

# Improved Chiral Olefin Metathesis Catalysts: Increasing the Thermal and Solution Stability *via* Modification of a C<sub>1</sub>-Symmetrical N-Heterocyclic Carbene Ligand

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**Abstract:** Four new ruthenium-based olefin metathesis catalysts that possess an N-heterocyclic carbene (NHC) ligand with benzyl (Bn) or *n*-propyl (*n*-Pr) N-alkyl groups have been prepared. The synthetic routes developed for the synthesis of the required dihydroimidazolium salts are general. Catalysts bearing larger NHC ligands with larger N-alkyl groups displayed improved thermal and solution state stability up to 80 °C. The reactivity of the new catalysts in

ring-closing metathesis is directly related to the increased steric bulk of the NHC ligand. The new catalysts have been evaluated in desymmetrization reactions and the nature of the N-alkyl group of the NHC ligands has been shown to have an important effect on the observed enantioselectivities.

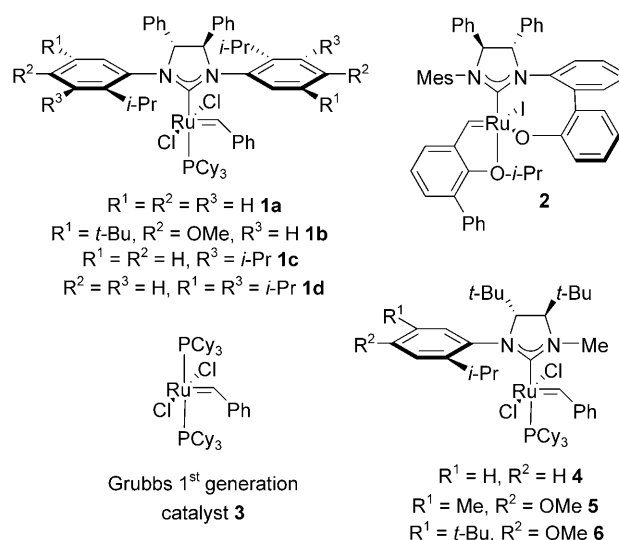
**Keywords:** asymmetric catalysis; desymmetrization; N-heterocyclic carbenes; olefin metathesis

## Introduction

The development of efficient asymmetric transformations using chiral Ru-based catalysts is an ongoing challenge in the field of olefin metathesis.<sup>[1]</sup> The further development and improvement of asymmetric metathesis transformations are inherently linked to modification of catalyst structure. Both Mo-based and Ru-based catalysts have been studied and while Ru-based catalysts have not reached the levels of efficacy provided by their Mo-based counterparts, the development of chiral Ru-based catalysts such as **1** and **2** has continued to gain momentum due to their stability to air and moisture and tolerance to functional groups (Figure 1).<sup>[2–4]</sup> Recently, our group reported the synthesis of catalyst **4**, bearing a C<sub>1</sub>-symmetrical N-heterocyclic carbene (NHC) unit, in which one of the N-substituents (typically large aryl groups) was replaced by a sterically unencumbered Me group. Further modification of the N-aryl group provided catalysts that were highly reactive and afforded good enantioselectivities in asymmetric desymmetrization reactions.<sup>[5]</sup> Interestingly, olefin metathesis catalysts bearing NHC ligands with N-alkyl groups are relatively few in number<sup>[6–8]</sup> compared to the variety of catalysts prepared with NHCs bearing various N-aryl groups. Catalysts **4**, **5** and **6** were both thermally sensi-

tive and unstable in solution, which is a drawback if one wants to perform more challenging transformations requiring longer reaction times.

