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Impact of NHC Ligand Conformation and Solvent Concentration on the Ruthenium-Catalyzed Ring-Closing Metathesis Reaction

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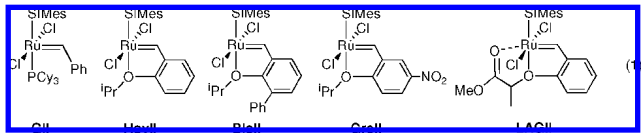
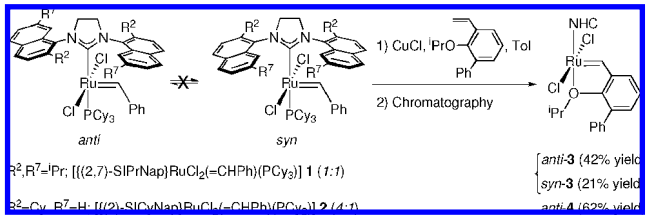
Ring-closing metathesis (RCM) reactions promoted by transition metal catalysts have gained enormous importance in synthetic organic chemistry.[1] Especially valuable was the introduction of ruthenium-based N-heterocyclic carbene complexes such as Grubbs' II (**GII**) a decade ago.[1] Since then, major research efforts have been directed toward optimizing the ligand sphere around the ruthenium center and have led, inter alia, to derivatives shown in eq 1.[2] Overall though, activities of these catalysts in RCM, while sufficient for laboratory-scale applications, are still relatively low for applications in larger-scale reactions.



Our entry into this fascinating field of research began via the identification of saturated NHCs that feature substituted naphthyl side chains.[3] The ligands are present as a mixture of *anti* and *syn* conformers, and preliminary data with two of these NHCs, (2,7)-SIPrNap and (2)-SICyNap, outlined their high catalytic activity in the RCM of **GII** type precatalysts (used as isomeric mixtures).[3c] The substitution pattern on the naphthyl side chains confers a high degree of conformational stability,[3a,4] and we were therefore intrigued by the prospect of metathesis-active NHC−ruthenium complexes that are only distinguished by the relative orientation of their side chains.[5]

Scheme 1. Preparation and Separation of Catalysts **3** and **4**



To enhance the possibility of separating such complexes and at the same time ensure high catalytic activity, we decided to prepare phosphine-free ruthenium precatalysts that are analogues to Blechert's catalyst (**BleII**).[2b] Complex **3** was prepared from an *anti*/*syn* mixture (ca. 1:1) of **1** by metathesis with *o*-isopropoxy-*m*-phenylstyrene (Scheme 1). Careful chromatographic workup of the isomeric mixture led to the isolation of the two complexes *anti*-**3** (first compound eluted) and *syn*-**3** in 63% overall yield. When the same reaction was performed with an *anti*/*syn* (4:1) mixture of **2**, only the first isomer, namely *anti*-**4**, was isolated from the column (62% yield).[6] The assignment of the respective isomers was verified through X-ray structural studies of complexes *anti*-**3** and *anti*-**4** (Figure 1).

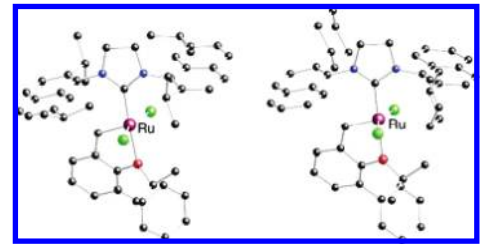


Figure 1. Ball-and-stick drawings of *anti*-**3** (left) and *anti*-**4** (right).

RCM activities (27 °C, 0.1 M substrate/CD_2Cl_2) of complexes *anti*-**3**, *syn*-**3**, and *anti*-**4** were then benchmarked against Blechert's SIMes-derived catalyst (**BleII**) using a series of substrates (**5**−**15**, Figure 2) and following their conversion by ^{1}H NMR spectroscopy. Selected kinetic data are shown in Figure 2 (see the Supporting Information for more details). As anticipated based on our earlier studies on **GII** derivatives, the modification of the NHC structure has a beneficial effect on the reactivity profile and the following overall order of activity can be deduced: *anti*-**3** ≥ *anti*-**4** > *syn*-**3** > **BleII**. Somewhat surprising is the fact that differences in activity favoring (2,7)-SIPrNap and (2)-SICyNap over SIMes increase with bulkier substrates that give tri- and tetrasubstituted cyclic olefins or with dienes that produce six-membered cycloolefins.[7] Here, both *anti*-**3** and *anti*-**4** clearly outperform *syn*-**3** and in particular **BleII**, and the overall reactivity profile puts them among the most active RCM catalysts known.

While the higher reactivity of the new catalysts as well as the clear differences between *anti*-**3** and *syn*-**3** looked very interesting, we were puzzled by the fact that the **BleII** catalyst seemed to perform better than originally reported by Blechert et al.[2b] A closer inspection of their report shows that the reaction conditions used, except for substrate concentration (and catalyst loading), were identical. This prompted us to examine the dependence of reaction concentration on RCM activity. To do so, we chose the overall most active precatalyst (*anti*-**3**, 0.1 mol %) and moderately bulky substrate **7**. Figure 2 (below right) shows that reaction rates indeed increase dramatically with increasing substrate-to-solvent concentrations. Using Blechert's dilution (0.01 M substrate/CD_2Cl_2) or a 0.04 M concentration does not lead to full conversion of **7**, while a high concentration (0.8 M) ensured complete conversion after only 21 min. More significantly, a reaction run in an open vessel without any solvent gave quantitative yields of the product within 2 min, without generating any byproducts that arise from ADMET.[8,9]

