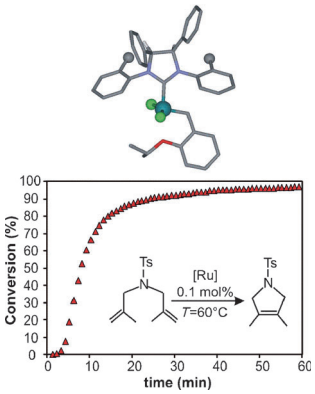
Cat power: Judicious backbone substitution of N-heterocyclic carbenes (NHCs) leads to stable Ru metathesis catalysts with frozen NHC conformations. This finding not only permits the isolation of complexes that are among the most active catalysts in the ring-closing metathesis of hindered olefins (see graphic; Ts = *p*-toluenesulfonyl), but also provides fundamental mechanistic insights on the role of *N*-aryl substituent conformations on catalyst activity.



Homogeneous Catalysis

*A. Perfetto, C. Costabile, P. Longo, V. Bertolasi, F. Grisi** ..... ▮▮▮▮–▮▮▮▮

Probing the Relevance of NHC Ligand Conformations in the Ru-Catalysed Ring-Closing Metathesis Reaction

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Probing the Relevance of NHC Ligand Conformations in the Ru-Catalysed Ring-Closing Metathesis Reaction

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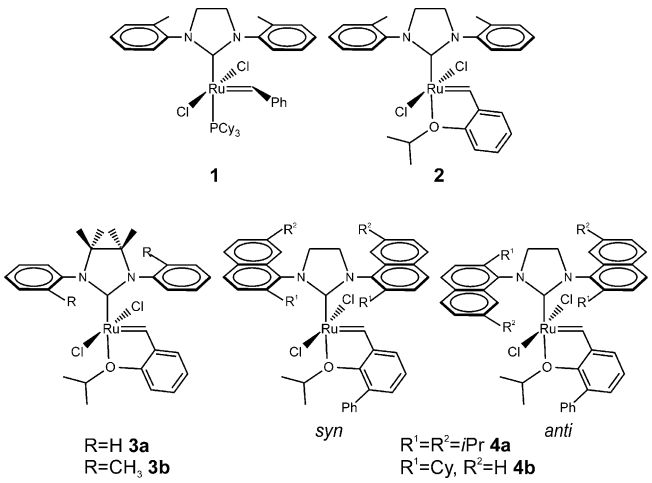
Ring-closing metathesis (RCM) promoted by transition-metal catalysts has become an indispensable tool in synthetic organic chemistry.[1] The introduction of Ru complexes bearing an N-heterocyclic carbene (NHC) ligand has marked a turning point in the development of increasingly efficient catalysts.[2] Successful design of NHC–Ru catalysts has been achieved by fine-tuning of the stereoelectronic properties of the NHC ligand and has led, inter alia, to a series of ruthenium catalysts bearing NHCs with varying degrees of N-heterocyclic backbone and/or aryl side chain substitution (e.g., **1**–**4** in Scheme 1) that give positive enhancement for RCM reactions.[3,4] In general, *N*-aryl bulk was found to increase activity, whereas increased backbone substitution decreased activity but increased catalyst lifetime.

We have recently identified a class of Ru catalysts containing N-heterocyclic carbene ligands with methyl groups on the NHC backbone in a *syn* and *anti* orientation.[5,6] No-



Scheme 1. Backbone and/or *N*-aryl substituted complexes.

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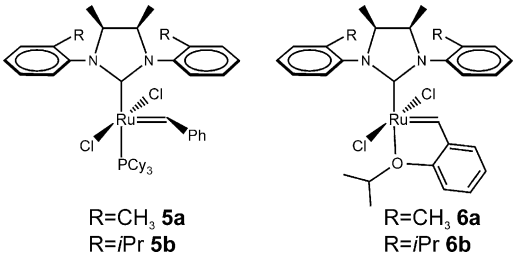
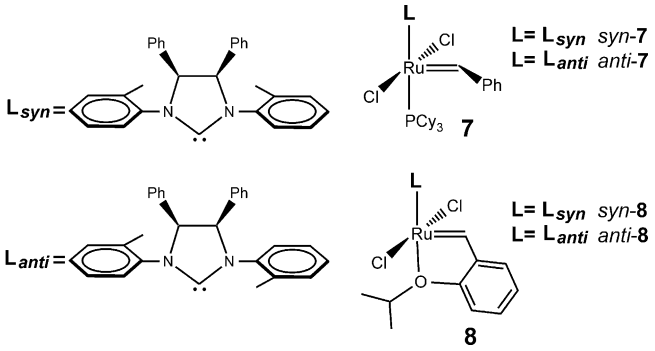


