# Relevance of *cis*- and *trans*-dichloride Ru intermediates in Grubbs-II olefin metathesis catalysis ($H_2IMesCl_2Ru{=}CHR$)†

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**Using density functional theory with the B3LYP and M06 functionals, we show conclusively that the $(H_2IMes)(Cl)_2Ru$ olefin metathesis mechanism is bottom-bound with the chlorides remaining *trans* throughout the reaction, thus attempts to effect diastereo- and enantioselectivity should focus on manipulations that maintain the *trans*-dichloro Ru geometry.**

Olefin metathesis[1] has become a powerful ubiquitous reaction for forming carbon–carbon double bonds. Improved ruthenium olefin metathesis catalysts exhibiting higher initiation rates,[2] differential monomer reactivity,[3] enantioselectivity,[4] and improved thermal stability[5] have been reported recently.

A long-standing controversy[6] has been whether the mechanism involves an isomerization from the initial *trans*-dichloro Ru (Fig. 1b) to a *cis*-dichloro Ru geometry (Fig. 1c) leading to a side-on mechanism. This mechanism was proposed by Grubbs[7] to rationalize the observed reactivity and selectivity, but without direct experimental evidence. We report here first principles studies showing conclusively that the mechanism is bottom-bound, with the chlorides remaining *trans* throughout the reaction, which explains available experimental evidence. Thus attempts to effect stereo- and enantioselectivity should focus on manipulations that maintain the *trans*-dichloro Ru geometry.

It is generally believed that the mechanism[8] of Ru catalyzed olefin metathesis involves a symmetric process in which a Ru carbene coordinated with a substrate olefin (square pyramidal) rearranges *via* a pseudorotation to a metallacyclobutane (trigonal bipyramidal) which then rearranges productively to form a coordinated product olefin and a new Ru carbene (square pyramidal). The structures for the various intermediates have been established from low temperature $^1$H-NMR studies,[9] X-ray crystallography structural data of isolated stable intermediates,[10] and theoretical investigations.[11]

Based on their density functional theory (DFT) studies (BP86) on the relative energies of the bottom- and side-bound pathways, Cavallo and Correa concluded[11b] that the preferred reaction pathway is a delicate balance between electronic, steric, and solvent effects.[12] This has led to several reports considering the side-bound pathway as highly significant, if not the most likely operative pathway.[3,6] We consider that this lack of a clear understanding of the catalytic pathway (side *vs.* bottom) is hindering the development of selective metathesis catalysts. To provide a basis for assessing the side- and bottom-bound metathesis pathways, we applied DFT methods to investigate the relative energies and the expected $E:Z$ olefin product ratio of the *cis*- and *trans*-dichloro Ru pathways for the metathesis of *E*- and *Z*-2-butene with the Grubbs-II benzylidene catalyst (Fig. 1a).

Truhlar and Zhao reported[13] that medium-range non-covalent interactions (dispersion forces) can have a dramatic effect on the ruthenium tricyclohexylphosphine ($PCy_3$) bond dissociation energies for both the first and second generation Grubbs catalysts. The M06-class[14] of density functionals extend DFT to contain a number of new parameters which were fitted against several databases of experimental data. The M06 functional is a new hybrid *meta*-GGA exchange–correlation functional that leads to impressive accuracy for a very large validation set of systems, including van der Waals dimers, reactions, and transition metal complexes.[15] Chen *et al.* recently validated[8a,16] M06-L predicted values with gas-phase collision-induced phosphine dissociation (CID) experiments by tandem ESI-MS on Ru and Au complexes. We have shown that the B3LYP flavor of DFT with the LACV3P++** basis set properly describes the energies of intermediates relevant to olefin metathesis.[17]

Here we apply both the M06 and B3LYP functionals to compare the *cis*- and *trans*-dichloro Ru metathesis mechanism pathways. Jaguar 7.0 (release 207) software[18] was used for all calculations. We performed geometry optimizations in the gas phase at the B3LYP/LACVP** level. The B3LYP analytic Hessian was calculated to obtain the vibrational frequencies,

