Designed Stereoselectivity

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Building Stereoselectivity into a Chemoselective Ring-Opening Metathesis Polymerization Catalyst for Alternating Copolymerization**

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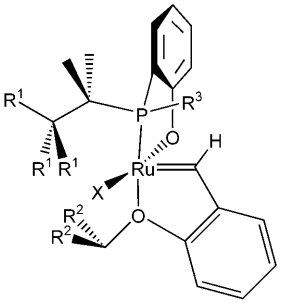
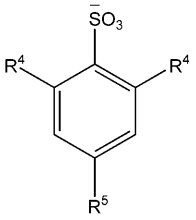
Chemoselectivity, regioselectivity, and stereoselectivity in homogeneous catalysis are ordinarily difficult to separate from one another. Some time ago, we reported the mechanism-based design of a chemoselective ring-opening metathesis polymerization (ROMP) catalyst **1** for the alternating copolymerization of norbornene and cyclooctene wherein two diastereomeric carbenes interchange by inversion at the stereogenic ruthenium center after each productive metathesis step.[1,2] Here we report ruthenium-based catalysts in which chemo- and stereoselectivity are mechanistically designed according to a simple scheme involving bulky sulfonates **4a–4f** (Scheme 1) as substitutes for the usual halide ligands, with the two types of selectivity determined by the steric bulk in two orthogonal planes.

We have pushed the original catalyst's (**1**)[2] performance in terms of sequence selectivity (75% alternation with strong dependence on the temperature and the norbornene/cyclooctene ratio, see also Figure S7 in the Supporting Information) to the limit by developing more bulky bidentate phosphines. Complex **2** shows a higher activity for copolymerization, and the faster initiating (see Figure S6 in the Supporting Information) variant **5**, in particular, is able to produce a copolymer within seconds after catalyst addition, as evident by the immediate formation of a gel. The less-strained cyclooctene seems to react cleanly at a competitive rate with only one diastereomeric form of the carbene, whereas norbornene shows the same high activity towards both. A polymer produced from a 1:5 mixture of norbornene and cyclooctene contains about 10% polynorbornene units, as expected for this high selectivity which seems to be only controlled by strain[3] release of monomers. Unexpectedly, the stereochemistry of the olefinic moieties was close to 90% *trans*, which inspired us to design for Z (or *cis*) selectivity (see bottom spectrum in Figure 1).



1: R^1 = H, R^2 = Cy, R^3 = Ph, X = Cl
2: R^1 = Me, R^2 = Me, R^3 = Ph, X = Cl
2a: R^1 = Me, R^2 = Me, R^3 = Ph, X = **4a**
2b: R^1 = Me, R^2 = Me, R^3 = Ph, X = **4b**
2c: R^1 = Me, R^2 = Me, R^3 = Ph, X = **4c**
2d: R^1 = Me, R^2 = Me, R^3 = Ph, X = **4d**
2e: R^1 = Me, R^2 = Me, R^3 = Ph, X = **4e**
2f: R^1 = Me, R^2 = Me, R^3 = Ph, X = **4f**
3: R^1 = H, R^2 = Me, R^3 = *t*Bu, X = Cl
3a: R^1 = H, R^2 = Me, R^3 = *t*Bu, X = **4b**
3b: R^1 = H, R^2 = Me, R^3 = *t*Bu, X = **4c**
3c: R^1 = H, R^2 = Me, R^3 = *t*Bu, X = **4d**
5: R^1 = Me, R^2 = Cy, R^3 = Ph, X = Cl



4a: R^4 = H, R^5 = Me
4b: R^4 = R^5 = Me
4c: R^4 = R^5 = *i*Pr
4d: R^4 = R^5 = Cy
4e: R^4 = R^5 = *t*Bu
4f: R^4 = R^5 = H

Scheme 1. Catalysts tested in co- and homopolymerizations.

