

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/278134411>

Novel Olefin Metathesis Ruthenium Catalysts Bearing Backbone-Substituted Unsymmetrical NHC Ligands

ARTICLE in ORGANOMETALLICS · NOVEMBER 2014

Impact Factor: 4.13 · DOI: 10.1021/om500731k

CITATION

1

READS

11

3 AUTHORS:



Veronica Paradiso

Università degli Studi di Salerno

2 PUBLICATIONS 1 CITATION

SEE PROFILE



Valerio Bertolasi

University of Ferrara

395 PUBLICATIONS 7,638 CITATIONS

SEE PROFILE



Fabia Grisi

Università degli Studi di Salerno

38 PUBLICATIONS 504 CITATIONS

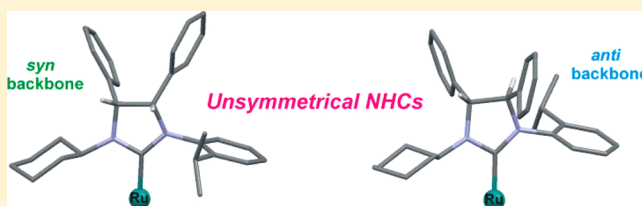
SEE PROFILE

Novel Olefin Metathesis Ruthenium Catalysts Bearing Backbone-Substituted Unsymmetrical NHC Ligands

Veronica Paradiso,[†] Valerio Bertolasi,[‡] and Fabia Grisi^{*,†}[†]Dipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano, Salerno, Italy[‡]Dipartimento di Chimica and Centro di Strutturistica Diffattometrica, Università di Ferrara, Via L. Borsari 46, I-44100 Ferrara, Italy

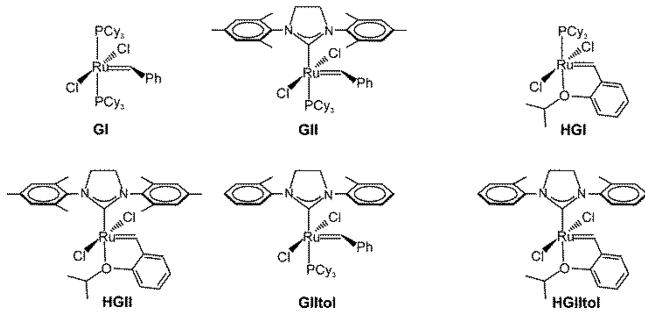
Supporting Information

ABSTRACT: Stable Ru-based catalysts containing unsymmetrical N-heterocyclic carbene (NHC) ligands with phenyl substituents on the backbone in *syn* and *anti* stereochemical relationships have been easily prepared and fully characterized. Preliminary investigation revealed that, depending on the backbone configuration, the new Ru complexes displayed different catalytic behaviors in representative olefin metathesis reactions.



With the advent of well-defined Ru-based catalysts, olefin metathesis has revolutionized synthetic chemistry, providing a convenient and reliable way for synthesizing small molecules as well as macromolecular materials.¹ The introduction of NHCs as ancillary ligands has led to improved, user-friendly Ru metathesis catalysts (Chart 1) and has permitted significant advancements in a multitude of challenging reactions, such as those involving sterically demanding substrates^{1,2} or requiring high selectivity.^{1,3}

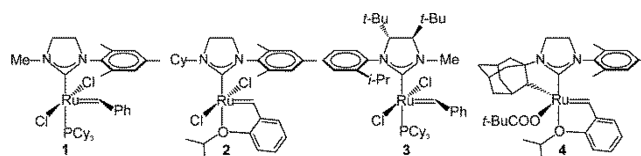
Chart 1. Commercial Ru-Based Metathesis Catalysts



The possibility of directly influencing catalyst performance by altering the stereoelectronic properties of the NHC ligand has indeed attracted much attention from the catalysis community. Many efforts have been dedicated to the development of unsymmetrical NHC (uNHC) frameworks, characterized by different steric bulkiness in vicinity to the carbenic center, that have shown significant changes in the reactivity and selectivity of the resulting catalysts (Chart 2).^{4–6}

Taking inspiration from our previous studies on Ru complexes incorporating modified NHCs,⁷ we wondered whether the introduction of differently oriented substituents on the backbone of uNHCs could offer additional options to modulate the catalytic properties of the corresponding

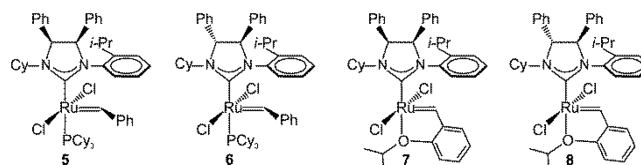
Chart 2. Selected Ru catalysts with N-Alkyl/N-Aryl NHCs



complexes. To the best of our knowledge, the impact of changing the backbone configuration of uNHCs on catalytic behavior has not yet been investigated.