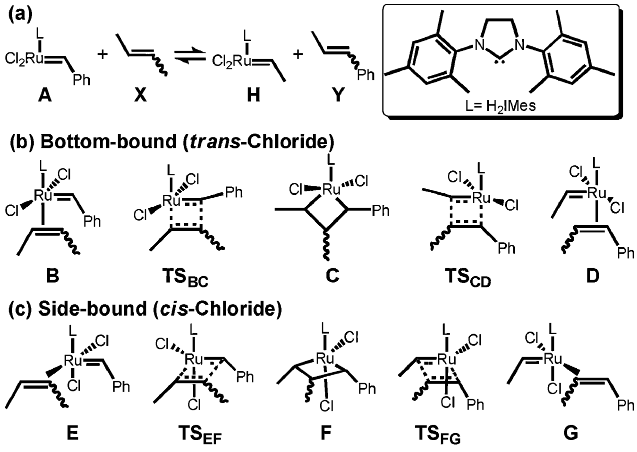

**Fig. 1** (a) Metathesis reaction of 2-butene with Grubbs-II benzylidene catalyst to produce β-methyl styrene. Proposed geometries for the (b) bottom-bound and (c) side-bound metathesis pathways.

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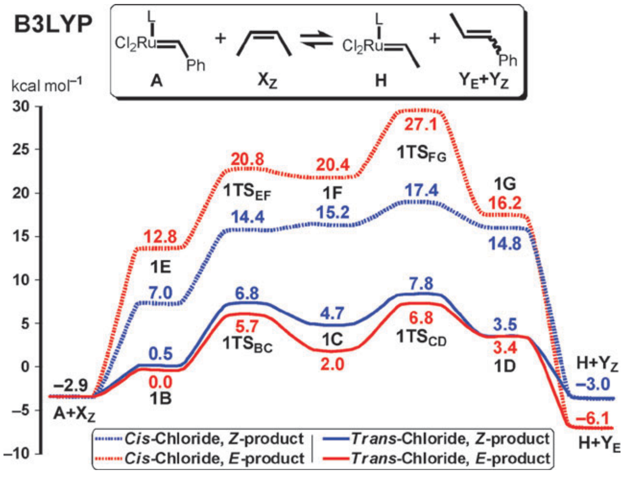

**Fig. 2** B3LYP computed energy profile ($\Delta H$ in $CH_2Cl_2$ at 298 K in kcal mol$^{-1}$) for the bottom- and side-bound metathesis pathways for *Z*-2-butene with Grubbs-II benzylidene catalyst.

which in turn were used to obtain the zero point and thermodynamic corrections at 298 K. Single point energies were computed with the B3LYP and M06 functionals with LACV3P++**(2f) for Ru and 6-311++G** basis sets[19] for all other atoms. Solvent corrections for $CH_2Cl_2$ are based on single point self-consistent Poisson–Boltzmann continuum solvation calculations (using $\varepsilon = 8.93$ and $R_0 = 2.33$ Å) using the PBF module in Jaguar.

Fig. 2 shows the B3LYP computed $\Delta H$ profile (kcal mol$^{-1}$, 298 K in $CH_2Cl_2$) for the side-bound (dotted line) and bottom-bound (solid line) reaction for $(H_2IMes)(Cl)_2Ru{=}CHPh$ (Grubbs-II) metathesis catalyst with *Z*-2-butene. The coordination of *Z*-2-butene to the 14-electron activated species **A** is endothermic by 2.9 (*E*) and 3.4 (*Z*) kcal mol$^{-1}$ for the bottom-bound pathway, while it is 15.7 (*E*) and 9.9 (*Z*) kcal mol$^{-1}$ for the side-bound geometry. The olefin coordinated structure (**1B** and **1E**) leads to the metallacyclobutane (**1C** and **1F**), followed by productive rupture of the ruthenacycle *via* transition states $\mathbf{1TS_{CD}}$ and $\mathbf{1TS_{FG}}$ leading to structures where the product (*E*- or *Z*-β-methyl styrene) is coordinated (**1D** and **1G**).

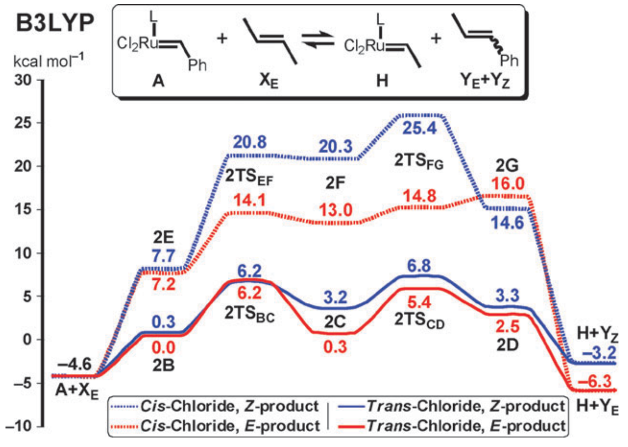

**Fig. 3** B3LYP computed energy profile ($\Delta H$ in $CH_2Cl_2$ at 298 K in kcal mol$^{-1}$) for the bottom- and side-bound metathesis pathways for *E*-2-butene with Grubbs-II benzylidene catalyst.