Therefore, we modified the parent catalyst **2** by replacement of the chloride with more bulky anions. Catalysts **2a–2f** could easily be prepared by overnight reaction of the halide-containing precursor **2** with excess silver sulfonates **4a–4f** in benzene, with clean conversion into new carbene species, which were used in situ. For polymerization experiments, a norbornene/cyclooctene ratio of 1:20 was chosen to ensure almost complete alternation (solvent: CH_2Cl_2; norbornene/catalyst ratio = 2000:1). The reactivity of the sulfonate complexes is much lower, and the following relative rates are found: **5**/**2**/**2a**/**2d** = 1:(1/30):(1/300):(1/750) (see Table S4 in the Supporting Information).

^{13}C NMR analysis of the polymers[4] in $CDCl_3$ reveals a systematic trend (Figure 1). Almost no signals for polynorbornene can be detected around δ = 133–134 ppm. Whereas the chloride catalyst **2** mainly produces two sharp signals at δ = 134.9 and 128.5 ppm, which can be assigned to an alternating unit with *trans* stereochemistry (*ttt* triads for both termini), progressively increasing the bulkiness of the sulfonates (**2a**–**2d**) increases the amount of *cis* double bonds up to 51%. We explain this by the mechanism depicted in Scheme 2. The substituents marked with green on the phosphorus atom control the chemoselectivity by discriminating cyclic monomers by their ring strain, as has been

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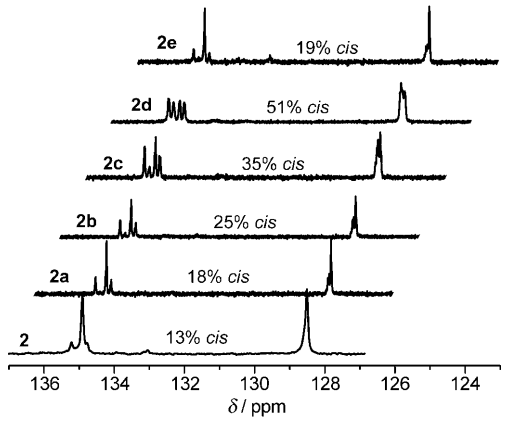
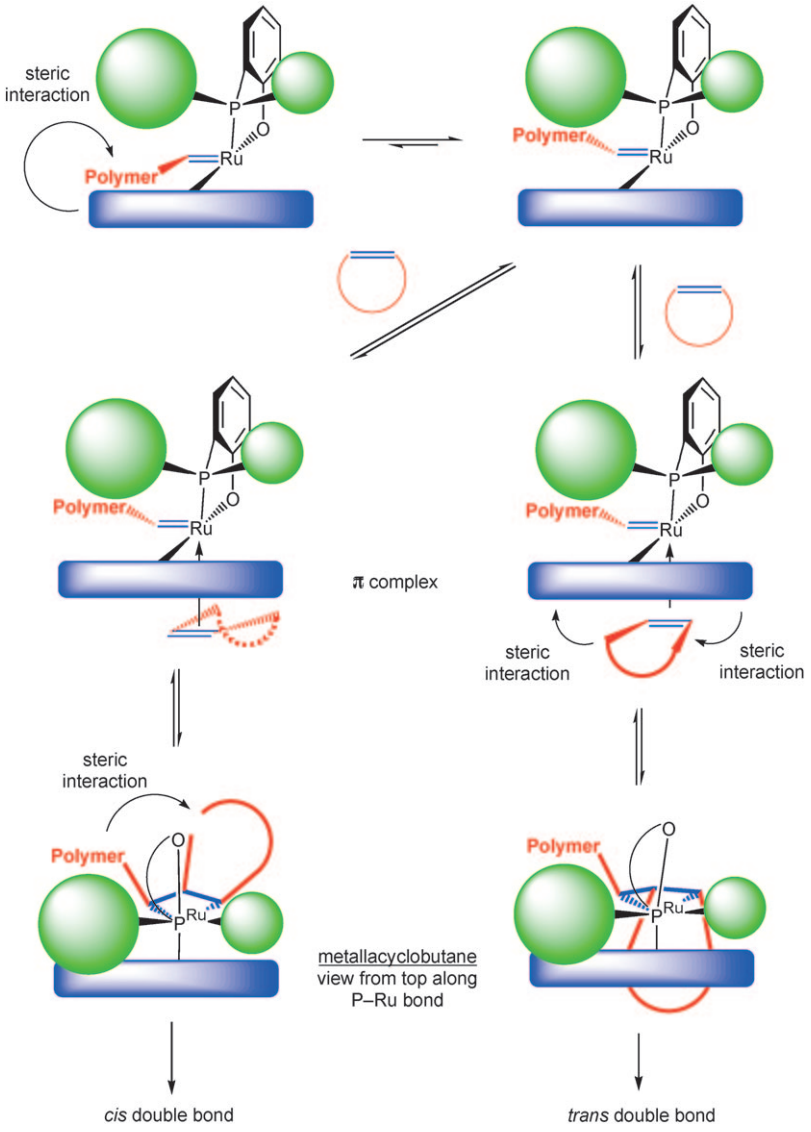