Scheme 2. The s*yn* NHC backbone substituted complexes.

tably, the *syn* complexes with *o*-tolyl N-substituents (**5a** and **6a**, Scheme 2) are among the most efficient catalysts in the formation of hindered olefins through RCM. The origin of this enhanced reactivity has been ascribed to the *syn* disposal of methyl groups on the backbone that induces a preferential *syn* orientation of the *N*-tolyl rings, thus providing a more accessible active space at the metal.[6a,b] A preferred *syn* orientation of *N*-tolyl substituents was already suggested by Grubbs for catalysts **1** and **2**.[7] Nevertheless, no direct evidence has been up to now reported to confirm this hypothesis.

In an attempt to further constrain *N*-aryl rings to adopt a *syn* conformation, thus enhancing catalyst efficiency, we decided to prepare monophosphine and phosphine-free NHC Ru precatalysts with more encumbered *syn* backbone substituents, replacing methyl with phenyl groups. The synthesis of the NHC ligand precursor with *syn* phenyl groups on the backbone was easily accomplished in two steps starting from the commercially available *meso*-1,2-diphenylethylenediamine, allowing significant time saving with respect to the five-step synthesis required for the analogous *syn* methyl backbone substituted NHC (see the Supporting Information).

The phosphine-containing complex (**7**, Scheme 3) was prepared by treatment of the appropriate imidazolinium tetrafluoroborate with $(CF_3)_2CH_3COK$ and $RuCl_2(=CHPh)(PCy_3)_2$ in toluene at 60 °C.[8] Surprisingly, chromatographic workup of the crude reaction mixture led to the isolation of two isomeric compounds in 58% overall yield. The major product (second eluted compound, 42%) was identified as the isomer with *syn*-oriented *N*-tolyl groups (*syn*-**7**). The minor isomer was assigned to be the conformation with the two methyl groups of the *N*-tolyl substituents on the NHC



Scheme 3. NHC Ru complexes **7** and **8**.

ligand disposed in an *anti* relationship (*anti*-**7**, 16%).[9] The two isomers of **7** were both converted in the corresponding phosphine-free complexes *syn*-**8** and *anti*-**8** (95 and 84% yield, respectively) by treatment with 2-isopropoxystyrene in the presence of CuCl.[11] Solution-state structure of complex **8**, determined by NMR analysis, revealed the presence of only one isomer (*syn*-**8**). The structural assignment of *syn*-**8** was unambiguously established by X-ray diffraction (Figure 1).[10a]

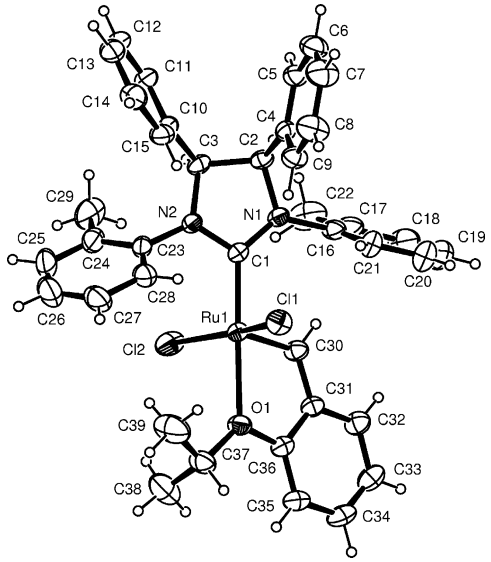


Figure 1. ORTEP[10b] view of complex *syn*-**8** with the thermal ellipsoids at 30% probability.

Characterisation of complex *anti*-**8** by ^{1}H,^{13}C and various 2D NMR experiments revealed the presence of two isomers, corresponding to the different arrangement of the *anti* oriented *N*-tolyl groups of the NHC (**8B** and **8C** of Figure 2).

Unfortunately, in spite of numerous attempts, we were unable to grow crystals of *anti*-**8** suitable for X-ray analysis; moreover, NMR characterisation of the complex did not allow us to unambiguously assign the exact geometry to the most stable species in solution.

