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# 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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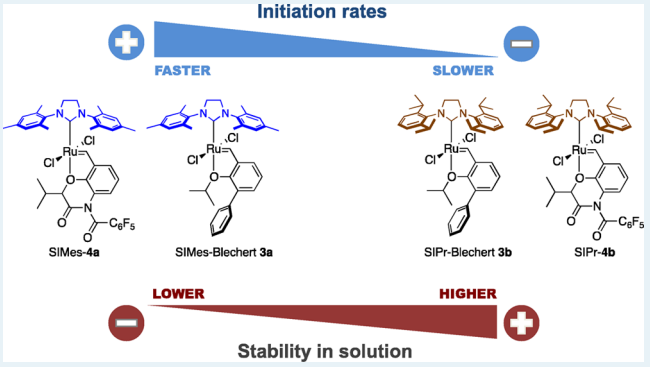
Supporting Information

**ABSTRACT:** Synergic effects between ancillary N-heterocyclic carbenes [(1,3-bis(2,4,6-trimethylphenyl)-1,3-imidazoline-2-ylidene or 1,3-bis(2,6-di*iso*propylphenyl)-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 **4** was compared with Grela and Blechert complexes bearing modified *iso*propyloxy 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 ligands[3] 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 products[6] 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 ligand[8] and the carbene leaving group[9] have attracted considerable attention, and mechanistic studies have begun to reveal their respective roles. Cavallo and co-workers have reported important computational studies,[8b−f] notably a topographic steric map[8d] based on the buried volume[10] 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 carbenes on the initiation step of Hoveyda type complexes have also been performed.[9] Plenio and co-workers have carried out

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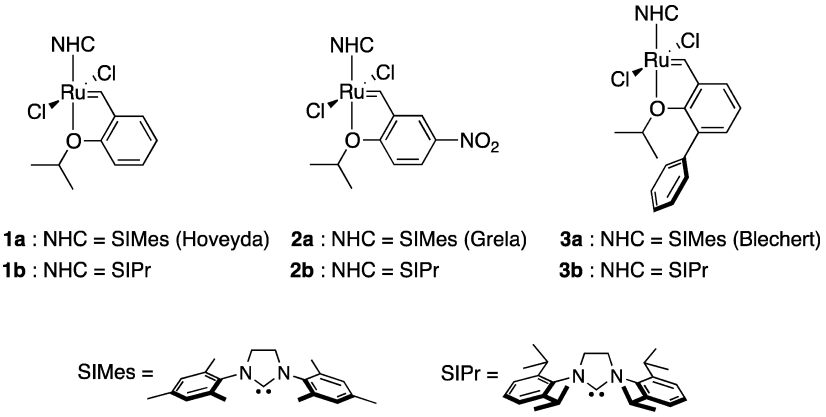


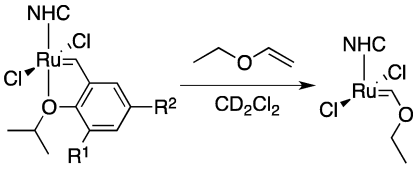

**Figure 1.** Ru-based precatalysts for olefin metathesis.

detailed studies of the mechanism of the initiation step in a range of Grubbs–Hoveyda type complexes.[9j] 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.[9h] 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.[11] In this manuscript, we report a unique approach demonstrating strong synergic 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

**Table 1. Initiation Rate Constants for Precatalysts 1–3.**[a]




Pre-catalysts **1-3**

| | NHC catalysts | | $k_{init}$ (L mol$^{-1}$ s$^{-1}$)[a] | | $k_{init}$ ratio SIMes/SIPr |
|---|---|---|---|---|---|
| entry | SIMes | SIPr | SIMes | SIPr | |
| 1 | **1a** | **1b** | 0.026 | 0.003 | 8.7 |
| 2 | **2a** | **2b** | 0.317 | 0.037 | 8.6 |
| 3 | **3a** | **3b** | 3.402 | 0.668 | 5.1 |

[a]The $k_{init}$ was monitored by UV/visible spectrophotometry at 298 K in dichloromethane (see the Supporting Information for full details).

established Hoveyda type complexes, **1–3**,[12,13] incorporating three modified *iso*propyloxy-chelating benzylidene groups in respective association with two NHCs [(1,3-bis(2,4,6-trimethylphenyl)-1,3-imidazoline-2-ylidene (SIMes) and 1,3-bis(2,6-di*iso*propylphenyl)-1,3-imidazoline-2-ylidene (SIPr)] ligands (Figure 1). For this purpose, the SIPr Blechert complex **3b**,

