catalysts

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Review

On the Structure of Chiral Dirhodium(II) Carboxylate Catalysts: Stereoselectivity Relevance and Insights

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Abstract: Modern experiments have offered alternative interpretations on the symmetry of chiral dirhodium(II) carboxylate complexes and its relationship to their level of enantioselectivity. So, this contribution is to provide an insight on how the knowledge around the structure of these catalysts has evolved with a particular emphasis on the impact of this knowledge on enantioselectivity prediction and catalyst design.

Keywords: dirhodium(II) complexes; asymmetric synthesis; chiral catalysis; catalyst design; metal-carbene chemistry; symmetry

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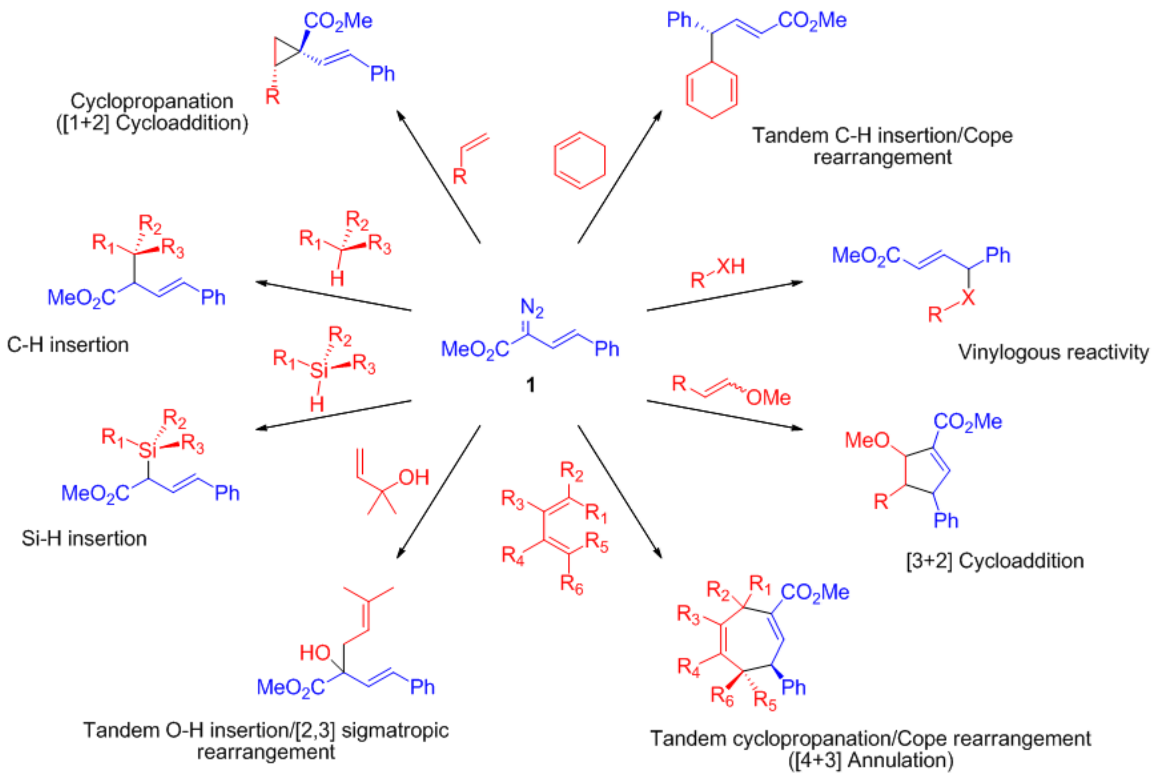
1. Introduction

Chiral dirhodium(II) paddlewheel complexes are among the most attractive catalysts that found a widespread application in the fields of metal-nitrene and metal-carbene transformations [1–15]. This immense interest originates from their exceptional ability to effectively catalyze a broad spectrum of reactions with high levels of chemo-, regio- and stereo-selectivity. These transformations involve aziridinations [16–18], C-H insertions [7,19,20], ylide transformations [21–25], Lewis acid-promoted reactions [21,26–30], cross-coupling reactions [31], cyclopropanation and cyclopropenation reactions [32–35]. In fact, they have proven their potential, particularly, in the field of asymmetric synthesis. As an example to showcase the utility of these complexes, methyl styryldiazoacetate (1), in the presence of a suitable substrate and a dirhodium(II) catalyst, can undergo a range of chemical transformations including cyclopropanation [36–38], C-H insertion [39,40], Si-H insertion [41], tandem cyclopropanation/Cope rearrangement [42,43], tandem O-H insertion/[2,3] sigmatropic rearrangement [44], vinylogous reactivity [45,46], tandem C-H insertion/Cope rearrangement [47,48], or [3+2] cycloaddition [49] generating a variety of useful synthetic entities in excellent diastereo- and enantioselectivity (Scheme 1).