Therefore, herein we report the synthesis and characterization of four new olefin metathesis catalysts bearing uNHCs that combine *N*-cyclohexyl and *N*-isopropylphenyl groups and *syn* or *anti* phenyl substituents on the backbone (Chart 3). We

Chart 3. New Ru Complexes with Unsymmetrical NHCs



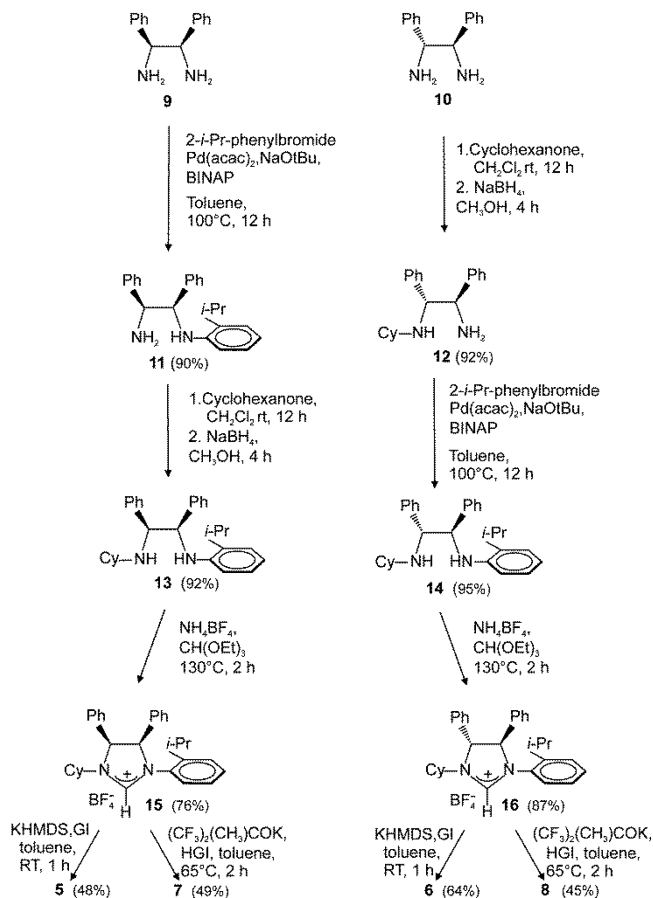
also show the dramatic influence of the relative disposal of phenyl groups on the backbone on catalyst efficiency, as well as the behavior of chiral catalysts in asymmetric transformations.

The synthesis of the new imidazolium salts **15** and **16** was easily accomplished in three synthetic steps starting from the corresponding commercially available diamines **9** and **10**, as described in Scheme 1. In situ deprotonation of **15** and **16** with a strong base and reaction with RuCl₂(=CHPh)(PCy₃)₂ (**GI**; Chart 1) or RuCl₂(=CH-*o*-iPrO-Ph)(PCy₃) (**HGI**; Chart 1)

Received: July 17, 2014

Published: October 22, 2014

Scheme 1. Synthesis of Ruthenium Complexes 5–8



afforded respectively the desired Grubbs II (**5** and **6**) and Hoveyda–Grubbs II (**7** and **8**) type complexes in moderate to good yields (45–64%). (see Scheme 1). It is worth underlining that, while **6** and **8** are chiral complexes, **5** and **7** are actually racemic mixtures of chiral complexes, whose resolution will be undertaken in future work.

All of the complexes were found to be stable both in the solid state and in solution for extended periods of time.⁸ Solution-state structures of phosphine-containing complexes **5** and **6**, determined via NMR analysis, revealed the presence of two rotational isomers, which are very likely caused by different orientations of the benzylidene unit with respect to the N substituents of the uNHC ligand (*syn* and *anti*).⁹ Unfortunately, any attempt to grow crystals of **5** and **6** of sufficient quality for X-ray structure analysis failed.