According to density functional theory (DFT) studies on the complex stability, four minimum energy structures were

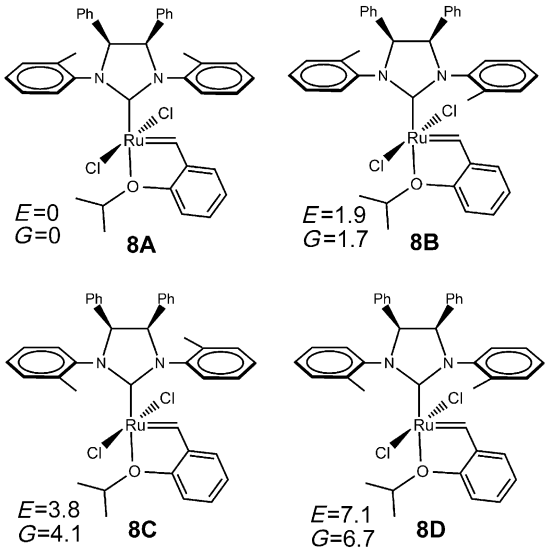


Figure 2. Isomers of complex **8**. For each isomer internal and free energies in CH_2Cl_2, obtained by DFT calculations, are reported in kcal mol^{-1}. See the Supporting Information for further details.

located for complex **8**. Internal and free energies in CH_2Cl_2 are reported in Figure 2, whereas structures are shown in the Supporting Information. Lowest energy structure **8A** corresponds to the most abundant *syn*-**8** isomer, characterised by X-ray diffraction as well. Moreover, **8B** was found to be more stable than **8C**, possibly indicating **8B** as the major *anti* form. The high energy of **8D** would explain the presence of only three isomers experimentally observed.

Reaction thermodynamics for the isomerization process from the minor isomer to the major isomer of *anti*-**8** were derived from VT ^{1}H NMR analysis ($\Delta H^{\circ} = -1.5$ kcal mol^{-1} and $\Delta S^{\circ} = -4.0$ kcal mol^{-1} K^{-1}; see the Supporting Information). The comparison of calculated and experimental energy differences strongly indicates **8B** as the major *anti* isomer. Indeed, calculated ΔE between **8B** and **8C** is 1.9 kcal mol^{-1} (Figure 2); this is in good agreement with experimental ΔH of 1.5 kcal mol^{-1}.

To the best of our knowledge, this is the first time that stable rotational isomers of *N*-tolyl complexes have been isolated. In fact, the other known *N*-tolyl catalysts (**1**, **2**, **5a** and **6a**) exist as mixtures of conformational isomers in the solid state as well as in solution.[3b,6a,7] Therefore, the high degree of conformational stability observed is strictly correlated to the presence of phenyl substituents on the NHC backbone.

The behaviour of the new complexes, **7** and **8**, was tested in some standard RCM reactions (Table 1). The RCM reaction of each substrate was followed by using ^{1}H NMR spectroscopy. Selected kinetic data are shown in Figure 3 (see the Supporting Information for more details). Interestingly, a marked difference in reactivity profiles is observed for **7** and **8** with different conformations of the NHC ligand.[12] Indeed, *syn*-**7** and *syn*-**8** perform better than their *anti* analogues in all the examined RCM reactions (Figure 3 and