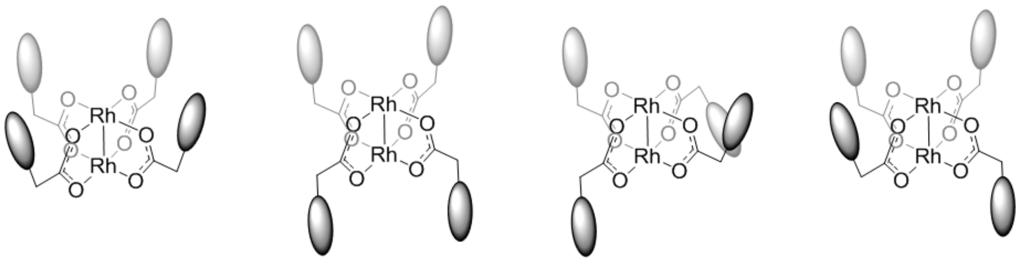
Chiral dirhodium(II) carboxylate complexes constitute a very important class of dirhodium(II) catalysts. Their structure consists of two rhodium atoms connected together through a unique dirhodium bridge. This dirhodium axes is connected to four chiral electron withdrawing carboxylate ligands and they have two vacant axial positions available for carbene binding [50,51]. Although several highly enantioselective dirhodium(II) carboxylate catalysts have been reported to date [2,52] and their application spectrum has expanded dramatically, limited evidence is known on how chirality is tailored at the active center of these complexes by its four chiral carboxylate ligands. As a consequence, this article is providing an insight on how the knowledge around the structure of dirhodium(II) carboxylate complexes has evolved. This is with a particular emphasis on the impact of this knowledge on enantioselectivity prediction and catalyst design. To the best of our knowledge, this topic was last reviewed by Hansen and Davies in 2008 [53] and since then subsequent investigations have offered alternative interpretations on the symmetry of chiral dirhodium(II) carboxylate complexes and its relationship to their level of enantioselectivity.



Scheme 1. Dirhodium(II)-mediated chemistry of methyl styryldiazoacetate (1) with different substrates.

2. Ligand Blocking Groups Arrangements

Generally for chiral dirhodium(II) carboxylate complexes, it is agreed that the ligand blocking groups can adapt either an up (*α*) or down (*β*) positions around the catalyst core. It was also assumed that, the ligand's blocking group cannot be situated in the periphery of the dirhodium(II) core as it would bump into the neighboring ligand [36,53]. Thus, by taking into account the *α*- and *β*-arrangements for all four ligands, four possible conformations can be mainly considered: *α*,*α*,*α*,*α* (C_4-symmetry), *α*,*α*,*β*,*β* (C_2-symmetry), *α*,*β*,*α*,*β* (D_2-symmetry) and *α*,*α*,*α*,*β* (C_1-symmetry) (Figure 1) [2,4,36,53,54].