As such, we sought to improve the stability of the catalysts through varying the N-alkyl group in catalysts **4** and **6**. It was hoped that this modification

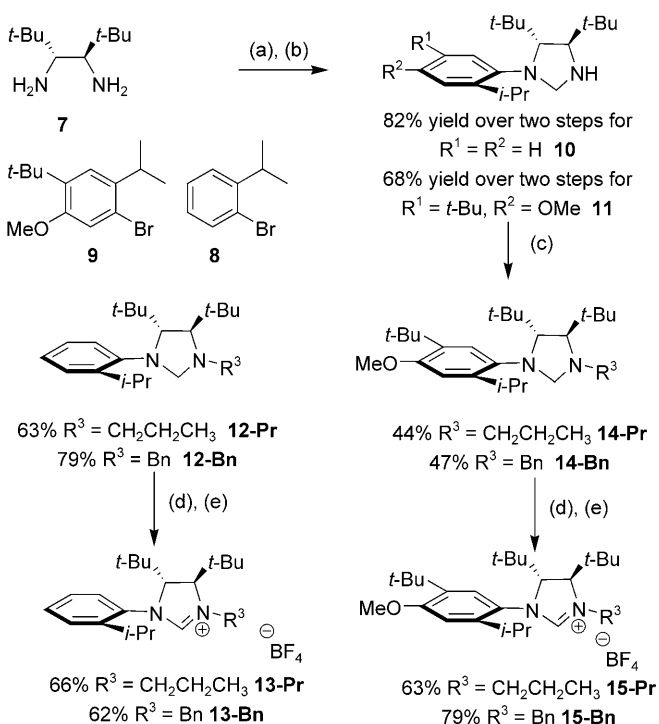


**Figure 1.** Olefin metathesis catalysts.

would improve catalyst stability (particularly their stability in solution) and allow for  $^1\text{H}$  NMR analysis of the NHC's rotational behavior. In turn, we sought to study the effects of N-alkyl substitution on catalyst reactivity and selectivity in enantioselective desymmetrization.

## Results and Discussion

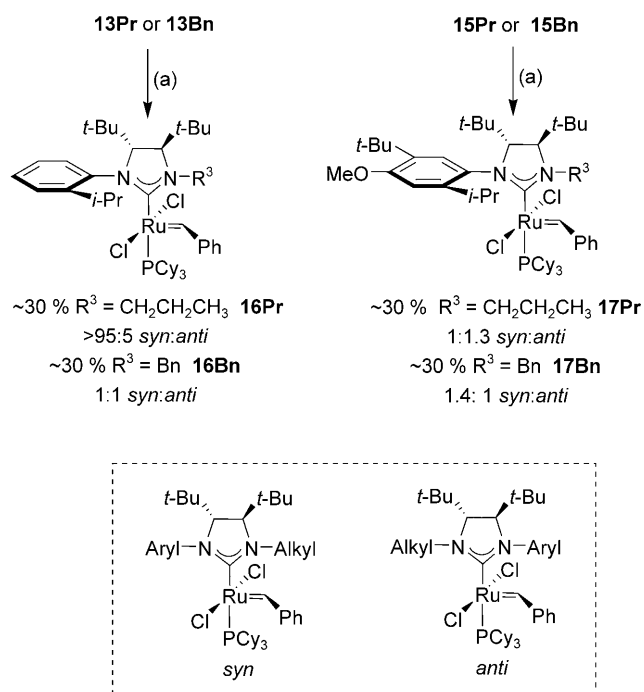
In order to study the effect of the N-alkyl substituents on their corresponding NHCs and Ru-based olefin metathesis catalysts, efficient synthetic protocols were required to prepare the dihydroimidazolium salt precursors. The amins **10** and **11** were prepared from a Buchwald–Hartwig amination of diamine **7** and the aromatic bromides **8** and **9** (Scheme 1). Following the cross-coupling, the resulting diamine was cyclized in the presence of paraformaldehyde to afford the amins **10** and **11** in 82% and 68% yield over two steps, respectively. The amins **10** and **11** could be alkylated with alkyl bromides when subjected to  $\text{K}_2\text{CO}_3$  in acetone and high temperatures in a sealed tube vessel.<sup>[9,10]</sup>



**Scheme 1.** Synthesis of new N-heterocyclic carbene ligands via N-alkylation; reaction conditions: (a)  $\text{Pd}_2(\text{dba})_3$  (5 mol%),  $(t\text{-Bu})_3\text{PHBF}_4$  (20 mol%),  $\text{NaO}-t\text{-Bu}$  (4 equiv.), **8** or **9**,  $\text{PhMe}$ ,  $100^\circ\text{C}$ , 24 h; (b) paraformaldehyde (1 equiv.),  $\text{CH}_2\text{Cl}_2$ ,  $21^\circ\text{C}$ , 24 h; (c)  $\text{R}^3\text{CH}_2\text{Br}$ ,  $\text{K}_2\text{CO}_3$ , acetone,  $100^\circ\text{C}$ , sealed tube, 12–48 h; (d)  $\text{I}_2$ ,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $21^\circ\text{C}$ , 24 h; (e)  $\text{NaBF}_4$ ,  $\text{Na}_2\text{SO}_3$ ,  $21^\circ\text{C}$ .