Figure 1. ^{13}C NMR spectra showing the alternating copolymerization of norbornene and cyclooctene in CH_2Cl_2 with increasing *cis* content from bottom to top using asymmetric catalysts **2**–**2d** prepared in situ and low selective catalyst **2e**. (See ^1H NMR spectra in Figures S8 and S14 in the Supporting Information.)

shown previously.[1] The introduction of a bulky sulfonate (marked with blue), on the one hand, forces the propagating polymer chain to turn away from it. On the other hand, π complexation of the olefin to the metal center *trans* to the phosphine ligand and subsequent formation of a metallacyclobutane will happen in such a way as to obtain a compromise between a) the steric repulsion of the cycloolefin and the sulfonate and b) the steric interaction between the all-*cis* substituents in the metallacyclobutane structure. Whether the former or latter interaction is stronger will determine the stereochemical outcome. According to that mechanistic picture, we believe that, in first generation Grubbs systems, chemoselectivity is controlled by changing substituents in the plane containing the carbene, the ruthenium atom, and the phosphorus center, which during the catalytic cycle, also contains the metallacyclobutane, whereas the *E*/*Z* ratio is influenced by substituents in a plane perpendicular to the first one. To test the orthogonality of the *E*/*Z* control from the alternation, symmetric variants **3**–**3c** of the catalyst system were used for homopolymerization of norbornene; in these cases a similar trend was observed with slightly less than 50% *cis* double bonds produced with the most Z-selective catalyst in this series, **3c**, (see Figure S9 in the Supporting Information).

The situation, however, gets more complicated if one tries the polymerizations with analytically pure catalysts or even bulkier sulfonates (**2e**). Detailed synthetic procedures and NMR spectra are given in the Supporting Information. Isolated **2a** yields the same polymer as **2a** prepared in situ. Polymerizations with pure **2d**, however, show a decrease in *Z* selectivity from 51 to 36%, which is still better than with catalyst **2** or **2a** (see Figures S11 and S12 in the Supporting Information). The isolation and structural characterization of **2d** clearly shows that a ruthenium sulfonate with the sulfonate group *cis* to the phosphine has been prepared in the in situ synthesis. The crystal structures of complexes are shown for **2d** (Figure 2), **2e** (Figure 3), **2a**, and **2f** (see Figures S1 and S5 in the Supporting Information). Solvent effects suggest an explanation for the difference in *Z* selectivity for the complexes with the bulkiest sulfonates. If one changes the solvent from CH_2Cl_2 to hexane, in situ prepared **2e** shows an increase in *Z* selectivity from 19 to 42% (see Figure S14 in the Supporting Information), whereas a slight decrease is observed for in situ prepared **2d** (51 to 42%; see Figure S13 in the Supporting Information). In the latter case this might be due to a change in transition-state energies, whereas with **2e** dissociation of the sulfonate ligand most likely happens to a greater extent in the more polar solvent. Furthermore, the



Scheme 2. Mechanistic explanation of the stereochemistry of double bonds.