NMR analyses of the phosphine-free complexes **7** and **8** suggested the formation of rotamers with an *anti* arrangement of the benzylidene moiety, which was confirmed by obtaining the single-crystal X-ray structures of **7** and **8** (Figure 1).¹⁰ The short distances between the ruthenium center and the hydrogen linked to the carbon atom of the cyclohexyl substituent at the nitrogen of the NHC ring (C25–H25···Ru = 2.39 Å for complex **7**; C25A–H25A···Ru = 2.52 and 2.48 Å for the two independent molecules in the asymmetric unit of complex **8**) as well as the C–H···Ru bond angles (C25–H25···Ru = 126° for **7**; C25A–H25A···Ru = 122 and 123° for the two independent molecules of **8**) strongly suggest the existence of anagostic interactions.¹¹

In solution, evidence of these interactions for both complexes is provided by downfield-shifted ¹H NMR signals for H25 (5.70

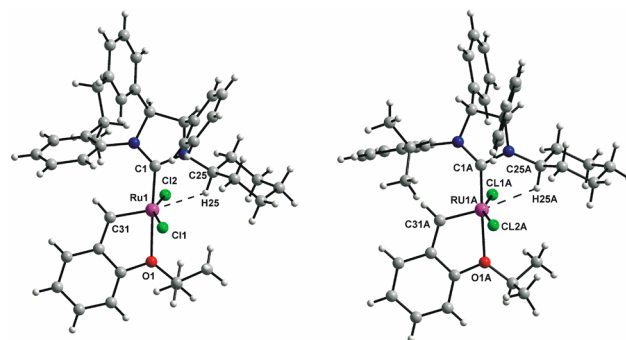


Figure 1. Crystal structures of complexes **7** (left) and **8** (right) showing C–H···Ru interactions.

ppm) and H25A (5.61 ppm) and by a slightly lower value of ¹J(C25,H25) and ¹J(C25A,H25A) coupling constants (130 Hz), in comparison to those of their corresponding ligand precursors. The role of these interactions in the structural stability and reactivity of complexes **7** and **8** is currently under investigation.

The catalytic efficiency of the new complexes **5**–**8** was first evaluated in the ring-closing metathesis (RCM) reactions of diethyl diallylmalonate (**17**), diethyl allylmethylmalonate (**18**), and diethyl dimethylmalonate (**19**) (Table 1).¹² The RCM of each substrate was monitored by ¹H NMR spectroscopy, and selected kinetic data are depicted in Figure 2 (see also the Supporting Information).

Complexes **6** and **8** with *anti* phenyl groups on the NHC backbone performed better than their *syn* analogues **5** and **7** in all of the tested RCM reactions. Of particular significance, *anti* complexes **6** and **8** disclosed an unexpectedly high propensity to the ring closure of the most hindered diolefins **18** and **19**, competing with the commercial catalysts **GIItol** and **HGIItol**,

Table 1. RCM of Malonate Derivatives **17**–**19** with Catalysts **5**–**8**

Entry ^a	Substrate	Product	Catalyst (mol%)	t (min)	Yield ^b (%)
1			5 (1)	60	52
2			6 (1)	20	>97
3			GIItol (1)	35	>97
4			7 (1)	20	>99
5			8 (1)	4	>99
6			HGIItol (1)	3	>99
7			5 (1)	60	72
8			6 (1)	60	90
9			GIItol (1)	60	79
10			7 (1)	60	94
11			8 (1)	8	>99
12			HGIItol (1)	8	>99
13			5 (5)	60	22
14			6 (5)	60	57
15			GIItol (5)	60	70
16			7 (5)	60	45
17			8 (5)	60	>97
18			HGIItol (5)	60	>97

^aRuns with catalysts **5**, **6**, and **GIItol** were carried out in CD₂Cl₂ at 30 °C, while runs with catalysts **7**, **8**, and **HGIItol** were performed in C₆D₆ at 60 °C. ^bYields based on NMR analysis.