Although the yields were mediocre in some cases, unreacted starting materials could easily be isolated and efficiently recycled. The activated electrophile benzyl bromide reacted relatively quickly (12 h), producing the benzyl-substituted amins **12-Bn** and **14-Bn** in 79% and 47% isolated yield, respectively. The unactivated electrophile  $n\text{-PrBr}$  required a much longer reaction time ( $>36$  h) and the  $n\text{-Pr}$  amins **12-Pr** and **14-Pr** were obtained in 63% and 44% isolated yields, respectively. We believe the difficulties observed in the functionalization of amins **10** and **11** may be due to the adjacent  $t\text{-Bu}$  group on the dihydroimidazolium ring. All attempts to alkylate with bulkier branched electrophiles failed: N-alkylation using  $i\text{-Pr}$  halides or cyclopropyl bromide were unsuccessful at installing branched functionality. Oxidation of the amins could be carried out by treatment with  $\text{I}_2$  and  $\text{NaHCO}_3$  in  $\text{CH}_2\text{Cl}_2$ . Following counter-ion exchange, the salts **13-Pr** (66%), **13-Bn** (62%), **15-Pr** (63%) and **15-Bn** (79%) could be isolated and characterized.

With the required dihydroimidazolium salts in hand, we proceeded to prepare the corresponding Ru-based catalyst systems (Scheme 2). The first series of catalysts prepared were from the series of dihydroimidazolium salts containing the 2- $i\text{-PrC}_6\text{H}_4$  group as the N-aryl substituent. Dihydroimidazolium salts **13-Pr** and **13-Bn** were each treated with  $(\text{CF}_3)_2\text{CH}_3\text{COK}$  and Grubbs 1<sup>st</sup> generation catalyst **3** in toluene at

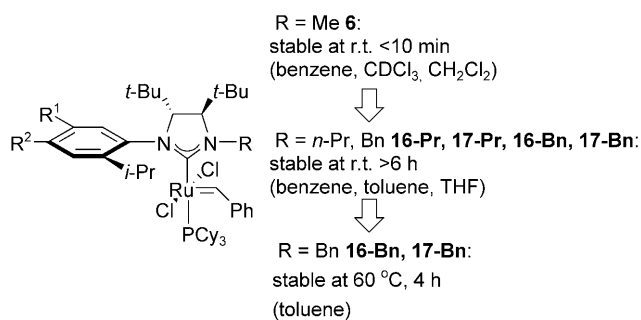


**Scheme 2.** Synthesis of new catalysts; reaction conditions: (a)  $(\text{CF}_3)_2\text{CH}_3\text{COK}$  (1.5 equiv.),  $\text{PhMe}$  then  $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$  **3** (1 equiv.),  $60^\circ\text{C}$ , 3 h. Only the major *syn* rotational isomer is shown above.

60 °C for 6 h to afford the corresponding catalysts **16-Pr** and **16-Bn** in ~30% yield.<sup>[11]</sup> In an identical manner, the dihydroimidazolium salts **15-Pr** and **15-Bn** containing bulkier N-aryl groups were also treated with (CF<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>COK and Grubbs 1<sup>st</sup> generation catalyst in toluene to afford the corresponding catalysts **17-Pr** and **17-Bn** in ~30% yield, respectively.

All catalysts were isolated as a mixture of rotational isomers (*syn*: N-alkyl group *syn* to the benzylidene unit, see Scheme 2), where NOE and <sup>1</sup>H NMR studies were used to deduce the ratio of NHC rotational isomers present in the precatalyst at room temperature. The ratio of *syn* and *anti* isomers for each catalyst is indicated in Scheme 2. The *n*-Pr bearing catalyst **16-Pr** was obtained as almost exclusively *syn*, while catalyst **16-Bn** was isolated as a 1:1 mixture of *syn*:*anti* isomers. Using a bulkier N-aryl group did not improve the preference for the *syn* isomer. The *n*-Pr catalyst **17-Pr** was isolated in a 1:1.3 *syn*:*anti* ratio and catalyst **17-Bn**, was isolated in a ratio of 1.4:1 *syn*:*anti* isomers.