As a result, neat reactions with other substrates at lower catalyst loadings were performed with *anti*-**3** (Table 1). In some cases, namely for the tosylamide-derived substrates, the products were solids at room temperature and impeded simple, neat reaction runs. Here, a concentrated hexane solution of *anti*-**3** was added to the neat substrates giving pure solid products with almost the same

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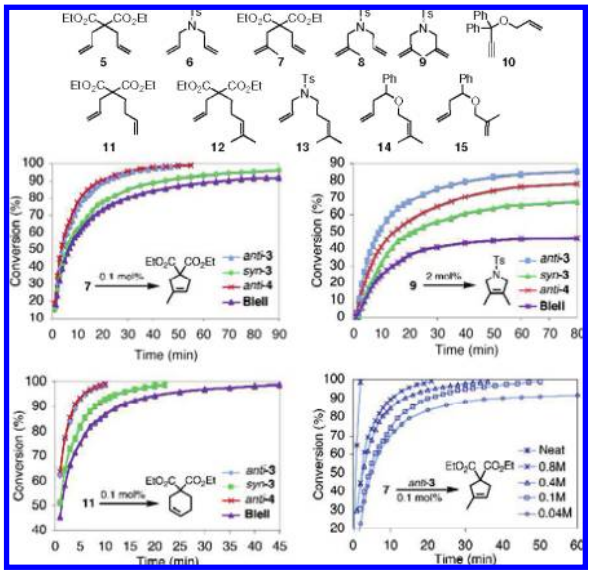

Figure 2. Substrates (above, catatyst loadings for **5**−**8**, **10**−**14**; 0.1 mol %, for **15**; 0.2 mol %; for **9**; 2 mol %), kinetic data for RCM of **7**, **9**, and **11**, and concentration dependence for conversion of **7** with *anti*-**3** (below).

efficiency as that of the neat reactions. Overall, catalyst loadings could be significantly lowered compared to the runs performed in solution. Although not optimized, between 50 and 250 ppm of precatalyst *anti*-**3** at room temperature suffice for virtually complete conversion to give ring-closed disubstituted and trisubstituted five- and six-membered rings. Generation of ethylene gas is not necessary for the reaction to proceed (entries 13−15). In the case of the representative enyne substrate **10**, a concentrated CH_2Cl_2 solution already ensures unprecedented levels of activity (entries 9,10). Also notable is the very low catalyst loading (0.2 mol %) needed to obtain the tetrasubstituted olefin from **9** (entry 8). This product is normally only produced with heating and substantially higher catalyst loadings. Turnover numbers reaching 20 000 (entries 2,10,12) and turnover frequencies of 240 000 per hour (entries 1,11,13) for complete conversion certainly approach values needed for larger-scale industrial applications of the RCM reaction.[10]

Table 1. RCM (25°C) with *anti*-**3** at Low Catalyst Loadings

entry	olefin	conditions	*anti*-**3** (ppm)	*t* (min)	yield (%)[a]
1	**5**	neat	250	1	99 (97)
2[b]	**5**	neat	50	120	97
3[c]	**6**	0.5 M Hex	250	5	98 (96)
4[c]	**6**	0.5 M Hex	100	12	97
5	**7**	neat	250	30	98 (97)
6[c]	**8**	0.5 M Hex	250	9	99
7[c]	**8**	0.5 M Hex	100	18	97
8[c]	**9**	0.5 M Hex	2000	480	97
9[c]	**10**	0.5 M DCM	100	4	99
10[c]	**10**	0.5 M DCM	50	30	99
11	**11**	neat	250	1	99
12[b]	**11**	neat	50	120	98
13	**12**	neat	250	1	99
14[c]	**13**	0.5 M Hex	250	5	99
15	**14**	neat	250	480	96
16	**15**	neat	250	480	97

[a] Yields based on NMR analysis. Selected isolated yields in brackets. [b] Runs with **GII** did not go to completion under these conditions but showed appreciable amounts of product [after 2 h: 72% (**5**) and 58% (**11**), after 24 h: 87% (**5**) and 72% (**11**)](ref 6). [c] DCM = CH_2Cl_2, Hex = *n*-hexane.

In conclusion, we have identified ruthenium metathesis catalysts that show improved reactivity profiles for the RCM and where clear differences exist between the respective conformers of the NHC ligand. While testing these new catalysts, we discovered that substantially higher reaction rates could be obtained when more concentrated substrate/solvent mixtures were employed. This ultimately led to the RCM forming five- and six-membered rings of a variety of substrates with catalyst loadings of just 50−250 ppm of *anti*-**3**. This simple and practical way for improving the reactivity and the lifetime of *anti*-**3** seems to be applicable to other ruthenium metathesis catalysts and should extend their usefulness in chemical synthesis. The intriguing reactivity differences between *anti*-**3** and *syn*-**3** are now the subject of a mechanistic study that will be extended to metathesis reactions using chiral derivatives of the ligands described here.[11]

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Supporting Information Available: Experimental procedures, kinetic data, and CIFs for *anti*-**3** and *anti*-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) See the Supporting Information for details.
(7) The results seem counterintuitive given the overall higher steric bulk of (2,7)-SIPrNap and (2)-SICyNap compared to SIMes (ref 3a).We believe that this is due to the fact that one of the sides on the naphthyl moieties is more open than in SIMes and, as a consequence, bulky substrates can approach the metal center more easily.
(8) To our knowledge, this is the first study relating reactivity to reaction concentration since productive RCM was introduced. Early studies on substrates such as **5** with less selective/active Schrock's and Grubbs' I catalysts showed that productive RCM needed dilutions of at least 0.1 M; see: (a) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978. (b) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. For more recent relevant reports, see: (c) Dinger, M. B.; Mol, J. C. *Adv. Synth. Catal.* **2002**, *344*, 671. (d) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991. (e) Maifeld, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228.
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