Synergic Effects Between N-Heterocyclic Carbene and Chelating Benzylidene–Ether Ligands Toward the Initiation Step of Hoveyda–Grubbs Type Ru Complexes

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⊥Supporting Information

ABSTRACT: Synergic effects between ancillary N-heterocyclic carbene (NHC) ancillary ligands [(1,3-bis(2,4,6-trimethylphenyl)-1,3-imidazoline-2-ylidene) or 1,3-bis(2,6-disopropylphenyl)-1,3-imidazoline-2-ylidene] and chelating benzylidene–ether ligands were investigated by studying initiation rates and kinetic profiles of Hoveyda–Grubbs (HG) type Ru complexes. A newly designed Ru-benzylidene-oxazinone precatalyst was compared with Grela and Blechert complexes bearing modified isoproploxy chelating leaving groups and with the standard HG complex to understand how the ancillary and the leaving ligands interact and influence the catalytic activity.

KEYWORDS: N-heterocyclic carbenes, olefin metathesis, kinetic studies, Hoveyda–Grubbs type complexes, chemical stability

INTRODUCTION

The development of efficient catalytic systems dedicated to the formation of C–C double bonds from simple to highly functionalized alkenes represents a great challenge in modern organic synthesis. In addressing this challenge, olefin metathesis has become an extremely versatile tool,1 simplifying synthetic routes to numerous complex and valuable natural and unnatural products dramatically.2 Breakthroughs made in the last two decades have applied mechanistic understanding in the design of innovative and well-defined homogeneous precatalysts, increasing the appeal of this highly atom efficient reaction technology. Major improvements in Ru-based precatalysts were achieved through the incorporation of N-heterocyclic carbene (NHC) ancillary ligands3 and by structural modification of the reactive carbene leaving group.4 Modification of the NHC ligands has led to enhanced reactivity, allowing the use of low precatalyst loadings,5 even with sterically demanding olefins.5b,d,f The stereoselective formation of enantio-enriched metathesis products6 and the synthesis of challenging (Z) olefins can now be achieved.7 Modification of the reactive carbene has allowed the development of fast-initiating Ru-precatalysts, enabling metathesis at low temperatures.4 The roles of the NHC ligand8 and the carbene leaving group9 have attracted considerable attention, and mechanistic studies have begun to reveal their respective roles. Cavallo and co-workers have reported important computational studies,8b−d notably a topographic steric map9b based on the buried volume10 of numerous NHCs. Recently Grubbs, Houk, and co-workers reported useful theoretical calculations to explain the Z selectivity observed with NHC-chelating Ru complexes.8g Intensive studies that explain the effect of the reactive carbones on the initiation step of Hoveyda type complexes have also been performed.9 Plenio and co-workers have carried out

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detailed studies of the mechanism of the initiation step in a range of Grubbs−Hoveyda type complexes.\(^9\) By screening a range of sterically or electronically modified 2-alkyloxy benzylidene Ru complexes, they deduced that the initiation mode depended on both the electronic or steric properties of the Ru complex involved and the size of the olefin substrate. Density functional theory calculations have also been carried out, confirming that the competition between initiation modes may be finely balanced.\(^9\) Despite the tremendous effort to understand the initiation step, the role of the NHC ligand on the initiation rate has never been investigated for full Hoveyda type complexes, and no extensive mechanistic study considering both the NHC ligand and the leaving carbene moiety has been published.\(^1\) In this manuscript, we report a unique approach demonstrating strong synergetic effects between the NHC ligand and the benzylidene leaving group nature, which has led to the design and discovery of a stable and fast-initiating metathesis precatalyst.