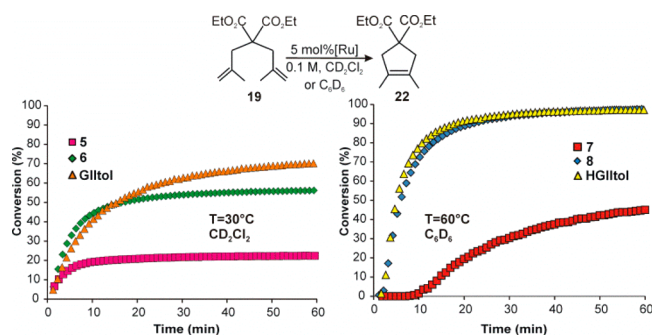


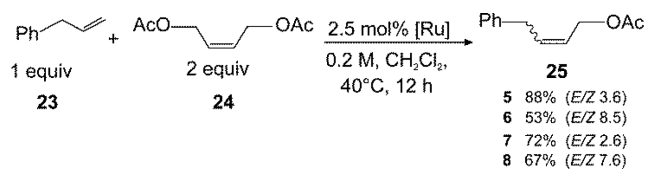
Figure 2. RCM conversion of 19.

which, as is known, are highly active in difficult RCM reactions (see Table 1 and Figure 2).^{2a} Moreover, rather surprisingly, the phosphine-containing complex 5 with *syn* phenyl groups on the NHC backbone was found to show an unusually lower reactivity toward the less encumbered malonate derivative 17 with respect to the more encumbered substrate 18 (see also the Supporting Information).

Although the RCM catalytic behavior of complexes 5–8 requires further experimental and theoretical investigation to be fully rationalized, it clearly appears that the configuration of the backbone plays a crucial role in the catalyst activity, contributing to create differently shaped reactive pockets around the metal. The relevance of the NHC backbone configuration was already well established for Ru complexes bearing *syn* and *anti* backbone substituted symmetrical NHCs.⁷ Nevertheless, a similar response was not obvious or predictable for Ru complexes bearing uNHCs, which are structural motifs characterized by a high level of dissymmetry and increased flexibility. Moreover, the RCM catalytic behavior of the newly synthesized Ru complexes bearing uNHCs is inverted with respect to the analogous *syn* and *anti* Ru complexes with symmetrical NHCs previously reported,^{7a–c} strongly indicating a combined effect of backbone configuration and N substituents which is not trivially interpretable.

The catalytic performances of catalysts 5–8 were then compared in the CM of allylbenzene (23) and *cis*-1,4-diacetoxy-2-butene (24),¹² illustrated in Scheme 2. In contrast with

Scheme 2. CM of Substrates 23 and 24



previous RCM results, in this reaction the *syn* complexes disclosed higher activity than their *anti* congeners, reaching high levels of conversions associated with an unusually low *E/Z* ratio of around 3. It is worth noting that such a pronounced difference in selectivity between *syn* and *anti* complexes was not observed with analogous Ru complexes bearing symmetrical NHCs.^{7a,b} This result is very significant, because it clearly indicates that the presence of differently oriented phenyl groups on the NHC backbone strongly influences not only catalyst activity but also catalyst selectivity, altering the steric environment of key metathesis intermediates.^{5b,d}

As a further remark, it is important to point out that complexes 5 and 6, characterized by *syn* and *anti* NHC

backbone configurations, respectively, were obtained as mixtures of *syn* and *anti* rotational isomers.⁹ Although at the moment we are not able to assess the influence of *syn* and *anti* rotational isomers of 5 and 6 on catalyst activity, we cannot exclude, as already reported by Collins,^{6b} that all the significant reactivity from these catalysts occurs from only one of the two rotational isomers or that possible NHC rotation during the catalytic cycle can heavily contribute to determine their reactivity. However, the fact that the reactivity profiles of 5 and 6 resemble those of 7 and 8 (obtained as *anti* rotational isomers only) in both RCM and CM is strongly indicative of the primary role of the backbone configuration on catalyst behavior with respect to the existence of rotamers.

Finally, the chiral catalysts 6 and 8 were tested in model asymmetric ring-closing metathesis (ARCM) reactions (Scheme 3 and Table 2).

