2Cl_2 or C_6H_6). GC/FID quantification was established by constructing calibration curves of peak area vs concentration in the relevant concentration regime to account for the dependence on detector response for substrates, products, and decane (internal standard in catalytic runs). Yields in catalytic runs were determined from the integrated peak areas referenced against decane, and compared with the integration ratio of substrate to internal standard at time zero (t_0).

Representative RCM Reaction. A 10 mL Schlenk tube was charged with diene **1** (200 μL of a 750 mM solution, 0.15 mmol), **A*** (20 μL of a 75 mM solution, 0.0015 mmol, 1 mol %), decane (100 μL of a 1.5 M solution, 0.15 mmol; internal GC standard), and C_6D_6 (450 μL). A ∼20 μL aliquot was removed to assess the initial ratio of **1**/decane by GC/FID. In parallel, a J. Young NMR tube was charged with **HII** (50 μL of a 30 mM solution, 0.0015 mmol), TMB (6 μL of a 32 mM solution, 0.0005 mmol, 0.3 mol %, internal NMR standard), and C_6D_6 (515 μL), and subjected to ^1H NMR analysis to establish the starting ratio of **HII**/TMB. The catalyst solution was added to the Schlenk flask, and the NMR tube was rinsed with C_6D_6 (2 × 100 μL) to give a final substrate concentration of 100 mM. The reaction was stirred open to a well-purged N_2 glovebox at ambient temperature (27 ± 2 °C) and monitored by periodically removing aliquots (∼20 μL; quenched with ∼10 equiv KTp per Ru and diluted to 1 mL with C_6H_6) for GC/FID analysis. RCM was 95% complete at 10 min. At this stage, an aliquot was quickly transferred to a J. Young NMR tube,

dx.doi.org/10.1021/cs500539m | ACS Catal. 2014, 4, 2387−2394

removed from the box, chilled (0 °C) to arrest catalysis, and analyzed within <10 min (^{1}H NMR). The extent of crossover was assessed by integrating the singlet for **HII** (16.71 ppm) vs the doublet for **HII*** (16.71 ppm; d, $^1J_{CH}$ = 167 Hz).

Reuptake at Lower RCM Conversions. These experiments were carried out similarly (50% scale) in a Rotaflo NMR tube to permit in situ ^{1}H NMR analysis. Once the initial ratio of **1**/decane was established for **1**/**A***/TMB/decane solutions (C_6D_6), **HII** was added using a gastight syringe. The NMR tube was quickly sealed and shaken at RT for 15 s, then inserted into a precooled (10 °C) NMR probe to slow the reaction. ^{1}H NMR spectra (1 min acquisition time) were collected for 45 min; ∼50% conversion of **1** was observed after a total of 19 min in the NMR probe.

CM Reactions. These experiments were carried out similarly, but using a sand bath for heating in the glovebox. For full experimental details, see the SI.

Representative Procedure for Background CM of HII and A*. A solution of **HII** (75 μL of a 30 mM solution, 0.0023 mmol), TMB (24 μL of a 32 mM solution, 0.00076 mmol, 0.3 mol %), and C_6D_6 (2.1 mL) was loaded into a 50 mL Kontes flask, resulting in a headspace-to-solution volume ratio of 24:1. The starting ratio of **HII**/TMB was established by ^{1}H NMR analysis, after which the sample was returned to the Kontes flask, and ^{13}C-labeled 2-isopropoxystyrene **A*** (30 μL of a 75 mM solution, 0.00224 mmol) was added; the final Ru concentration was 1 mM. The stirred solution was vented each time an aliquot was removed for ^{1}H NMR analysis. After each measurement, the aliquot was immediately returned to the Kontes flask. The extent of crossover was assessed from the relative integrations of the alkylidene signals for **HII** vs **HII*** (see Figure 2). No dissolved C_2H_4 was detected.

Confirmation of Stilbene Formation. The background reaction was repeated on larger scale to enable detection of the stilbenoid self-metathesis products. A stirred solution of **HII** (0.015 mmol, 1 equiv) and 2-isopropoxystyrene **A** (0.015 mmol, 1 equiv) in benzene (14.4 mL, final concentration 1 mM) was allowed to equilibrate at RT for 92 h. Formation of the *cis*- and *trans*-stilbenes **6** was confirmed by GC/MS analysis of the concentrated reaction mixture. MS (ESI): *m*/*z* calcd for $C_{20}H_{24}O_2$: 296.2; found: 296.2.

