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COMMUNICATION

Helicenes as chirality inducing groups in transition metal catalysis: the first helically chiral olefin metathesis catalyst

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Abstract: Helical chirality is a novel enantioselectivity inducing element in transition metal catalyzed transformations. The principle is illustrated herein for the example of asymmetric olefin metathesis. We describe the synthesis of the first helically chiral Ru-NHC alkylidene complex from an aminohelicene-derived imidazolium salt, which was ligated to the first generation Hoveyda-Grubbs catalyst. Kinetic data were aquired for benchmark test reactions and compared to an achiral catalyst. The helically chiral Ru-catalyst was evaluated in asymmetric RCM and ROM/CM reactions, which proceeded with promising levels of enantioselectivity. Extensive NMR-spectroscopic investigations and a DFT geometry optimization were performed. These results led to a topographic steric map and calculation of percent-buried-volume values for each quadrant around the metal centre.

Asymmetric syntheses through transition metal catalyzed reactions have evolved from academic curiosities into industrially relevant processes for the production of pharmaceuticals, crop protecting agents and other fine chemicals. Asymmetric (or enantioselective) catalysis requires the presence of a chiral ligand at the metal, which induces either directly or indirectly a dissymmetry around the catalytically active centre. For a successful enantioinduction the chiral information needs to be embedded in a steering ligand, which is tightly bound to the metal throughout the entire catalytic cycle. In this regard, *N*-heterocyclic carbenes (NHC's) are particularly suitable due to their high σ-donor capacity and strong M-NHC bond.[1-2] In most cases described so far NHC-ligands have been chirally modified by introducing centres of chirality, either in the *N*-substituent or in the NHC-backbone (**Figure 1**).[3-4] The former approach offers not only the advantage of a convenient ligand synthesis from homochiral primary amines, but also the opportunity for tuning the electronic ligand properties through backbone substituents. It has, for instance, been demonstrated that the reactivity of Ru-metathesis catalysts with unsaturated NHC ligands can be improved by increasing the σ-donor capacity of the ligand through introduction of donor substituents in the backbone.[5] Unfortunately, enantioselectivities are normally low for this ligand design if the chiral *N*-substituent can freely rotate around the C-N-bond,[6] whereas higher levels of enantioselectivity are observed with multicyclic,[7] bidentate[8] or cyclometalated NHC's.[9] On the downside, opportunities for steric and electronic modulation through backbone substituents are restricted for these ligand systems. The alternative approach to chiral NHC-ligands requires one or two centres of chirality in the backbone. One of the earliest examples for this strategy is the first chiral Ru-metathesis catalyst **5a**.[10] This approach has later been used for other chiral metathesis catalysts with unsymmetrical NHC ligands.[11-12] In catalysts such as **5a** the stereoinduction relies on a so-called "gearing"-effect:[13-15] the *N*-aryl substituents rotate out of plane to avoid steric interaction with the substituents in the backbone. In the process, one of the two enantiotopic coordination hemispheres becomes more crowded than the other.

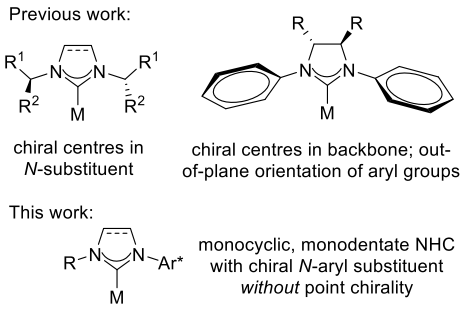

Figure 1. Implementation of chirality in monodentate and monocyclic NHC's.

We wondered whether enantiocontrol in asymmetric transition metal catalysis is possible even for the most straightforward NHC-ligand design (monocyclic, monodentate, chiral information only in the *N*-substituent) if chirality elements other than point chirality are used. A literature search revealed only two examples that strictly fall into this category. Andrus and coworkers described a Rh-NHC complex with planary chiral *N*-*para*-cyclophane substituents for enantioselective conjugate addition of boronic acids,[16] and Sankararaman and coworkers developed a Pd-NHC complex substituted with a chiral *para*-cyclophane for enantioselective hydrogenation.[17] Other transition metal NHC-catalysts with "non-classical" elements of chirality (i. e. planar or axial chirality) have either bidentate[18-20] NHC ligands or carry additional centres of chirality.[19, 21]