It was envisioned that the larger N-alkyl groups in catalysts **16-Pr**, **16-Bn**, **17-Pr** and **17-Bn** would impart both a greater thermal stability and stability in solution. Catalyst **6** decomposed in solution at ambient temperature in less than 10 min. Catalysts **16-Pr**, **17-Pr**, **16-Bn** and **17-Bn** bearing the *n*-Pr and Bn groups were all found to be stable for hours in solution in benzene, toluene, or THF at room temperature (Figure 2).<sup>[12]</sup> The benzyl catalyst **17-Bn** was the most stable at higher temperatures. For example, **17-Bn** was stable in an NMR tube in toluene-*d*<sub>8</sub> when heated to 60 °C for up to 4 h before the solution slowly darkened and the benzylidene peaks in the <sup>1</sup>H NMR slowly began to decrease in intensity. However, heating the toluene-*d*<sub>8</sub> solutions of **17-Bn** to 80 °C rapidly resulted in the formation of a brownish-black solution and complete disappearance of any benzylidene peaks. It should be noted that catalysts **16-Pr** and **17-Pr** did decompose in the solid state over a period of 4–5 months. It was initially expected that catalysts **16-Bn** and **17-Bn** might decompose through insertion into the benzylidene unit as previously reported by



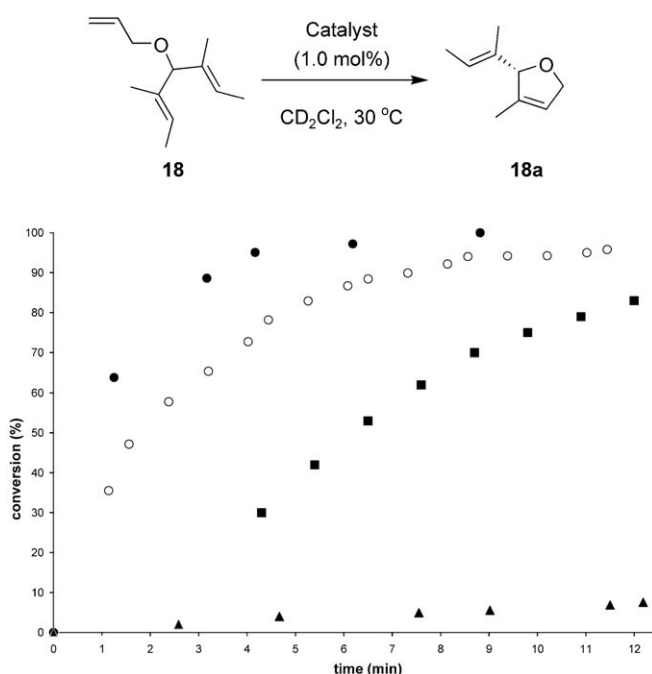
**Figure 2.** Improved thermal and solution stability through variation of the N-alkyl group of the NHC ligand.

Blechert<sup>[13]</sup> and Grubbs.<sup>[14]</sup> However, **16-Bn** and **17-Bn** are stable over the same period of 4–5 months. Thus, even a relatively small alkyl group can increase the steric bulk of the NHC ligand to such a point as to increase the catalyst's thermal and solution stability.

In order to gain further understanding of the NHC dynamics in these catalysts, 2D EXSY experiments were undertaken on catalysts **16-Bn** and **17-Bn** to calculate the rate of rotation of the NHC ligand. When **16-Bn** or **17-Bn** was heated in an NMR tube in toluene-*d*<sub>8</sub> at 40 or 50 °C, 2D EXSY experiments revealed no rotation of the NHC in the precatalyst.