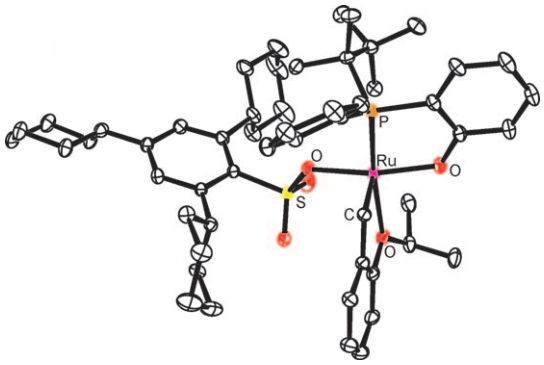


Figure 2. Crystal structure of complex **2d** (ORTEP plot, 20% probability ellipsoids). Crystal structures for complexes **2a** and **2f** are given in the Supporting Information.

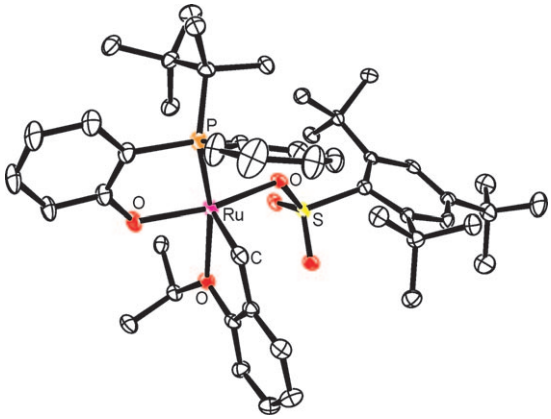


Figure 3. Crystal structure of complex **2e** (ORTEP plot, 20% probability ellipsoids).

crystal structure of **2e** shows a distinct elongation of the Ru–O_3SAr bond versus that in **2d** [2.141(4) Å versus 2.076(2) Å]. The great steric bulk of the *ortho-tert*-butyl groups in **2e** results in the sulfur atom also being twisted out of the aromatic plane.

Another indication for a weaker Ru–O_3SAr bond comes from comparing the chemical shifts (CH_2Cl_2) of the carbene proton (see Table S3 in the Supporting Information). Whereas the chloride catalyst **2** displays a doublet at $\delta =$ 15.65 ppm, the corresponding signals are shifted downfield for **2a** to $\delta = 16.29$ ppm and even further for **2b** ($\delta =$ 16.44 ppm), **2c** ($\delta = 16.54$ ppm), and **2d** ($\delta = 16.55$ ppm). One would expect that a larger electron donation by larger aliphatic groups on the sulfonate would result in an upfield shift of this proton, but exactly the opposite is observed. This finding may be explained by a looser binding of the sulfonate ligand, which as a consequence makes the ruthenium center more electropositive. Only if one compares the chemical shift of **2a** ($\delta = 16.29$ ppm) versus **2f** ($\delta = 16.34$ ppm) can one see that the more electron rich tosylate produces an upfield shift compared to the benzenesulfonate because the substitution in the *para* position leads to no increased steric interaction to counteract the electronic (inductive) effect. In general, one probably has to consider both effects, since there is a decrease in the chemical shift to $\delta = 16.43$ ppm for the even more bulky and more electron-donating **2e**. A similar trend is given for the chemical shifts of the carbene carbon atom: **2** ($\delta =$ 284.58 ppm), **2a** ($\delta = 295.31$ ppm), **2b** ($\delta = 296.17$ ppm), **2c** ($\delta = 297.01$ ppm), **2d** (297.00 ppm), **2e** ($\delta = 297.12$ ppm), and **2f** ($\delta = 295.69$ ppm). One may therefore hypothesize, that sulfonate dissociation begins to spoil the *Z* selectivity with **2d**, which is suppressed when there is an excess of the sulfonate salt in the in situ experiment. An experimental test of the conjecture was done by adding 0.15 equivalents of silver sulfonate **4d** to isolated complex **2d**, which pushes the *Z* selectivity in the polymerization back up to 51%. Nevertheless, the size of sulfonate **4d** is most probably close to the limit, where dissociation can still be controlled, since we observe low selectivity with the even bulkier **4e** in CH_2Cl_2.