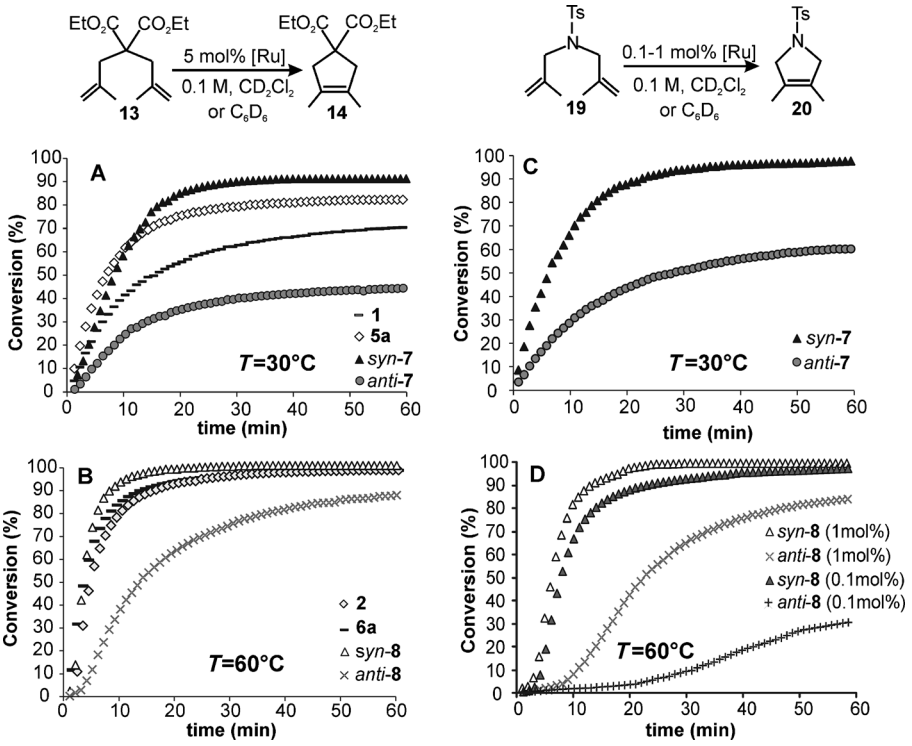


Figure 3. Kinetic data for the RCM of **13** (**A** and **B**) and **19** (**C** and **D**).

Table 1), and the observed trend is more pronounced with bulkier substrates that give tri- and tetrasubstituted cyclic olefins. Figure 3A shows the results for the challenging RCM of diethyl dimethallylmalonate **13** promoted by *syn*-**7** and *anti*-**8**. For comparison, the plots of two other *N*-tolyl complexes **1** and **5a**, which are efficient catalysts for hindered substrates, are also reported. Compound *syn*-**7** not only clearly outperforms *anti*-**7**, but it is also more efficient than complexes **1** and **5a**, reaching 92% conversion within 30 min. The latter represents the best result achieved in the RCM of **13** with a monophosphine Ru complex to date. The same reactivity profile is observed for the ring-closing of **13** carried out with the corresponding phosphine-free complexes *syn*-**8**, *anti*-**8**, **2** and **6a** (Figure 3B). Although the differences in overall activity are less evident than for phosphine-based complexes, it is worth noting that *syn*-**8** displays the highest activity (98% conversion in 20 min), emerging as one of the most efficient catalysts in the formation of tetrasubstituted olefins through RCM. Furthermore, *syn*-**8** reveals a high ability to promote ring-closing metathesis reactions at catalyst loadings as low as 0.5 to 0.05 mol%. Full conversion is reached at catalyst loading 0.05 mol% for substrates **15** and **17** (Table 1, entries 21 and 27), whereas nearly quantitative yields are registered at 0.5 and 0.1 mol% for the sterically demanding diolefins **13** and **19**, respectively (Table 1, entries 16 and 33). As for *anti*-**8**, the same low catalyst loading experiments emphasise the striking difference in activity compared with the *syn* isomer (Table 1). Notably, comparison of separated *syn* and *anti* conformers of *N*-tolyl catalysts **7** and **8** in RCM reactions provides the first direct evidence that NHC ligands incorporating correctly oriented *N*-tolyl groups are responsible for enhanced reactivity in RCM reactions.

The crucial role of *N*-tolyl group orientation on catalyst activity was furthermore confirmed by DFT calculations. In particular, we compared the behaviour of *syn*- and *anti*-**7**, by modelling the determining energy transition state structures of the RCM catalytic cycle of **13** for all possible *N*-tolyl orientations. Indeed, as already reported by some of us, highest energy transition states, involved in the RCM of **13** promoted by similar catalysts, such as **5a** (Scheme 2), were shown to be those leading the coordinated substrate structure to the first metallacycle intermediate.[6b]

The corresponding four possible structures and free and internal energies of transition states for **7** are shown in Figure 4. Lowest energy structure **TS-A** presents *syn* *N*-tolyl groups in an *anti* relationship with respect to the backbone phenyl groups. In fact, this N-group orientation minimises the internal NHC repulsions as well as the repulsions of Ru ligands with the incoming substrate **13** and accounts for the higher activity of *syn*-**7**.[13]