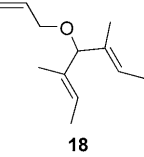
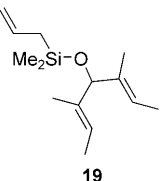
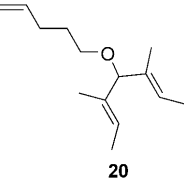
Catalysts **4** and **6** were both previously observed to cyclize the *meso*-triene **18** at much faster rates than the corresponding catalyst **1a** bearing a C<sub>2</sub>-symmetrical bulky NHC ligand. Gratifyingly, catalysts in which the N-alkyl group was modified were also highly active when compared to **1a** over the same time period. When the cyclization of **18** using catalyst **16-Pr** was monitored by <sup>1</sup>H NMR, >90% conversion was observed after only 10 min., which is similar to catalyst **4** (Figure 3). The substitution of the *n*-Pr group for a Bn group again resulted in a highly active species as catalyst **16-Bn** achieved 80% conversion after 12 min., although it was slightly less active than the parent catalyst **4**.<sup>[15]</sup>

With the above results in hand, the efficacy of the new catalysts in three desymmetrization reactions of *meso*-trienes was studied (Table 1).<sup>[16]</sup> The cyclization of **18** to form a five-membered ring gave *ees* for the



**Figure 3.** Ring-closing metathesis of **18** using catalysts **4** (●), **16-Pr** (○), **16-Bn** (■) and **1a** (▲). Conversions determined by <sup>1</sup>H NMR spectrum of reaction mixture.

**Table 1.** Comparison of new ARCM catalysts in enantioselective desymmetrizations.

|                                                                                                 |              | Catalyst (2.5 mol%)<br>CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 2 h<br>[M] = 0.055 |                              |                                                     |
|-------------------------------------------------------------------------------------------------|--------------|------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------------|
| Triene                                                                                          |              | triene                                                                             | product                      |                                                     |
| Triene                                                                                          | Cat.         | <i>syn:anti</i> ratio of cat.                                                      | <i>ee</i> [%] <sup>[a]</sup> | Conv. [%] <sup>[b]</sup> , yield [%] <sup>[c]</sup> |
| <br><b>18</b>  | <b>4</b>     | > 95:5                                                                             | 82                           | > 98                                                |
|                                                                                                 | <b>16-Pr</b> | > 95:5                                                                             | 82                           | > 98                                                |
|                                                                                                 | <b>16-Bn</b> | 1:1                                                                                | 77                           | > 98, 50                                            |
|                                                                                                 | <b>6</b>     | 4:1                                                                                | 81                           | > 98                                                |
|                                                                                                 | <b>17-Pr</b> | 1:1.3                                                                              | 60                           | > 98, 40                                            |
|                                                                                                 | <b>17-Bn</b> | 1.4:1                                                                              | 73                           | > 98, 45                                            |
| <br><b>19</b>  | <b>4</b>     | > 95:5                                                                             | 6                            | > 98                                                |
|                                                                                                 | <b>16-Pr</b> | > 95:5                                                                             | 40                           | > 98                                                |
|                                                                                                 | <b>16-Bn</b> | 1:1                                                                                | 25                           | > 98                                                |
|                                                                                                 | <b>6</b>     | 4:1                                                                                | 94                           | > 98                                                |
|                                                                                                 | <b>17-Pr</b> | 1:1.3                                                                              | 90                           | > 98, 77                                            |
|                                                                                                 | <b>17-Bn</b> | 1.4:1                                                                              | 33                           | 60                                                  |
| <br><b>20</b> | <b>4</b>     | > 95:5                                                                             | 60                           | > 98                                                |
|                                                                                                 | <b>16-Pr</b> | > 95:5                                                                             | nd <sup>[e]</sup>            | 0                                                   |
|                                                                                                 | <b>16-Bn</b> | 1:1                                                                                | 45                           | 55                                                  |
|                                                                                                 | <b>6</b>     | 4:1                                                                                | 86                           | > 98                                                |
|                                                                                                 | <b>17-Pr</b> | 1:1.3                                                                              | 75                           | > 98, 71 <sup>[d]</sup>                             |
|                                                                                                 | <b>17-Bn</b> | 1.4:1                                                                              | 40                           | 60                                                  |

[a] Enantiomeric excesses determined by chiral GC: see Supporting Information for chromatograms.