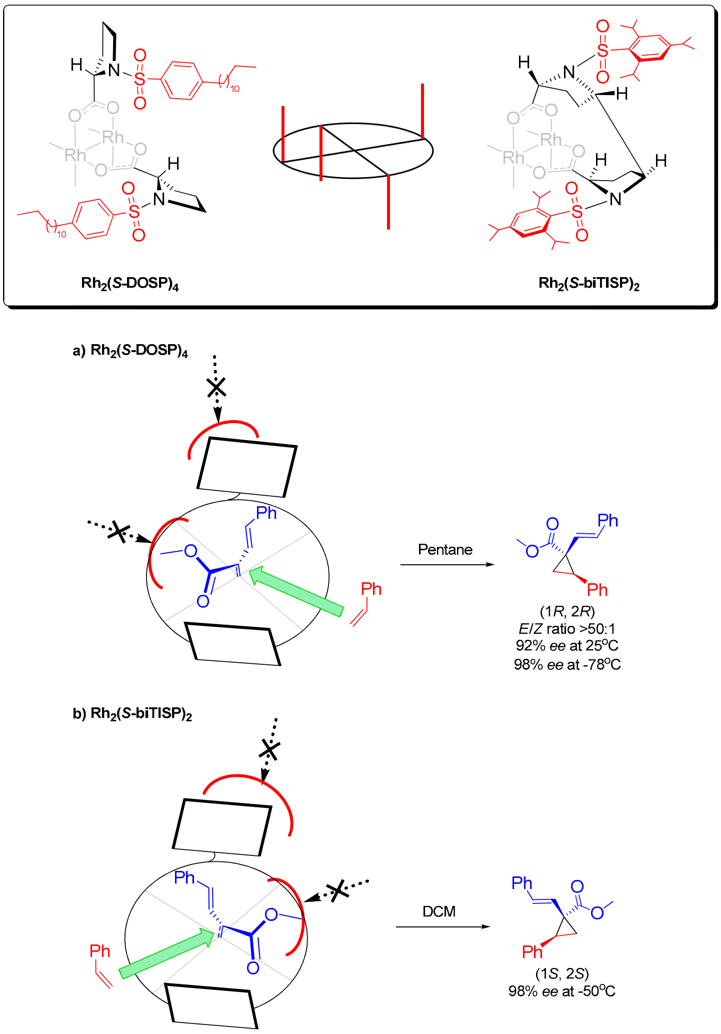


α,α,α,α (C_4-Symmetry) **α,α,β,β (C_2-Symmetry)** **α,β,α,β (D_2-Symmetry)** **α,α,α,β (C_1-Symmetry)**

Figure 1. Main arrangements of ligand's blocking groups around the dirhodium(II) core and their point groups (the sterically blocking groups around the rhodium active sites are depicted as ovals) [2,4,36,53,54].

2.1. *α,β,α,β-Conformation*

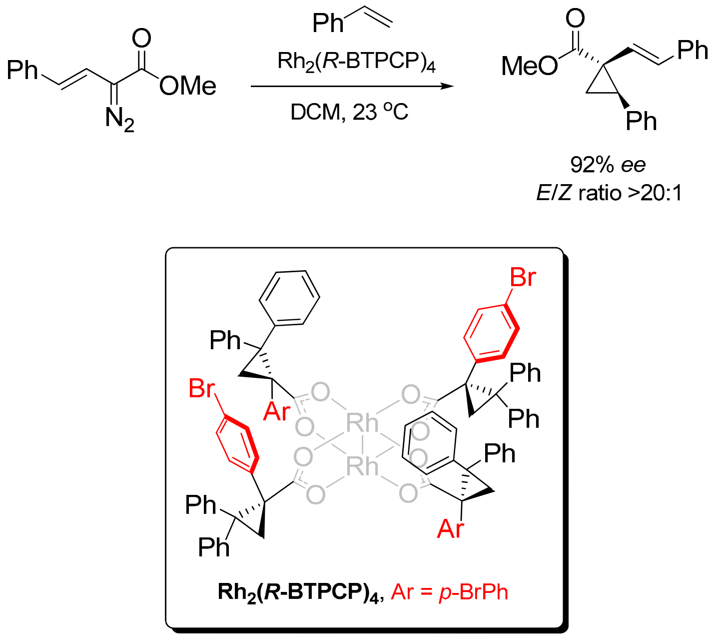
Initially, Hansen and Davies suggested that catalysts having two different carbene-formation sites should not lead to high enantiocontrol [53]. In other words, complexes with *α*,*α*,*β*,*β*- and *α*,*β*,*α*,*β*-arrangements (having C_2- and D_2-symmetry, respectively) are the only effective catalysts in terms of enantioselectivity as they possess two equivalent catalyst faces. While complexes with $\alpha,\alpha,\alpha,\alpha$- and $\alpha,\alpha,\alpha,\beta$-conformations, which have non-equivalent catalyst faces, are likely to induce low or no enantioinduction as their more accessible and kinetically active face is achiral. This previous proposal from Davies et al. originates from their discovery of Rh_2(*S*-DOSP)$_4$ catalyst (Scheme 2) [36], which offered extraordinary enantioselectivity in a wide range of chemical transformations (up to 99% *ee*) [7,13,36,40,42,44,47,48,55–68]. This exceptional enantioselectivity of Rh_2(*S*-DOSP)$_4$ was proposed to originate from a favored $\alpha,\beta,\alpha,\beta$-arrangement of ligands adapted during catalysis. The arrangement that leads to a catalyst with two equivalent rhodium active sites and adequate sterically overburden groups that can limit the trajectories approaching the axial carbene ligand (Scheme 2) [7,13,36,53]. For example, low temperature Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of styrene with methyl styryldiazoacetate resulted in the generation of the corresponding cyclopropane product in more than 50:1 E/Z diastereomeric ratio and 98% *ee* (Scheme 2a) [13,69]. A general model was then proposed to explain the observed stereochemical outcome [13,36,68,70]. In this model, Rh_2(*S*-DOSP)$_4$ is assumed to favor the $\alpha,\beta,\alpha,\beta$-conformation during catalysis at which, the *si*-face of the metal-carbene complex is protected by a ligand blocking group. The substrate will approach from the *re*-face to generate the product in the observed absolute configuration (Scheme 2a).