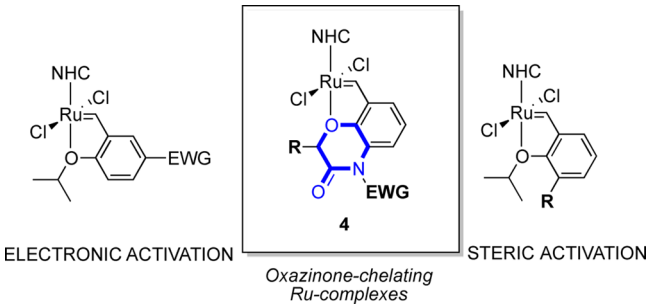
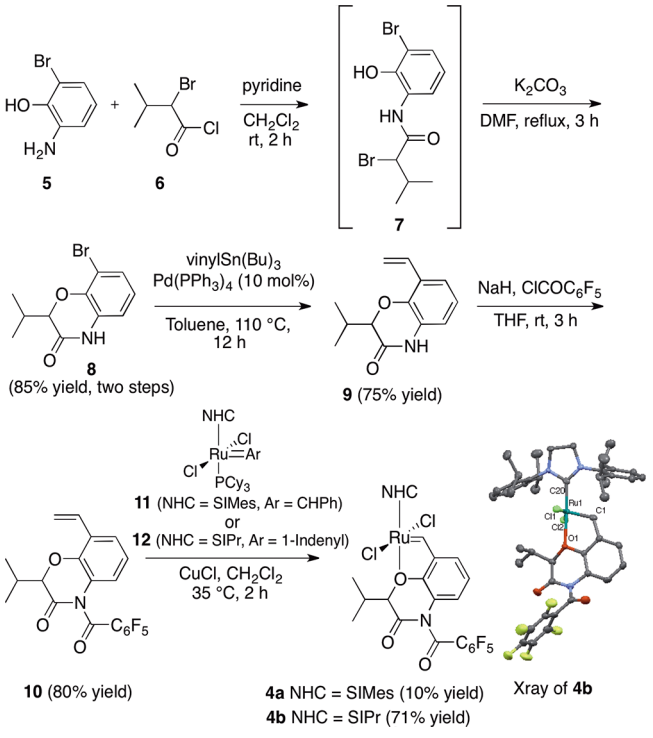



**Figure 2.** New design of benzylidene-chelating Ru complexes.

**Scheme 1. Synthetic Route for Ru Complexes 4a–b**




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]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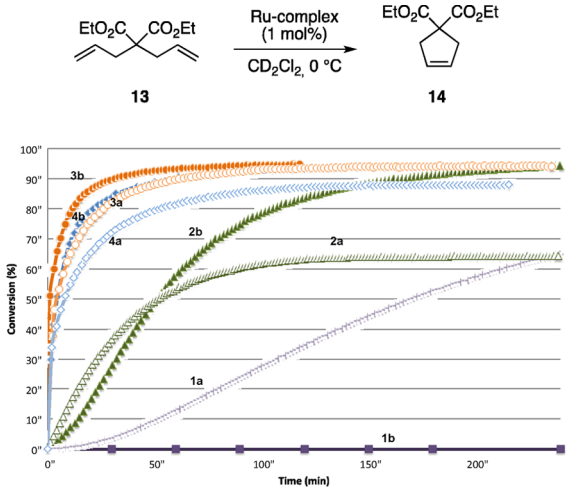


**Figure 3.** Reaction profiles of precatalysts **1**–**4** for RCM of DEDAM **13**. Reaction conditions: precatalyst (1 mol %), $CD_2Cl_2$ (0.2 M), 0 °C. Conversions were monitored by $^1$H NMR spectroscopy. Precatalyst: **1a** (+), **1b** (■), **2a** (△), **2b** (▲), **3a** (○), **3b** (●), **4a** (◊), **4b** (♦).

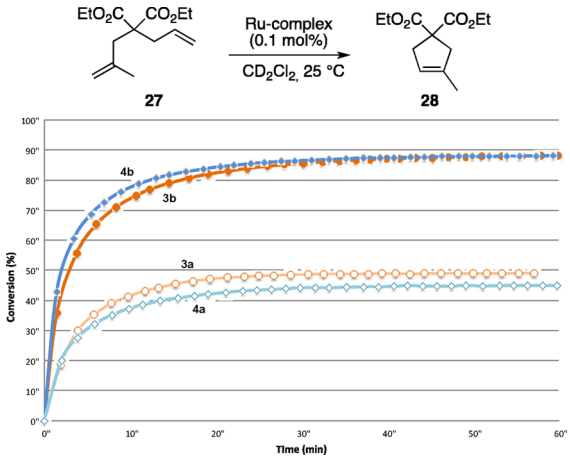


**Figure 4.** Reaction profiles of precatalysts **3**–**4** for RCM of DEMAM **27**. Reaction conditions: precatalyst (0.1 mol %), $CD_2Cl_2$ (0.2 M), 25 °C. Conversions were monitored by $^1$H NMR spectroscopy. Precatalyst: **3a** (○), **3b** (●), **4a** (◊), **4b** (♦).