[b] Determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

[c] Isolated yields after chromatography. Product loss is mainly due to their high volatility.

[d] Conversion of **20** is > 98%; only the products resulting from cyclization and dimerization are observed.

[e] nd = not determined.

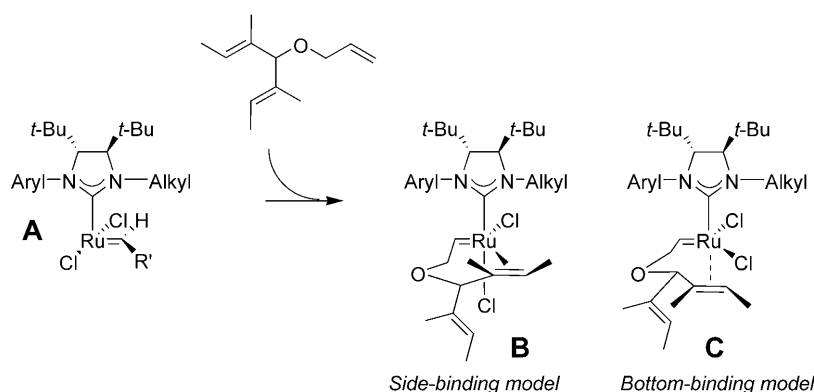
new N-alkyl-substituted catalysts **16-Pr** (82% *ee*) and **16-Bn** (77% *ee*) that were similar to what was obtained for catalysts **4** and **6** (81–82% *ee*). When examining the new catalysts that were derivatives of parent catalyst **6**, **17-Pr** and **17-Bn** afforded lower *ees* (60% and 73%, respectively) in the cyclizations of **18**.

The cyclization of the triene **19** forms a six-membered ring and had provided low *ees* with catalyst **4**. The new catalysts **16-Pr** and **16-Bn** caused slight increases in the *ee* in this transformation. While only 6% *ee* was observed with **4**, 40% and 25% *ee* were observed for catalyst **16-Pr** and **16-Bn**, respectively. Although these results were encouraging, catalyst **6** still provided the highest *ee* in the cyclizations of **19**. Modification of the N-alkyl group in catalyst **6** had a deleterious effect on the *ee* in the cyclization of **19**. Both catalysts bearing the larger N-alkyl groups but with the identical N-aryl group as **6** (**17-Pr** and **17-Bn**), produced lower *ees* in the cyclization of **19** (90 and 33% *ee*, respectively).

Finally, all catalysts were surveyed in the more challenging cyclization of triene **20** to form a seven-membered ring. While catalyst **4** afforded 60% *ee* in

the desymmetrization, catalyst **16-Pr** only succeeded in dimerizing **20** while **16-Bn** afforded a lower *ee* of 43% with only 55% conversion. Although Figure 2 clearly shows that **16-Pr** and **16-Bn** are lower in reactivity than the analogous catalyst **4**, the inability to cyclize **20** was surprising. Catalyst **6** had provided an 86% *ee* in this reaction. Modification of the N-alkyl group in catalyst **6** slightly lowered the reactivity, but caused large drops in the levels of enantioselectivity. The substitution of the N-Me group in catalyst **6** for an *n*-Pr group (catalyst **17-Pr**) caused the *ee* in the cyclization of **20** to drop to 75% *ee*. An even larger change was observed when the cyclization was carried out with catalyst **17-Bn**, where a 40% *ee* was observed.

The dramatic effects of the N-alkyl groups on the *ee* of the desymmetrization reactions are interesting. Cavallo and co-workers have provided theoretical studies into the origin of stereinduction in asymmetric metathesis reactions using catalyst **1a**.<sup>[17]</sup> These studies suggest a model where the N-aryl group of the NHC ligand exerts an influence over the propagating alkylidene and the substrate is bound to the catalyst



**Figure 4.** Possible intermediates in the cyclizations of *meso*-triene **18** with catalysts bearing  $C_1$ -symmetrical NHC ligands.