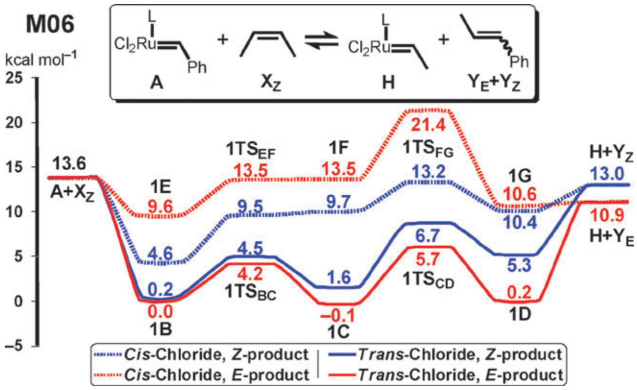

**Fig. 4** M06 computed energy profile ($\Delta H$ in $CH_2Cl_2$ at 298 K in kcal mol$^{-1}$) for the bottom- and side-bound metathesis pathways for *Z*-2-butene with Grubbs-II benzylidene catalyst.

Interestingly, the formation of the *Z* olefin product *via* the side-bound pathway (Fig. 2. blue dotted line), is ~10 kcal mol$^{-1}$ lower in energy ($\mathbf{1TS_{FG}}$) than that for the *E* olefin product. This suggests that if the side-bound pathway could be made operative, the stereochemistry would be retained, not consistent with experimental observations.[20] In contrast, the favored bottom-bound pathway shows a barrier of 9.7 and 10.7 kcal mol$^{-1}$ for the formation of *E* and *Z* olefin products respectively. Given the low barriers calculated, we expect the *E* : *Z* ratio to be dominated by the thermodynamic difference of 3.1 kcal mol$^{-1}$ corresponding to an *E*:*Z* ratio of 146 : 1 at ~40 °C, which agrees with the experimental *E*:*Z* ratio of >20 : 1 ($^1$H-NMR detection limit).[21]

Fig. 3 shows the B3LYP $\Delta H$ profile (kcal mol$^{-1}$, 298 K in $CH_2Cl_2$) for the analogous metathesis reaction with *E*-2-butene for which an increased rate of formation of the *E* product is predicted by the bottom-bound pathway. However, the side-bound pathway lies 9.8 and 18.6 kcal mol$^{-1}$ ($\mathbf{2TS_{BC}}$ *vs.* **2G** and $\mathbf{2TS_{CD}}$ *vs.* $\mathbf{2TS_{FG}}$) higher in energy than the bottom-bound pathway for the *E* and *Z* product pathways respectively.

The *cis*-dichloro pathway lies above the *trans*-dichloro pathway by 10.0 and 9.2 kcal mol$^{-1}$ for the metathesis with *Z*- and *E*-2-butene respectively in $CH_2Cl_2$ for the production of any isomer of β-methyl styrene. This, in addition to the

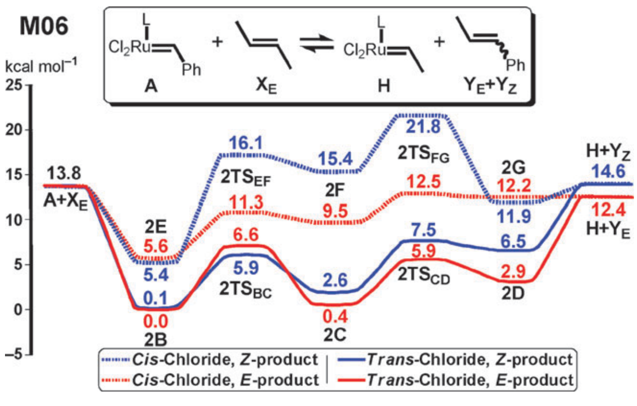

**Fig. 5** M06 computed energy profile ($\Delta H$ in $CH_2Cl_2$ at 298 K in kcal mol$^{-1}$) for the bottom- and side-bound metathesis pathways for *E*-2-butene with Grubbs-II benzylidene catalyst.

predicted inconsistency in the stereoisomer ratio for the side-on pathway, indicates that *B3LYP predicts that the* trans-*dichloro Ru mechanism is the only operating pathway*.