Scheme 3. ARCM of Prochiral Trienes 26 and 27

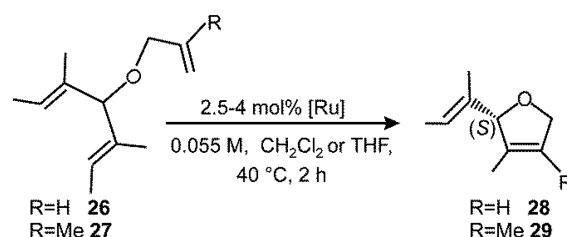


Table 2. ARCM of 26 and 27 with Catalysts 3, 6, and 8

entry ^a	substrate	catalyst (mol %)	additive	yield ^b (%)	ee ^c (%)
1	26	6 (2.5)	none	>98	18
2	26	6 (4.0)	NaI	>95	53
3	26	8 (2.5)	none	>98	19
4	26	8 (4.0)	NaI	>95	52
5 ^d	26	3 (2.5)	none	>95	82
6 ^d	26	3 (4.0)	NaI	>95	48
7	27	6 (2.5)	none	>95	42
8	27	6 (4.0)	NaI	>95	42
9	27	8 (2.5)	none	>95	42
10	27	8 (4.0)	NaI	>95	42
11 ^e	27	3 (2.5)	none	95	8

^aRuns without additive were carried out in CH₂Cl₂, while runs with NaI were performed in THF. ^bYields based on NMR analysis.

^cEnantiomeric excesses determined by chiral GC. ^dReferences 6a,b.

^eReference 6d.

The ARCM of 26 proceeded to full conversion, albeit in low enantiomeric excess (18–19%), with both catalysts (entries 1 and 3, Table 2). The employment of NaI as an additive to improve the enantioselectivity led to higher ee values (52–53% ee), as observed by Grubbs with chiral catalysts bearing C₂-symmetric NHCs (from 35% to 90% ee in the presence of NaI).¹³ On the other hand, this experimental evidence sharply contrasts with the results reported by Collins for the same ARCM reaction carried out with chiral catalysts possessing C₁-symmetric NHCs, such as 3, that are structurally much more similar to 6 and 8. Indeed, in that case the addition of NaI resulted in a significant drop in enantioselectivity, from 82% to 48% ee (entries 5 and 6, Table 2).^{6a,b}

The propensity of complexes 6 and 8 to ring-close hindered substrates prompted us to test them also in the challenging ARCM of 27 to form the tetrasubstituted cycloolefin 29. Both 6 and 8 efficiently performed the cyclization of 27 (>95%),

giving better enantiodiscrimination with respect to **3** (42% vs 8% ee) and mirroring the best results (in terms of conversion and enantioselectivity) obtained by Collins with modified versions of **3** (95% conversion, 43% ee).^{6d} The ARCM of **27** carried out with **6** and **8** in the presence of NaI gave no reaction (entries 8 and 10, Table 2). Very likely, the substitution of Cl[−] bound to Ru by I[−] ligands inhibits the reactivity of the catalysts toward substrates with increased steric bulk, such as **27**.

On the basis of these preliminary results, it appears that complexes **6** and **8** have catalytic properties that are intermediate between those of the Grubbs and Collins catalysts, deserving therefore deeper investigation. Further studies on the catalytic behavior of **6** and **8** in asymmetric olefin metathesis are underway.

In summary, we have presented the first example of stable Ru metathesis catalysts bearing unsymmetrical N-alkyl/N-aryl NHCs that differ in the relative orientation of phenyl groups on the backbone (*syn* or *anti*). For the Hoveyda–Grubbs type complexes **7** and **8**, an investigation of their crystal structure revealed rare C–H···Ru anagostic interactions, which were confirmed in solution by NMR spectral analysis. Preliminary studies on the catalytic behavior of complexes **5**–**8** revealed that chiral *anti* isomers **6** and **8** were highly efficient catalysts for sterically demanding RCM reactions and furthermore were able to successfully accomplish the challenging ARCM reaction, forming a tetrasubstituted olefin with moderate enantioselectivity. On the other hand, *syn* catalysts showed improved activities and *Z* selectivities in the CM reaction. These findings clearly demonstrate that different backbone configurations, allowing uNHCs to modulate their encumbrance around the metal, dramatically affect the properties of the catalyst. Accordingly, the present study opens new perspectives in fine tuning the steric and electronic properties of unsymmetrical NHC–Ru catalysts for specific applications.

More in general, the synthetic routes employed for the preparation of the backbone-substituted NHC ligand precursors should allow for easy modification of both the N-alkyl and the N-aryl moieties, thus offering new opportunities for various applications in organometallic catalysis as well as in organocatalysis.