in a “bottom-binding” arrangement (intermediate **C**, Figure 4). In this model, the effect of the N-aryl group on the NHC of the catalyst opposite to the alkylidene is not thought to influence the enantioselectivity of the ring closure. However, Grubbs and co-workers have proposed a “side-binding” mechanism where the propagating alkylidene is once again under the influence of the N-aryl group of the NHC ligand. In this model, the substrate is bound so that the olefin involved in the ring closure occupies a binding site *cis* to the NHC and the Cl atom has isomerized *trans* to the NHC (intermediate **B**, Figure 4).<sup>[18]</sup> The reaction between a triene such as **18** and the propagating species **A** could therefore afford two intermediates **B** or **C** (Figure 4). In these intermediates the alkylidene has moved from underneath the N-alkyl group to underneath the N-aryl group in accordance with recent work by Chen and co-workers.<sup>[19]</sup>

It is difficult to say with any certainty whether intermediate **B** or **C** (“side-binding” or “bottom-binding” model) is actually responsible for the observed *ee*'s in the desymmetrization reactions. However, it is clear that the N-alkyl group of the NHC ligand has a direct effect on the *ees* of the desymmetrization. These effects are more easily explained with intermediate **B**, where the “side-bound” alkene would more likely be influenced by the steric environment provided by the N-alkyl group.

## Conclusions

In summary, we have prepared four new Ru-based olefin metathesis catalysts that possess a chiral NHC ligand with Bn or *n*-Pr N-alkyl groups and are highly active in desymmetrization reactions. The synthetic routes developed for the synthesis of the dihydroimidazolium salts **13-Pr**, **13-Bn**, **15-Pr** and **15-Bn** should be applicable in the synthesis of other sterically demanding chiral dihydroimidazoliums for various applications in organometallic catalysis or organocatalysis.

The substitution of the N-Me group of the NHC ligand of catalysts **4** and **6** for the Bn and *n*-Pr groups successfully improved thermal and solution state stability. Notably, the increase in the overall stability of the catalysts allowed for NMR investigations which showed that no ligand rotation occurs in the precatalyst up to 80 °C, at which point the catalysts were observed to degrade. The catalysts **16-Pr** and **16-Bn** both show lower reactivities in ring closing than the parent catalyst **4**. This observation is in agreement with those of Grubbs and co-workers, who have observed large increases in reactivity in Ru-based catalysts bearing NHC ligands that are less sterically demanding.<sup>[14,20]</sup> The new catalysts have been evaluated in desymmetrization reactions of *meso*-trienes and have shown surprising results. The change of the N-alkyl group of the NHC ligands provided lower enantioselectivities in almost all cyclization reactions. This suggests that  $C_1$ -symmetrical NHCs such as those present in catalysts **4** and **5** may be optimal for desymmetrization reactions. These efforts should help the design of future generations of chiral catalysts where increased lifetime is needed, such as in the synthesis of tetrasubstituted olefins. Future efforts towards discerning the decomposition pathways of olefin metathesis catalysts bearing NHC ligands with N-alkyl groups are currently underway.

## Experimental Section

Full experimental details for the synthesis of all ligands and catalysts can be found in the Supporting Information.

### General Procedure for Asymmetric Desymmetrization Reactions

Triene was added to a solution of catalyst (2.5 mol%) in  $\text{CH}_2\text{Cl}_2$  (0.055 M), and the reaction stirred at 40 °C for 2 h. The reaction was then quenched with ethyl vinyl ether (approximately 0.1 mL) and cooled down to room temperature. The reaction mixture was then filtered on neutral alumina

and the solvent was evaporated. Further purification by flash chromatography was performed if needed (1–5% Et<sub>2</sub>O in pentane).

## Acknowledgements

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- [9] A reductive amination protocol was also investigated but often produced a complex mixture of by-products that were difficult to separate from the desired product, resulting in unreproducible yields.
- [10] The N-alkylation was very sensitive. Both Na<sub>2</sub>CO<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub> were ineffective as bases and other polar solvents (THF, DMF) were less effective.
- [11] Due to the thermal instability observed with other catalysts containing the N-alkyl-substituted NHCs, we attempted to prepare the catalysts using as little heating as possible. However, no catalyst formation was observed when conducting the reaction at room temperature. Heating of the reaction at lower temperatures (40°C) or heating the reaction mixture to 60°C followed by cooling to room temperature also failed to produce catalyst.
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