Competition Experiment between Styrene and Styrenyl Ether A. Experiment carried out with **GII**. To a Rotaflo NMR tube containing TMB (5.6 mg, 0.033 mmol) in 0.95 mL C_6D_6 was added a solution of **A** (21 μL, 0.126 mmol) and an equimolar amount of styrene (added by syringe until integration vs **A** indicated a 1:1 ratio). A solution of **GII** was then added (0.27 mL of a 37.4 mM solution in C_6D_6; 0.010 mmol, 8 mol %), and the mixture was shaken well. The solution was heated in a thermocouple-controlled oil bath at 40 °C, and monitored by ^{1}H NMR over 64 h. Disappearance of the characteristic olefinic signals due to **A** (5.69 ppm, dd, $^3J_{HH}$ = 17.9 Hz, $^2J_{HH}$ = 1.7 Hz, 1H; 5.16 ppm, dd, $^3J_{HH}$ = 11.2 Hz, $^2J_{HH}$ 1.7 Hz, 1H) and styrene (5.55 ppm, dd, $^3J_{HH}$ = 17.6 Hz, $^2J_{HH}$ =1.0 Hz, 1H; 5.02 ppm, dd, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 1.0 Hz, 1H) was measured by integration vs TMB at 12 and 64 h. Metathesis of **A** was found to proceed at ∼60% the rate of styrene.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, preparation of stock solutions, and representative ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail dfogg@uottawa.ca.

Author Contributions

‡J.M.B. and J.A.M.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NSERC of Canada.

■ ABBREVIATIONS

CM, cross metathesis; RCM, ring-closing metathesis; ROMP, ring-opening metathesis polymerization; TON, turnover number; TOF, turnover frequency; GC/FID, gas chromatography/flame ionization detector; I_A, interchange associative

■ REFERENCES

(1) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(2) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

(3) Miao, X.; Fischmeister, C.; Dixneuf, P. H.; Bruneau, C.; Dubois, J. L.; Couturier, J. L. *Green Chem.* **2012**, *14*, 2179−2183.

(4) Miao, X.; Malacea, R.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2911−2919.

(5) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. *Green Chem.* **2011**, *13*, 1448−1452.

(6) Malacea, R.; Fischmeister, C.; Bruneau, C.; Dubois, J.-L.; Couturier, J.-L.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 152−155.

(7) Djigoué, G. B.; Meier, M. A. R. *Appl. Catal., A* **2009**, *368*, 158−162.

(8) Rybak, A.; Meier, M. A. R. *Green Chem.* **2007**, *9*, 1356−1361.

(9) Barbasiewicz, M.; Michalak, M.; Grela, K. *Chem.—Eur. J.* **2012**, *18*, 14237−14241.

(10) Kniese, M.; Meier, M. A. R. *Green Chem.* **2010**, *12*, 169−173.

(11) Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11768−11769.

(12) Hryniewicka, A.; Kozłowska, A.; Witkowski, S. *J. Organomet. Chem.* **2012**, *701*, 87−92.

(13) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153−5157.

(14) Thiel, V.; Hendann, M.; Wannowius, K.-J.; Plenio, H. *J. Am. Chem. Soc.* **2012**, *134*, 1104−1114.

(15) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. *ACS Catal.* **2013**, *3*, 1929−1939.

(16) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.

(17) **GII** tends to out-perform **HII** in the RCM assembly of tetrasubstituted olefins (the steric bulk of which precludes associative reaction). See, for example, ref 12 and (a) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740−5745. (b) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318−9325. (c) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339−1342. (d) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589−1592. (e) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem.—Eur. J.* **2008**, *14*, 806−818.