■ ASSOCIATED CONTENT

■ Supporting Information

Text, figures, tables, and CIF files giving experimental details, compound characterization data, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for F.G.: fgrisi@unisa.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Dr. Chiara Costabile for helpful discussions and Dr. Patrizia Iannece and Patrizia Oliva for technical assistance. Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica is gratefully acknowledged.

■ REFERENCES

- (1) For reviews, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787. (c) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708–3742.
- (2) (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrod, Y. *Org. Lett.* **2007**, *9*, 1589–1592. (b) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339–1342.
- (3) (a) Colacino, E.; Martinez, J.; Lamaty, F. *Coord. Chem. Rev.* **2007**, *251*, 726–764. (b) Shahane, S.; Bruneau, C.; Fischmeister, C. *ChemCatChem*. **2013**, *5*, 3436–3459. (c) Kress, S.; Blechert, S. *Chem. Soc. Rev.* **2012**, *41*, 4389–4408.
- (4) (a) Tornatzky, J.; Kannenberg, A.; Blechert, S. *Dalton Trans.* **2012**, *41*, 8215–8225. (b) Hamad, F. B.; Sun, T.; Xiao, S.; Verpoort, F. *Coord. Chem. Rev.* **2013**, *257*, 2274–2292.
- (5) Selected examples of N-alkyl/N-aryl NHC–Ru complexes: (a) Vehlow, K.; Maechling, S.; Blechert, S. *Organometallics* **2006**, *25*, 25–28. (b) Ledoux, N.; Linden, A.; Allaert, B.; Mierde, H. V.; Verpoort, F. *Adv. Synth. Catal.* **2007**, *349*, 1692–1700. (c) Vehlow, K.; Wang, D.; Buchmeiser, M. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2615–2618. (d) Endo, K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527. (e) Thomas, R. M.; Keitz, B. K.; Champagne, T. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7490–7496. (f) Ablialimov, O.; Kedziorek, M.; Toborg, C.; Malinska, M.; Wozniak, K.; Grela, K. *Organometallics* **2012**, *31*, 7316–7319. (g) Rouen, M.; Borré, E.; Falivene, L.; Toupet, L.; Berthod, M.; Cavallo, L.; Olivier-Bourbigou, H.; Mauduit, M. *Dalton Trans.* **2014**, *43*, 7044–7049.
- (6) (a) Collins, S. K.; Fournier, P.-A. *Organometallics* **2007**, *26*, 2945–2949. (b) Fournier, P.-A.; Savoie, J.; Bédard, M.; Stenne, B.; Grandbois, A.; Collins, S. K. *Chem.—Eur. J.* **2008**, *14*, 8690–8695. (c) Savoie, J.; Stenne, B.; Collins, S. K. *Adv. Synth. Catal.* **2009**, *351*, 1826–1832. (d) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. *Org. Lett.* **2010**, *12*, 2032–2035.
- (7) (a) Grisi, F.; Costabile, C.; Gallo, E.; Mariconda, A.; Tedesco, C.; Longo, P. *Organometallics* **2008**, *27*, 4649–4656. (b) Grisi, F.; Mariconda, A.; Costabile, C.; Bertolasi, V.; Longo, P. *Organometallics* **2009**, *28*, 4988–4995. (c) Costabile, C.; Mariconda, A.; Cavallo, L.; Longo, P.; Bertolasi, V.; Ragone, F.; Grisi, F. *Chem. Eur. J.* **2011**, *17*, 8618–8629. (d) Perfetto, A.; Costabile, C.; Longo, P.; Bertolasi, V.; Grisi, F. *Chem. Eur. J.* **2013**, *19*, 10492–10496.
- (8) Complexes **5**–**8** are stable in the solid state over a period of 5–6 months and in C₆D₆ solution over 1–2 weeks.
- (9) *syn*: N-alkyl group located on the same side as the benzylidene unit (complex **5** *syn:anti* 0.3:1; complex **6** *syn:anti* 0.8:1). 2D-EXSY experiments at various mixing times as well as variable-temperature ¹H NMR experiments carried out in the range 25 °C < T < 70 °C showed no exchange between *syn* and *anti* rotamers.
- (10) A mixture of two conformational isomers was observed in solution for both **7** (major:minor 1:0.29) and **8** (major:minor 1:0.09). Very likely, these conformers originate in restricted rotation around the N–C(aryl) bond.
- (11) Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6908–6914.
- (12) Ritter, A. T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics* **2006**, *25*, 5740–5745.
- (13) (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228. (b) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840–1846.