Interestingly, the use of the electronically activated nitrostyrene leaving group in place of the styrene accelerated initiation 12-fold, whereas the use of SIPr instead of SIMes slowed initiation by 10-fold in both cases (so $k_{init}$ **1a** ≈ **2b**). In other words, replacement of the SIMes NHC by the SIPr ligand completely compensated for the activation effect arising from the additional electron-withdrawing nitro function. In 2002, Blechert showed that the incorporation of a large aromatic group *ortho* to the ether oxygen resulted in catalysts which underwent fast benzylidene exchange and argued that steric crowding weakened chelation and increased catalyst reactivity. Indeed, the Ph-substituted catalysts are significantly more reactive in both series. Blechert catalysts (**3a** and **3b**) are 2 orders of magnitude more reactive than parent systems **1a** and **1b** and a further order of magnitude more reactive than the corresponding Grela type catalysts. The above measurements tend to demonstrate that steric effects on benzylidene ether predominate in precatalyst activation. Moreover, it is important to note that even the presence of the SIMes NHC ligand cannot compensate for the absence of the steric effect of the ortho phenyl group ($k_{init}$ ratio **2a** vs **3b** = 0.317 vs 0.668) (Table 1, entries 2 and 3).

**Synthesis and Characterization.** The given results prompted us to propose an innovative design for a fast-initiating metathesis catalyst, which would combine properly balanced steric and electronic properties in a single chelating benzylidene ligand motif. We postulated that the synthetically accessible oxazinone ring system would allow additional moderate steric bulk while masking the latent donor properties of the nitrogen via interactions with flanking electron-withdrawing groups (Figure 2).

The (gram-scale) synthetic route to the novel Hoveyda type complexes **4a** and **4b** is shown in Scheme 1.[14] Commercially available **5** was condensed with acid chloride **6** in the presence of pyridine. Crude amide **7** was then heated in DMF in the presence of potassium carbonate to give the corresponding (2-bromo)oxazinone **8** in 85% overall yield after silica gel chromatography. Stille coupling with vinyltributyltin (10 mol % $Pd(PPh_3)_4$, toluene, reflux, 12 h) afforded (2-vinyl)benzo-oxazinone **9** in 75% isolated yield. The amido function was then reacted with pentafluorobenzoyl chloride in the presence of a suspension of NaH in THF at room temperature, yielding **10** (80% after silica gel chromatography). The route is highly modular and lends itself to the synthesis of precatalysts which admit a high degree of structural variation and therefore tuning of reactivity. The combination of the newly designed oxazinone type benzylidene **10** with the SIMes NHC ligand appeared exceptionally challenging (<10% isolated yield from Grubbs second-generation complex **11**[15a]) and revealed a highly reactive precatalyst **4a**, for which the initiation rate constant could not be accurately obtained. However, to our delight, the incorporation of the attenuating SIPr NHC ligand allowed the efficient synthesis of precatalyst **4b** (71% isolated yield from $M2_1$ **12**[15b]) with a measured initiation rate constant similar to the SIPr Blechert **3b** catalyst ($k_{init}$ = 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).[16] 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=C(1) and the Ru−C(20) bond distances were 1.81 and 1.97 Å, respectively, comparable to those reported previously for NHC-containing Hoveyda type complexes.[4f,12] The buried volume of the SIPr unit was 36.8 Å$^3$ (calculated for Ru-NHC = 2.00 Å and sphere radius = 3.50 Å).[10a] The value is one of the biggest reported in the literature for this kind of diaminocarbene Ru complex.[10b] Finally, the Cl(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.[4f,12] 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°).[4f,12] 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 $CD_2Cl_2$ at 0 °C),[17] the SIPr 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