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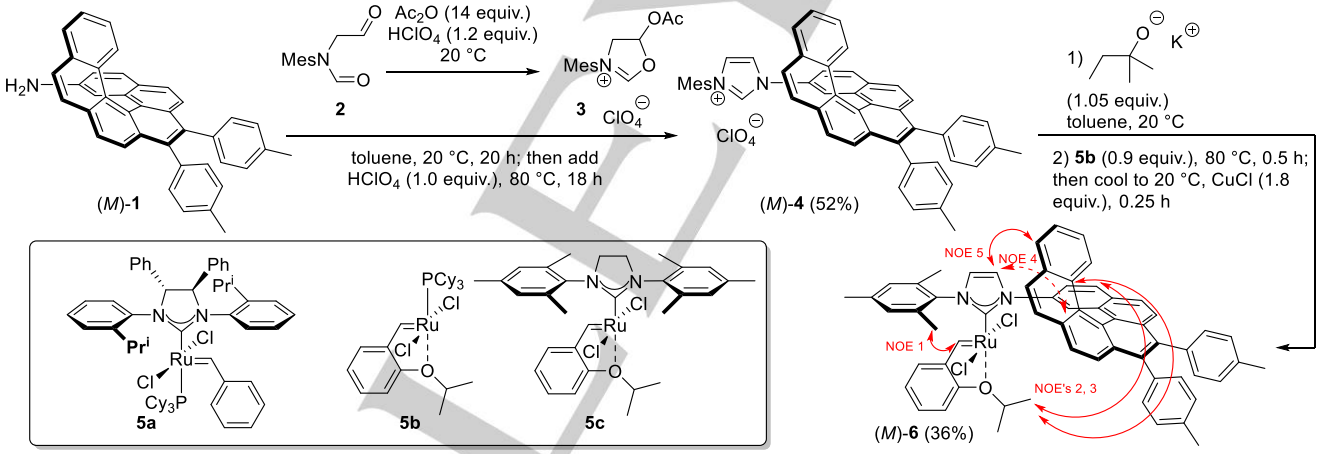
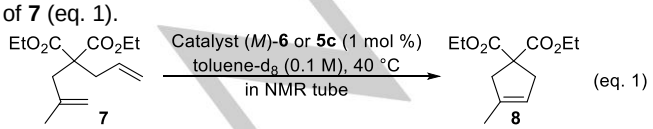
Helical chirality has so far been unexplored in asymmetric transition metal catalysis as a stereoinformation inducing element. Recent efforts by some of us have greatly facilitated the synthesis of enantiopure helicenes[22-23] via a diastereoselective Ni-catalyzed alkyne cyclotrimerization with point-to-helical chirality transfer.[24] This strategy has in the meantime been successfully applied to the synthesis of enantiopure aminohelicenes,[25-26] which we in turn expect to open the door to NHC ligands with helically chiral *N*-substituents and transition metal catalysts derived thereof. Literature precedence for transition metal-NHC complexes with *N*-helicenyl substituents is scarce,[27-28] and these have not been investigated in asymmetric catalysis. In addition, few other helicene substituted imidazolium salts have been synthesized via different routes, but not ligated to transition metals.[29-30]

As a proof of concept we investigated the feasibility of asymmetric olefin metathesis reactions,[14, 31-35] catalyzed by a helically chiral metathesis initiator which was designed according to the general principles outlined above and summarized in **Figure 1**. Our synthesis of such a catalyst (*M*)-**6** starts from enantiopure 2-amino[6]helicene ((*M*)-**1**).[26] To avoid steric overcrowding of the NHC ligand, which might result in problems upon ligation and low catalytic activity,[11] we aimed at the synthesis of an unsymmetrical NHC with just one *N*-helicenyl substituent. Unsymmetrical NHC's can be used to modulate steric congestion around the metal centre and influence conformational preferences arising from a rotation around the Ru-NHC bond.[36-37] As a substituent for the second nitrogen we chose an *N*-mesityl group, because we expected this substituent to be sufficiently bulky to stabilize the catalytically active 14-electron species arising from dissociation of the temporary ligand, but not too sterically demanding to inhibit any catalytic activity. For the synthesis of the required imidazolium salt Fürstner's method[38] was used. In this method, oxazolium salts such as **3** are reacted with amines, in our case 2-amino[6]helicene (*M*)-**1**. Imidazolium salt (*M*)-**4** was obtained in fair overall yield and its identity confirmed by MALDI-MS and NMR spectroscopy. It was converted to the carbene by deprotonation with K-amylate and subsequently treated with **5b**.[39] In the presence of the phosphine scavenger CuCl[40-41] the helically chiral Ru-alkylidene (*M*)-**6** was obtained. Like other NHC-Ru alkylidene complexes with a hemilabile *ortho*-isopropoxybenzylidene ligand,[40, 42] complex (*M*)-**6** is a dark green solid. The assigned structure was confirmed by MALDI-MS and a full NMR-spectroscopical characterization. Indicative for a successful ligation of the NHC ligand are the chemical shift values for the α-proton of the Ru-alkylidene unit (δ = 16.64 ppm for (*M*)-**6**, δ = 17.45 ppm for **5b**[40]) and for the methine proton of the isopropoxy substituent (δ = 4.90 ppm for (*M*)-**6**, δ = 5.28 ppm for **5b**[40]). Similar shifts to lower δ-values have also been observed for **5c** and were attributed to the increased σ-donor capacity of NHC ligands (**Scheme 1**).[40]



Scheme 1. Synthesis of a helically chiral Ru-NHC-metathesis catalyst (*M*)-**6**. Selected NOE-interactions are indicated by red arrows.