(18) Samojłowicz, C.; Bieniek, M.; Pazio, A.; Makal, A.; Woźniak, K.; Poater, A.; Cavallo, L.; Wójcik, J.; Zdanowski, K.; Grela, K. *Chem.—Eur. J.* **2011**, *17*, 12981−12993.
(19) Maechling, S.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2005**, *347*, 1413−1422.
(20) Johannes, M.; Altmann, K. H. *Org. Lett.* **2012**, *14*, 3752−3755.
(21) Garzon, C.; Attolini, M.; Maffei, M. *Eur. J. Org. Chem.* **2013**, *2013*, 3653−3657.
(22) Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929−8936.
(23) Nuñez, A.; Abarca, B.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Eur. J. Org. Chem.* **2011**, *2011*, 1280−1290.
(24) Danoun, G.; Ceccon, J.; Greene, A. E.; Poisson, J.-F. *Eur. J. Org. Chem.* **2009**, 4221−4224.
(25) van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E. Ring-Closing Metathesis: A How-To Guide. In *Olefin Metathesis: Theory and Practice*; Grela, K., Ed.; Wiley: Hoboken, NJ, 2014; pp 85−152.
(26) Bomgardner, M. M. *Chem. Eng. News* **2013**, *91* (43), 17.
(27) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961−7968.
(28) Lummiss, J. A. M.; Ireland, B. J.; Sommers, J. M.; Fogg, D. E. *ChemCatChem* **2014**, *6*, 459−463.
(29) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799.
(30) In the RCM assembly of tetrasubstituted cycloolefins, for example, just 60% recovery of **HII** was reported for one reaction carried out at 80 °C for 30 min, and 81% for another at 40 °C for 20 h. See ref 1.
(31) Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4510−4517.
(32) Vorfalt, T.; Wannowius, K. J.; Thiel, V.; Plenio, H. *Chem.—Eur. J.* **2010**, *16*, 12312−12315.
(33) Núñez-Zarur, F.; Solans-Monfort, X.; Pleixats, R.; Rodríguez-Santiago, L.; Sodupe, M. *Chem.—Eur. J.* **2013**, *19*, 14553−14565.
(34) A related set of experiments in the same study employed a ^{19}F-labelled styrenyl ether and came to the same conclusion using different (NMR, UV−vis) metrics. Again, however, electronic perturbation of the styrenyl ether (use of an electron-withdrawing fluorine substituent para to oxygen) can be anticipated to impede reuptake, and ethylene builds up in the sealed tube. The latter problem is discussed in more detail below.
(35) Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545−6558.
(36) Connon, S. J.; Rivard, M.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2003**, *345*, 572−575.
(37) Gulajski, L.; Michrowska, A.; Bujok, R.; Grela, K. *J. Mol. Catal. A: Chem.* **2006**, *254*, 118−123.
(38) Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S. P.; Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225−4228.
(39) Monfette, S.; Eyholzer, M.; Roberge, D. M.; Fogg, D. E. *Chem.—Eur. J.* **2010**, *16*, 11720−11725.
(40) Lysenko, Z.; Maughon, B. R.; Mokhtar-Zadeh, T.; Tulchinsky, M. L. *J. Organomet. Chem.* **2006**, *691*, 5197−5203.
(41) van Rensburg, W. J.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332−14333.
(42) Burdett, K. A.; Harris, L. D.; Margl, P.; Maughon, B. R.; Mokhtar-Zadeh, T.; Saucier, P. C.; Wasserman, E. P. *Organometallics* **2004**, *23*, 2027−2047.
(43) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.
(44) Ref 33 reports that the calculated barrier to binding of cyclopentene is lower than that for binding of **A**. This tends to suggest that uptake of product olefin by **Ru-1** should inhibit catalyst regeneration, a finding not readily reconciled with the experimental data described below.
(45) For selected examples, see: (a) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074−6086 (in this example, a deuterium-labelled NHC scrambles into olefinic products). (b) Mathew, J.; Koga, N.; Suresh, C. H. *Organometallics* **2008**, *27*, 4666−4670. (c) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546−2558. (d) Borowski, A. F.; Sabo-Etienne, S.; Christ, M. L.; Donnadieu, B.; Chaudret, B. *Organometallics* **1996**, *15*, 1427−1434 Deuterium scrambling from alkylidene ligands into the ancillary ligands has also been demonstrated; see refs 41 and 43.
(46) Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133−7145.
(47) Lummiss, J. A. M.; Oliveira, K. C.; Pranckevicius, A.; Santos, A.; dos Santos, E. N.; Fogg, D. E. *J. Am. Chem. Soc.* **2012**, *134*, 18889−18891.
(48) In a competition experiment, in which equimolar **A** and styrene were treated with **GII** (8 mol %) at 40 °C, loss of **A** was significantly slower. Values at 64 h: 38% styrene, vs 61% **A**.
(49) Marciniec, B.; Rogalski, S.; Potrzebowski, M. J.; Pietraszuk, C. *ChemCatChem* **2011**, *3*, 904−910.
(50) Schulz, M. D.; Wagener, K. B. *ACS Macro Lett.* **2012**, *1*, 449−451.
(51) Fogg, D. E.; Foucault, H. M. Ring-Opening Metathesis Polymerization. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds. Elsevier: Oxford, 2007; Vol. *11*, pp 623−652.
(52) Slugovc, C. *Macromol. Rapid Commun.* **2004**, *25*, 1283−1297.
(53) Demel, S.; Schoefberger, W.; Slugovc, C.; Stelzer, F. *J. Mol. Catal. A: Chem.* **2003**, *200*, 11−19.
(54) Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733−2736.
(55) Given the low starting concentration of both **HII** and **A***, the NMR experiments required a 3 h acquisition time. This period is double the time of the RCM experiment itself, precluding measurement of uptake prior to complete RCM. (These reactions cannot be concentrated without increasing the proportion of uptake, given that the background reaction revealed a rate dependence on the concentration of **A**.)
(56) Adlhart, C.; Chen, P. *Helv. Chim. Acta* **2003**, *86*, 941−949.
(57) McGrath, N. A.; Lee, C. A.; Araki, H.; Brichacek, M.; Njardarson, J. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9450−9453.
(58) van Lierop, B. J.; Reckling, A. M.; Lummiss, J. A. M.; Fogg, D. E. *ChemCatChem* **2012**, *4*, 2020−2025.