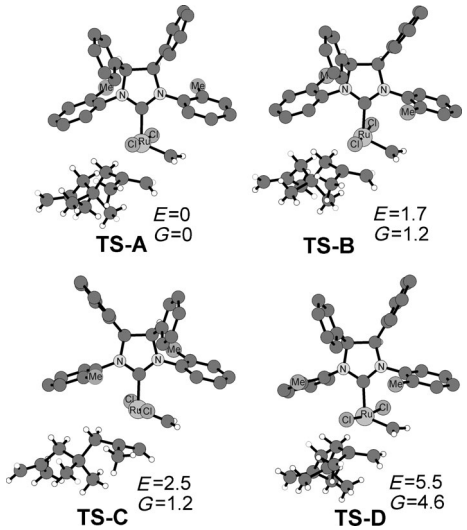
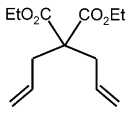
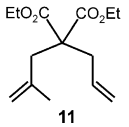
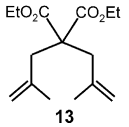
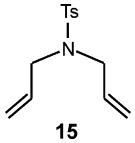
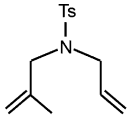
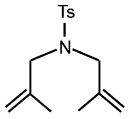


Figure 4. Determining energy transition state structures of the RCM catalytic cycle of **13** for all possible *N*-tolyl orientations of **7**. Internal and free energies, calculated in CH_2Cl_2, are in kcal mol^{-1}.

Table 1. RCM reactions with catalysts **7** and **8**.

Entry[a]	Substrate, Product	Catalyst [mol%]	*t* [min]	Yield [%][b]
1	 **9**	*syn*-**7** (1)	30	>98
2		*anti*-**7** (1)	60	70
3		*syn*-**8** (1)	5	>99
4		*syn*-**8** (0.1)	30	>99
5		*anti*-**8** (1)	12	>99
6		*anti*-**8** (0.1)	60	97
7	 **11**	*syn*-**7** (1)	35	>95
8		*anti*-**7** (1)	60	66
9		*syn*-**8** (1)	6	>99
10		*syn*-**8** (0.1)	60	95
11		*anti*-**8** (1)	60	95
12		*anti*-**8** (0.1)	60	74
13	 **13**	*syn*-**7** (5)	30	92
14		*anti*-**7** (5)	60	44
15		*syn*-**8** (5)	30	99
16		*syn*-**8** (0.5)	180	96
17		*anti*-**8** (5)	120	94
18	 **15**	*syn*-**7** (1)	25	>99
19		*anti*-**7** (1)	60	91
20		*syn*-**8** (0.1)	5	>99
21		*syn*-**8** (0.05)	7	>99
22		*anti*-**8** (1)	5	>99
23		*anti*-**8** (0.1)	25	94
24	 **17**	*syn*-**7** (1)	30	99
25		*anti*-**7** (1)	60	71
26		*syn*-**8** (0.1)	10	>99
27		*syn*-**8** (0.05)	14	99
28		*anti*-**8** (1)	7	>99
29		*anti*-**8** (0.1)	30	97
30	 **19**	*syn*-**7** (1)	60	97
31		*anti*-**7** (1)	60	60
32		*syn*-**8** (1)	30	99
33		*syn*-**8** (0.1)	60	97
34		*anti*-**8** (1)	120	90
35		*anti*-**8** (0.1)	180	46

[a] Runs with catalyst **7** were carried out in CD_2Cl_2 at 30 °C; runs with catalyst **8** were performed in C_6D_6 at 60 °C. [b] Yields based on NMR analysis.

In conclusion, employment of suitable substituted NHC backbone enables, for the first time, the facile synthesis of separated, stable conformers of *N*-tolyl Ru complexes (**7** and **8**). Compounds *syn*-**7** and *syn*-**8** are among the most efficient catalysts in the RCM of hindered olefins, requiring catalyst loadings as low as 0.05–0.5 mol%. Notably, the different performances of isolated *syn* and *anti* isomers of **7** and **8** provide the first unequivocal proof for the significance of correctly disposed *N*-aryl groups to successfully accomplish RCM reactions. To offer a deeper understanding of the relationship between NHC architecture and catalyst activity, studies on the influence of the NHC conformation of **7** and **8** in other olefin metathesis reactions are underway and will be reported in due course.

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Keywords: density functional calculations · homogeneous catalysis · N-heterocyclic carbenes · ring-closing metathesis · ruthenium

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[12] Intriguing reactivity differences between NHC–Ru complexes that are only distinguished by the relative orientation of their side chains (e.g., *syn*-**4** and *anti*-**4**) were already observed; see ref. [4].
[13] In structures **TS-B** and **TS-C**, the repulsion between one of the phenyls on the backbone and the eclipsed *N*-tolyl methyl are spread to the substrate through the chlorine, leading to a torsion of the substrate double bond axis with respect to $Ru{=}CH_2$ axis and, as a consequence, to an energy enhancement. As for substrate **13** model, $-$COOEt group has been replaced by $-CH_3$.

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