In the next step the catalytic activities of (*M*)-**6** and **5c** were investigated by NMR spectroscopic experiments. A representative example is the time-conversion curve for the RCM of **7** (eq. 1).



(eq. 1)

Although the helicenyl substituent in (*M*)-**6** leads to a notable deceleration of the initiation rate of the metathesis reaction compared to **5c**, a conversion of 97% for the RCM of **7** is still achieved after 40 minutes with 1 mol % (**Figure 2**). The RCM of diethyl diallylmalonate and the ring closing enyne metathesis of diphenylpropargyl allyl ether have similar kinetic profiles (see supporting information). The reduced activity of (*M*)-**6** points at a preferred orientation of the *N*-helicenyl substituent to the catalytically active centre. We also investigated the cross metathesis of allylbenzene and (*E*)-1,4-diacetoxy-2-butene to check whether the sterically demanding helicenyl substituent affects *E*/*Z*-selectivity, but similar yields and selectivities towards the *E*-product were observed with both catalysts.

As a test substrate for enantioselective RCM the allyl ether **9** was chosen (**Scheme 2a**), because this prochiral triene has previously been used to evaluate other chiral metathesis catalysts,[11, 34, 43]

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including **5a**.[10] Under optimized conditions (for details see supporting information) (*R*)-**10** was obtained in 56% ee with quantitative conversion of the starting material. Grubbs and coworkers reported for the same test reaction under similar conditions an ee of 35% at 82% conversion with catalyst **5a**.[10] Catalyst (*M*)-**6** was also tested in the ROM-CM-reaction of *meso*-**11** and styrene. With 1 mol % of catalyst the expected all-*cis*-configured cyclopentane **12** was obtained with high *E*-selectivity and 40% ee at 86% conversion (**Scheme 2b**). Although substantially higher enantioselectivities have been observed for these and similar substrates with chiral Schrock-type Mo-alkylidenes,[44] in particular the "chiral-at-Mo" catalysts,[45] the enantioinduction observed with (*M*)-**6** proves the concept outlined above.

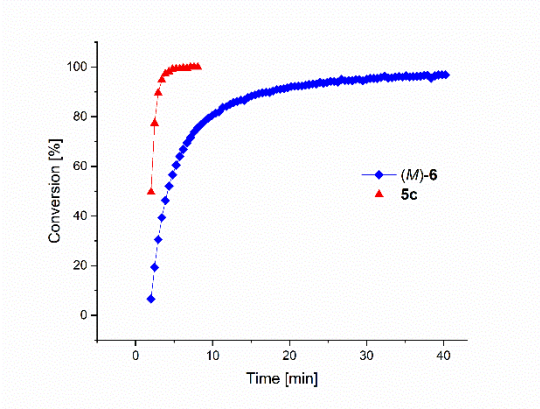
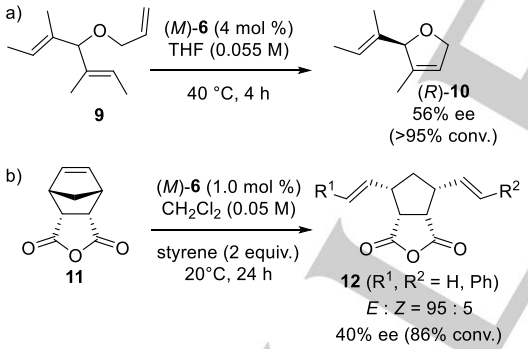


Figure 2. Catalytic activity of (*M*)-**6** and **5c** in the RCM of **7**.



Scheme 2. Enantioselective RCM (a) and ROM-CM catalyzed by (*M*)-**6**.

To gain further insight into its preferred conformation, a ROESY-experiment and a structure optimization using DFT-methods were performed for (*M*)-**6**. Selected NOE's are indicated by red arrows in the structure shown in **Scheme 1**: from NOE 1 it can be concluded that the *N*-mesityl substituent resides over the benzylidene unit and that free rotation around the Ru-NHC bond is not possible. NOE's 2 and 3 indicate spatial proximity of one *ortho*- and its vicinal *meta*-position and the isopropoxy group of the alkylidene unit. The other *ortho*-position of the helicenyl substituent is close to H4 of the NHC backbone (NOE 4). These three NOE's indicate that the helicene rotates out of plane around the N-C-bond and that it is locked in this conformation. This is supported by NOE 5 of backbone proton H4 with the opposite "upper" terminus of the helicene. These conclusions are confirmed by the results of the DFT-geometry optimization (**Figure 3a**).