We also performed single point energy calculations with the M06 functional using the same LACV3P++**(2f) basis set (Fig. 4 and 5). M06 agrees with B3LYP that the side-on process is substantially higher than the bottom-bound (on average M06 puts the rate limiting *cis*-chloride transition states 10.7 kcal mol$^{-1}$ more unfavorable than the *trans*-chloride transition states). In addition, M06 also predicts that if the side-bound pathway were operative, the rate of production of *Z* olefins would be much faster than that of *E* olefins when using *Z*-2-butene as substrate and the opposite when using *E*-2-butene.

The most notable difference between the M06 and B3LYP calculated potential energy surfaces is that M06 predicts that the binding for *Z*- and *E*-2-butene to Ru active species (**A**) is exothermic by 13.6 and 13.8 kcal mol$^{-1}$ while B3LYP finds this association to be endothermic by 2.9 and 4.6 kcal mol$^{-1}$, respectively. Chen *et al.* estimated[8a] gas phase ethylene and norbornene coordination energies by CID to a similar Ru complex and found them to be highly exothermic ($\sim$18 kcal mol$^{-1}$), thus we believe that the attractive non-covalent interactions described by the M06 functional are essential in the prediction of similar processes in transition metal complexes. However, we find that M06 and B3LYP are in relatively close agreement for the description of the metathesis process that does not involve the coordination or de-coordination of olefin. This is expected since B3LYP has been shown comprehensively to produce good descriptions of reaction profiles for transition metal complexes. However, B3LYP underestimates the coordination energy as a consequence of the lack of medium-range attractive interactions.

An upper bound for the energy of the rate-determining step can be estimated from initiation experiments performed[2] by Grubbs using UV-Vis and $^{31}$P-NMR spectroscopies.‡ Our barriers for both *E* and *Z* products are $\sim$10 kcal mol$^{-1}$ which is consistent with experimental upper bound from UV-Vis spectroscopy of $\sim$15 kcal mol$^{-1}$ and the upper bound of 18.8 kcal mol$^{-1}$ from $^{31}$P-NMR spectroscopy of a similar metathesis reaction.

We consider that two factors play an important role in making the *cis*-chloride pathway much worse than the *trans*-chloride. The electronic factor can be assessed by examining the barrier for the *E* metathesis with *E*-2-butene which indicates that the side-on pathway is 10.0 kcal mol$^{-1}$ with B3LYP but only 5.9 kcal mol$^{-1}$ with M06 worse than bottom-bound. In addition to electronic effects, the *Z* process imposes steric penalties for the side-on process which makes it an additional 10 kcal mol$^{-1}$ with B3LYP and 8.4 kcal mol$^{-1}$ with M06 higher than the *E* process. Our results show that the rates for the metathesis of *E*- or *Z*-2-butene *via* the *cis*-chloride pathway would be infinitesimal compared to the dominant *trans*-chloride pathway. However, if there were a way to prevent the bottom-bound pathway and stabilize the *cis*-dichloro geometry, then the side-bound could lead to retention of the diastereochemistry of the substrate olefin.

The popular B3LYP functional predicts endothermic olefin binding energies, while the new M06 functional predicts highly exothermic associations (consistent with experiment) for *E*- and *Z*-2-butene as a consequence of attractive medium-range interactions. We show that the bottom-bound pathway (through the *trans*-dichloro Ru geometry) is the only operative pathway in Grubbs-II metathesis catalysis. Both the computed barriers and the predicted *E*:*Z* olefin product ratio are consistent with experiment only for the bottom-bound pathway. Based on our results, we suggest that catalyst design should focus on *trans*-Ru dichloro or bottom-bound structures.

## Notes and references

‡ The authors estimate a minimum rate of 4 s$^{-1}$ at 5 °C which leads to $\sim$15 kcal mol$^{-1}$ as an upper limit for the energy of the rate determining step of a similar metathesis reaction. See ref. 2.

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