### RESULTS AND DISCUSSION

#### Initiation Rate Study.

The critical features were obtained through the initiation rate measurements of different established Hoveyda type complexes, \(^1\)−\(^3\)\(^12,\)\(^13\) incorporating three modified isopropoxy-chelating benzylidene groups in respective association with two NHCs [(1,3-bis(2,4,6-trimethylphenyl)-1,3-imidazoline-2-ylidine (SIMes) and 1,3-bis(2,6-disopropylphenyl)-1,3-imidazoline-2-ylidine (SIPr)] ligands (Figure 1). For this purpose, the SIPr Blechert complex 3b, which had never been described in the literature, was synthesized. The initiation rate constants were measured by monitoring the reactions of the selected precatalysts with ethyl vinyl ether using UV/vis spectrophotometry; the data are shown in Table 1.\(^9\)

![Figure 1. Ru-based precatalysts for olefin metathesis.](image)

![Figure 2. New design of benzylidene-chelating Ru complexes.](image)

**Table 1. Initiation Rate Constants for Precatalysts 1−3.**

<table>
<thead>
<tr>
<th>entry</th>
<th>NHC catalysts</th>
<th>(k_{\text{init}}) (L mol(^{-1}) s(^{-1}))</th>
<th>(k_{\text{init}}) ratio SIMes/SIPr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a SIMes, 1b SIPr</td>
<td>0.026, 0.003</td>
<td>8.7</td>
</tr>
<tr>
<td>2</td>
<td>2a SIMes, 2b SIPr</td>
<td>0.317, 0.037</td>
<td>8.6</td>
</tr>
<tr>
<td>3</td>
<td>3a SIMes, 3b SIPr</td>
<td>3.402, 0.668</td>
<td>5.1</td>
</tr>
</tbody>
</table>

\(^{a}\)The \(k_{\text{init}}\) was monitored by UV/visible spectrophotometry at 298 K in dichloromethane (see the Supporting Information for full details).
crowding weakened chelation and increased catalyst reactivity. Under the standard conditions (1 mol % catalyst loading, 0.1 M in CD$_2$Cl$_2$ at 0 °C), the SIPv Hoveyda type catalyst 4b (71% isolated yield from M2$_2$Cl$_2$) with a measured initiation rate constant similar to the SIPv Blechert 3b catalyst ($k_{\text{init}} = 0.571$ L mol$^{-1}$ s$^{-1}$).

The structure of complex 4b was confirmed by a single crystal X-ray diffraction study, revealing some important structural information (Scheme 1, see the Supporting Information for details). Complex 4b showed the usual distorted square-based pyramidal geometry around the metal center with coordination of the oxygen to the ruthenium center. The Ru=O bond distances were 1.81 and 1.97 Å, respectively, comparable to those reported previously for NHC-containing Hoveyda type complexes. The buried volume of the SIPv unit was 36.8 Å$^3$ (calculated for Ru-NHC = 2.00 Å and sphere radius = 3.50 Å). The value is one of the biggest reported in the literature for this kind of diaminoacarbine Ru complex. Finally, the C(1)=Ru(1)=Cl(2) and C(1)=Ru(1)=C(20) angles (158.1° and 102.7°, respectively) were in the range found for most Hoveyda type catalysts. However, the C(20)=Ru(1)=O(1) angle (170.2°) is one of the smallest reported in the literature (the range is from 174 to 180°). Complex 4a is quite unstable in solution, and all attempts to crystallize it have failed.

Kinetic and Stability Studies. The kinetic profiles of 4a–b were investigated, then compared with Hoveyda (1), Grela (2), and Blechert (3) type complexes (see the Supporting Information for full details). They are depicted in Figure 3. Under the standard conditions (1 mol % catalyst loading, 0.1 M in CD$_2$Cl$_2$ at 0 °C), the SIPv Hoveyda 1b was completely inactive in the Ring-Closing Metathesis (RCM) of the benchmark substrate 13. A significant improvement in the kinetic profile was observed with the SIMes-1a, which remained relatively low compared to the other catalysts.
active after reaching 63% conversion in 4 h. Grela type complexes SIMes-2a and SIPr-2b achieved an improved conversion rate compare to Hoveyda−Grubbs precatalysts. Despite a lower initiation rate, 2b surpassed precatalyst 2a, attaining conversions of 96% and 63%, respectively, after 4 h. Remarkable activity profiles were observed for the Blechert precatalysts SIMes-3a and the newly prepared SIPr-3b (conv > 90% after 1 h). To our delight, fast conversion was also observed with SIMes-4a and especially SIPr-4b, for which 90% conversion was achieved in less than 2 h. These initial experiments at low temperature seemed to follow a general trend, with catalytic behaviors in apparent correlation with the calculated initiation rate constants. Nevertheless, the kinetic profiles obtained under these standard conditions could not provide a sufficient discrimination between fast-initiating precatalysts. Therefore, complexes 3 and 4 were further evaluated at 1000 ppm [Ru] at 297 K in a more sterically demanding RCM process to generate the trisubstituted olefin product 28 (Figure 4).