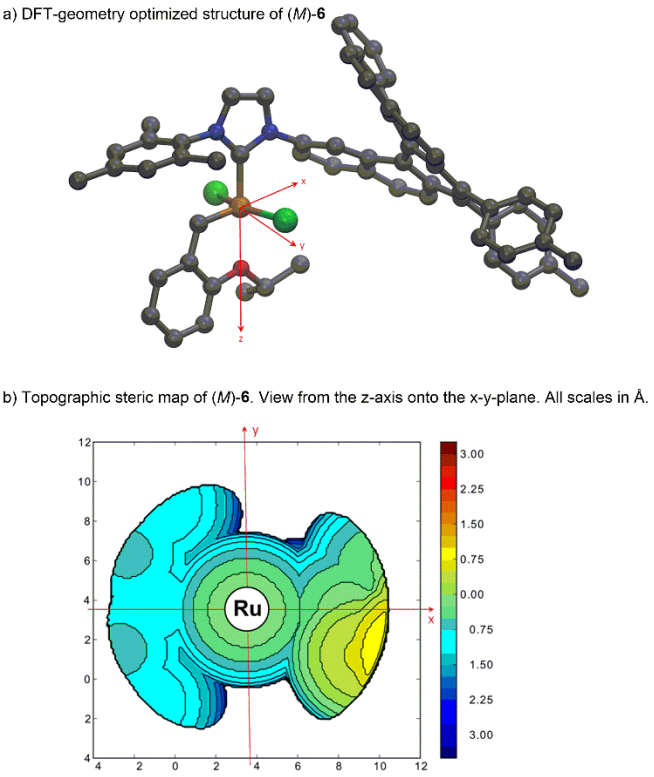


Figure 3. Ball-and-stick-representation of DFT-geometry optimized structure (a) and topographic steric map of (*M*)-**6** (b).

Based on the DFT-optimized structure of (*M*)-**6** a topographic steric map was prepared and the "percent buried volume" (%V_{bur}) value was calculated, using the SambVca 2.0 web tool (**Figure 3b**).[46] Topographic maps are a tool to visualize the distribution of steric hindrance around a metal centre. The coordination sphere is viewed as a projection along the z-axis onto the x-y-plane, which means that in our case the complex is viewed from the bottom. The steric extension along the z-axis is visualized by iso-contour curves, with red colour indicating high steric demand, and blue colour indicating low steric demand. "Percent buried volume" was introduced by Nolan, Cavallo and coworkers as a parameter to quantify the bulkiness of NHC ligands. It is defined as the relative amount of the total volume of a sphere around the metal that is occupied by the ligand.[47-48] For instance, for complex **5c** a %V_{bur} value of 33.7 was reported,[48-49] and for a derivative of its unsaturated IMes-analogue a %V_{bur} value of 31.9 was calculated.[48, 50] For our helically chiral complex (*M*)-**6** the overall %V_{bur} value was determined to 33.6. In the case of unsymmetrical NHC-ligands which are not freely rotatable around the M-NHC-bond an overall %V_{bur} value is only of limited relevance. Therefore the individual values for each four quadrants were determined. While the %V_{bur} values of northwest (NW), southwest (SW) and northeast (NE) quadrant vary only slightly (from 30.4 to 32.0), the south-east (SE) quadrant is sterically

significantly more congested than the other three, with a $\%V_{bur}$Max value of 40.5. In this regard (*M*)-**6** differs from other unsymmetrical but achiral Ru-NHC alkylidene complexes that have recently been analyzed in a similar fashion: for these complexes similar $\%V_{bur}$ values were obtained for adjacent eastern and western quadrants, respectively.[37]

In summary, we have devised a synthesis of the first olefin metathesis catalyst with a helically chiral NHC-ligand. NMR-spectroscopic investigations and DFT-calculations suggest that the complex is conformationally rigid and that the *N*-helicenyl substituent adopts a preferred conformation in which it rotates out of plane. This results in a steric differentiation of the enantiotopic hemispheres around the Ru-alkylidene unit. Initial experiments show promising levels of enantioselectivity. A further development of this novel concept for enantioinduction in transition metal catalysis appears to be worthwile and is currently under investigation in our laboratories.

Acknowledgements

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Helical chirality is a novel enantioselectivity inducing element for transition metal catalyzed transformations. The concept is exemplified for an enantioselective olefin metathesis catalyst.

Manfred Karras, Michał Dąbrowski, Radek Pohl, Jiří Rybáček, Jaroslav Vacek, Lucie Bednárová, Karol Grela, Ivo Starý, Irena G. Stará and Bernd Schmidt

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