Several examples of chemoselective metathesis have been reported in the literature. Stereogenic-at-metal ruthenium complexes bearing enantiomerically pure bidentate N-heterocyclic carbene/binaphthol ligands have been used by Hoveyda et al. to effectively catalyze the ring-opening cross-metathesis (ROCM) of norbornene derivatives with two equivalents of styrene.[5,6] Since chiral molybdenum catalysts would readily give polymers under these conditions, effects other than pure ring strain[3] have to account for this high chemoselectivity. Since this catalyst is stereogenic at the ruthenium center, one would expect, based on our previous mechanistic picture,[1] two different diastereomeric carbenes to take part in the catalytic cycle. If the highly strained norbornene would react faster than styrene with both sides, a ROMP polymer would be the expected result. It seems, however, that the release of ring strain is only needed to effect a change in the carbene's position to the energetically disfavored side. Once there, the norbornene unit on the carbene provides too much steric crowding so that only the smaller styrene can react.

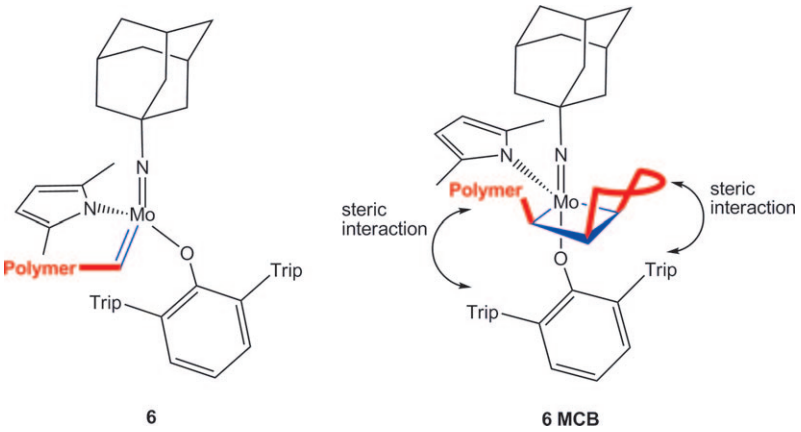
Similar, achiral catalysts have also been used to introduce chemoselectivity into polymers, taking advantage of a suitable set of monomers which have a higher tendency to form alternating linkages by kinetic control rather than undergoing homopolymerization based on thermodynamic aspects (strain release).[7–11] An early example is the alternating copolymerization of cyclopentene and norbornene using $RuCl_3$ in the presence of phenol as a co-catalyst or solvent.[8] Hydrogen-bonded solvent cages around the active site were proposed as an explanation, which prevents the more reactive but bulkier norbornene from performing two consecutive metathesis steps. An example of this extreme case in chemoselective copolymerization, where the rates of homopolymerization for both monomers tend to zero, is shown for the alternating copolymerization of the enantiomers of 1-methylnorbornene catalyzed by $ReCl_5$.[10] Blechert, Buchmeiser, and co-workers recently reported the synthesis of a highly alternating norbornene/cyclooctene copolymer with a *cis* content of approximately 50%, comparable to what we obtained with catalyst **2d**, using Grubbs-type initiators containing an unsymmetrical, chiral N-heterocyclic carbene ligand.[12] The high tendency for alternation was explained by an enhanced cyclooctene insertion rate into a norbornene-initiator-derived terminus and, vice versa, an enhanced norbornene insertion