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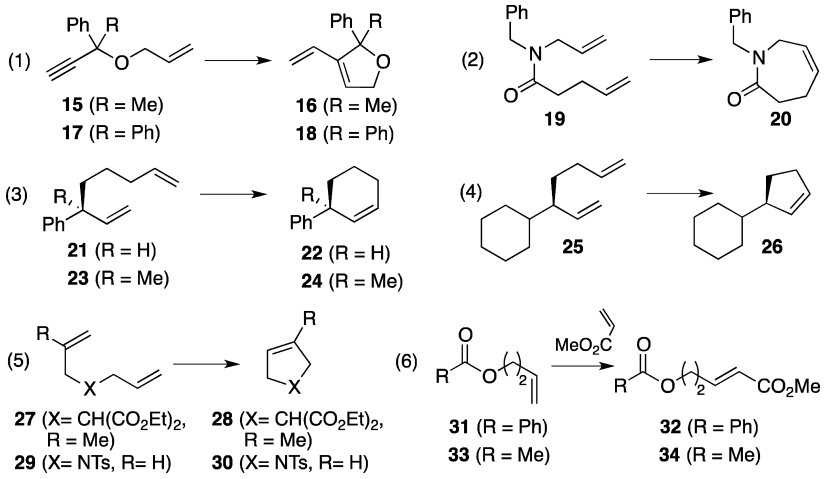
**Table 2. Room Temperature Metathesis Reactions Catalyzed by 3b and 4b at 0.5−0.05 mol %.**[a]




| entry | substrate | product | catalyst (mol %) | time | yield[b]/isolated yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **15** | **16** | **3b** (0.1) | 15 min | 96 (−) |
| | | | **4b** (0.1) | | 99 (98) |
| 2 | **17** | **18** | **3b** (0.075) | 15 min | 98 (−) |
| | | | **4b** (0.075) | | 97 (95) |
| 3 | **19** | **20** | **3b** (0.5) | 30 min | 90 (−) |
| | | | **4b** (0.5) | | 99 (98) |
| 4 | **21** | **22** | **3b** (0.5) | 15 min | 99 (−) |
| | | | **4b** (0.5) | | 99 (77) |
| 5 | **23** | **24** | **3b** (0.5) | 15 min | 99 (−) |
| | | | **4b** (0.5) | | 99 (93) |
| 6 | **25** | **26** | **3b** (0.05) | 15 min | 99 (−) |
| | | | **4b** (0.05) | | 99 (90) |
| 7 | **27** | **28** | **3b** (0.5) | 15 min | 99 (−) |
| | | | **4b** (0.5) | | 99 (97) |
| 8 | **29** | **30** | **3b** (0.1) | 15 min | 99 (−) |
| | | | **4b** (0.1) | | 99 (95) |
| 9[d] | **31** | **32** | **3b** (0.5) | 1 h | 38 (−)[e] |
| | | | **4b** (0.5) | | 42 (−)[f] |
| 10[d] | **33** | **34** | **3b** (0.5) | 1 h | 36 (−)[g] |
| | | | **4b** (0.5) | | 38 (−)[h] |

[a]Reaction conditions: catalyst (0.5−0.05 mol %), $CH_2Cl_2$ (0.1 M), 20 °C. [b]Yields were monitored by $^1H$ NMR spectroscopy with mesitylene as internal standard. [c]Isolated yield after silica gel chromatography. [d]4 equiv of methyl acrylate was used. [e]9% of self-metathesis product from **31** is also formed. [f]10% of self-metathesis product from **31** is formed. [g]7% of self-metathesis product from **33** is also formed. [h]7% of self-metathesis product from **33** is formed.

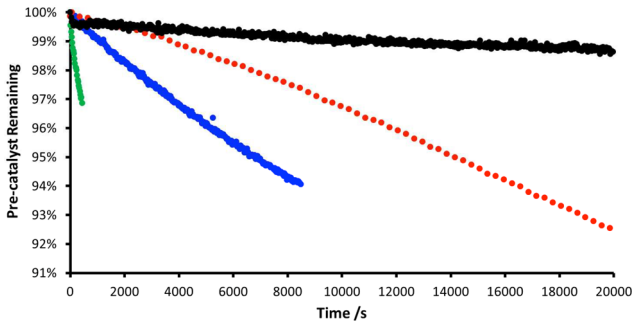



**Figure 5.** Chemical stability in solution of selected precatalysts **1a**, **3a**, **3b** and **4b**. Conditions: precatalyst, $CD_2Cl_2$ (0.1 mM), 25 °C. Precatalyst decomposition was monitored by UV/visible spectrophotometry (see the Supporting Information for full details). Precatalyst: **1a** (red curve), **3a** (green curve), **3b** (blue curve), **4b** (black curve).

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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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-**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 degradations 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 $k_{init}$ 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 $k_{init}$ 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.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectral data for all products, and kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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