Under these modified conditions, a clear and spectacular distinction between SIPr- and SIMes-based catalysts was observed. Under these modified conditions, a clear and spectacular distinction between SIPr- and SIMes-based catalysts was observed.
evidenced. The pronounced differences in the kinetic profiles observed for these fast-initiating catalysts resulted from the relative stabilities of the respective active species. Indeed, despite lower initiation rates, SIPr complexes 3b and 4b afforded much better conversion rates than their SIMes analogs. The decomposition rate of the SIMes-based active species has apparently increased faster than the decomposition rate of the SIPr-based one. In addition to an increased stability of the catalytically active species, the SIPr unit should also bring a significant stabilization to the precatalyst.

To gain a better understanding of precatalyst stabilities in solution, we also studied the chemical stability of the selected precatalysts 1, 3, and 4 in dichloromethane in the absence of olefin substrate.18 The decomposition within the first 5 h of SIMes− (1a and 3a) and SIPr-based precatalysts (3b and 4b) at low 10−4 M initial concentration was followed by UV spectrophotometry (Figure 5). Remarkably, the fast-initiating SIPr complexes 3b and 4b exhibited an extremely slow decomposition (only 1% loss after 5 h), whereas the SIMes−Hoveyda 1a decomposed more rapidly, reaching almost 8% loss after 5 h. Interestingly, the degradation rates of Blechert type precatalysts were significantly faster, and SIMes−based 3a (3% loss within 7 min) evidenced a higher instability than SIPr-based 3b (4% loss within 2 h). The increased stability provided by the SIPr-NHC ligand to precatalysts in solution may play a non-negligible role in the differences of kinetic profiles at low temperature (compare 1a vs 1b and 2a vs 2b in Figure 3)19 and, to some extent, account for the measured ratios of initiation rate constants. (SIMes/SIPr kfast ratio = 5−9, Table 1).

Catalytic Performance. Robust complex 4b combining a fast initiation rate constant and a stable catalytically active species was then evaluated in a selection of olefin transformations (Table 2). In the cases of ring-closing and enyne metatheses, excellent conversions and isolated yields were observed after 15−30 min of reaction, confirming the effectiveness of 4b. Moreover, extensive comparison with the newly synthesized fast-initiating SIPr Blechert precatalyst 3b evidenced no significant distinction. This illustrates the considerable advantage provided by SIPr-based fast initiation precatalysts. The cyclization of substrate 25 was catalyzed efficiently in the presence of a very low loading of 3b and 4b (500 ppm) and reached completion within 15 min. However, unexpectedly, in the case of the CM reaction, both precatalysts gave only moderate yields at 0.5 mol % (entries 9−10).

CONCLUSION

In conclusion, we have shown that the replacement of the SIMes NHC ligand by the SIPr one considerably decreased the initiation rate of Hoveyda type precatalysts (SIMes/SIPr kfast ratio = 5−9) while affording improved catalytic efficiency. Indeed, the SIPr unit conferred robustness both to the precatalyst in solution and to the catalytically active species. Moreover, the present study demonstrated that striking the correct balance between electronic and steric activation in the alkylidene leaving group, attenuated by the correct choice of NHC ligand, allowed the design of a highly efficient metathesis catalyst (4b). The latter combines high solution stability, increased active species stability, and a fast initiation rate constant. Because the interaction between the NHC and the benzylidene ether ligands can play a critical role in the catalyst performance, it appears essential that future Ru complex designs should consider this strong synergic effect to achieve higher metathesis selectivity.


(13) Catalysts 2b and 3a are not commercially available. For all studies, we used homemade complexes synthesized according to procedures reported in references 11e and 4c. e. Complex 3b had never been described in the literature. See the Supporting Information for its synthesis and characterization.