rate into a cyclooctene-initiator-derived terminus. In other words they speculated that the norbornene-initiator-derived terminus makes the catalyst more crowded, thereby providing steric energy for a faster cyclooctene insertion, but too bulky, with the result that it slows down consecutive norbornene incorporation. No explanation for the stereochemistry was given. Furthermore they recently reported for the same reaction high selectivity towards alternation and even higher *Z* selectivity (ca. 60%) by applying complexes containing nonchiral unsymmetrical N-heterocyclic carbene ligands.[13]

More than a decade ago, Grubbs and co-workers studied the influence of ligands in first generation ruthenium systems: "*Phosphines (donor), which are larger and more electron donating, and likewise halogens (acceptor), which are smaller and more electron withdrawing, lead to more active catalysts.*"[14] For this reason, we chose electron-withdrawing sulfonates as substitutes for chloride. It is at this point worth noticing that a Hoveyda–Grubbs type ruthenium complex with two trifluoromethanesulfonate ligands and a mixed anionic complex with one sulfonate and one chloride ligand have already been shown to be active catalysts.[15]

Inspired by mechanistic work by Eisenstein and co-workers,[16,17] the research groups of Schrock and Hoveyda recently published stereoselective molybdenum imido catalysts[18,19] with high *Z* selectivity that are very effective in enantioselective ring-opening/cross-metathesis[20] and also ROMP of norbornene derivatives (**6**).[21] Apparently there seem to be similarities between molybdenum and ruthenium systems, even though the molybdenum complexes (for example **6**) have a tetrahedral structure (Scheme 3). Theoretical investigations[16,17] on molybdenum, tungsten, and rhenium systems suggest that the more active catalysts require an acceptor ligand (an alkoxide) in combination with a donor ligand (a pyrrolide) to lower the energetic barrier that is governed by geometrical distortion during formation of the olefin π complex. The most stable π complexes are formed by a *trans* approach of the olefin with respect to the donor ligand. The subsequent cycloaddition produces the metallacyclobutane *trans* to the donor (**6 MCB**). The high *Z* selectivity reached with stereogenic-at-molybdenum–imido complexes arises from the combination of a big phenoxide acceptor ligand (in the catalyst *cis* to the metallacyclobutane) with a small (close to the metal) adamantylimido ligand, forcing the sterically favored *syn*-alkylidene to react with an olefin to give an all-*cis* metallacyclobutane (Scheme 3). Similar, the bulky sulfonates in the complexes in the present report would be *cis* to the metallacycle (Scheme 2).

Another study in which the stereochemistry of alkene metathesis was investigated was carried out about 30 years ago by Casey et al., who studied the degenerate metathesis of terminal alkenes,[22,23] and at the same time Basset and co-workers speculated that large ligands in the metal sphere may direct the approach of the incoming olefin and thus influence the stereochemistry.[24] Recently Verpoort and co-workers reported a remarkable steric impact on the *E/Z* selectivity in the cross-metathesis of allylbenzene and acrylonitrile.[25] For a more detailed discussion of these last three examples, see the Supporting Information.



Scheme 3. Stereogenic-at-metal molybdenum complex **6** published by Schrock and Hoveyda for the *Z*-selective polymerization of norbornene derivatives and proposed metallacyclobutane structure **6 MCB** with all-*cis* substituents.

In conclusion, we have shown that in first generation Grubbs systems chemoselectivity is controlled by changing the substituents in the plane containing the carbene, the ruthenium atom, and the phosphorus atom, whereas the *E/Z* ratio is influenced by substitution in a perpendicular plane with respect to the first one. This puts a bulky anionic substituent *cis* to the metallacycle. Current work is based on designing further ligands that fulfil the above-mentioned requirements to extend the applications to a broad range of metathesis tasks.

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