Scheme 2. Structure, D_2-symmetry and facial enantioselectivity in enantioselective cyclopropanation of styrene with methyl styryldiazoacetate of Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-biTISP)$_2$ as proposed by Davies et al. (**a**) Rh_2(*S*-DOSP)$_4$-catalyzed reaction [13,36,69], (**b**) Rh_2(*S*-biTISP)$_2$-catalyzed reaction [13,71].

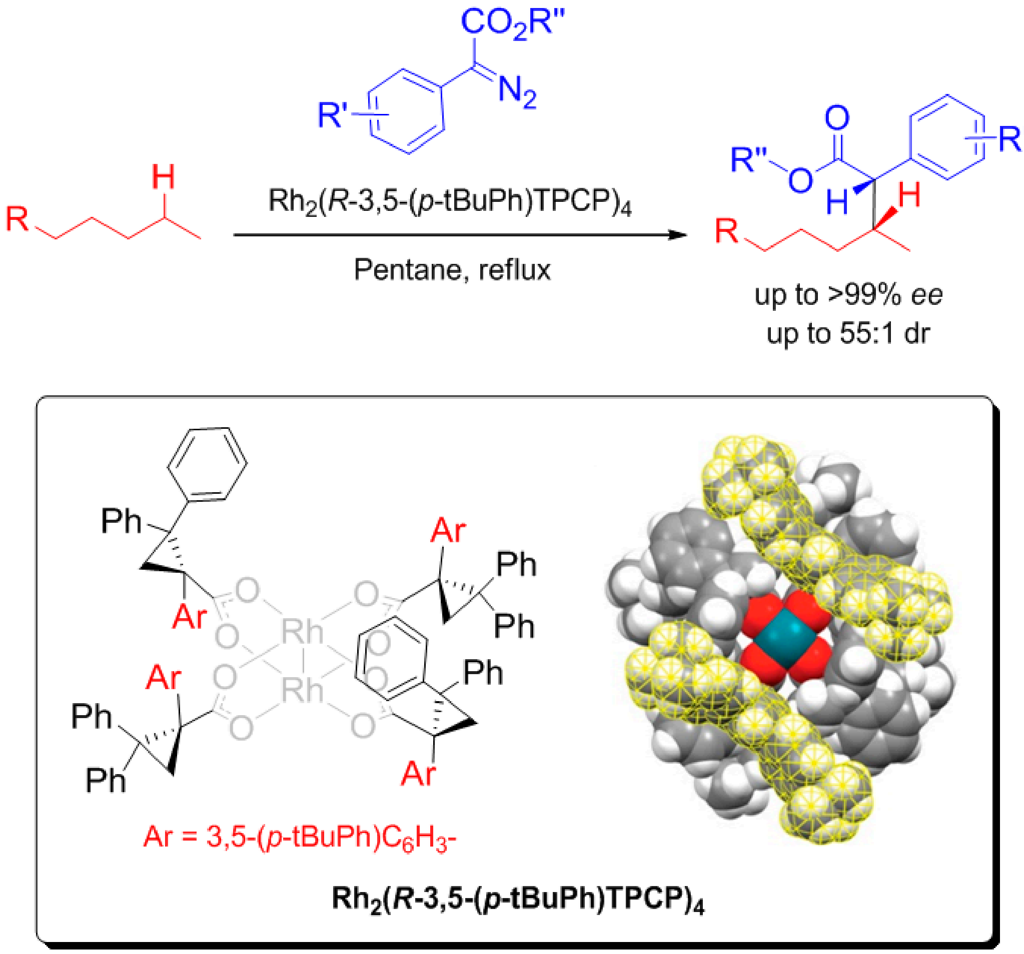
To support the D_2-symmetry hypothesis of Rh_2(*S*-DOSP)$_4$, the authors introduced the second generation prolinate-based complex, Rh_2(*S*-biTISP)$_2$ (Scheme 2) [13,71,72]. As the ligands themselves possess a C_2-symmetry, Rh_2(*S*-biTISP)$_2$ was anticipated to adapt the higher D_2-symmetrical structure. More importantly, the complex was expected to be more rigid at which, the ligands are conformationally locked in the $\alpha,\beta,\alpha,\beta$-arrangement around the catalyst active centers. For this catalyst, not only both faces are equivalent but also all staggered binding orientations of the axial carbene ligands are identical with respect to the approaching substrate [13,53,71]. As expected by the authors, Rh_2(*S*-biTISP)$_2$ demonstrated excellent enantioselectivity in the enantioselective intermolecular cyclopropanation of styrene with methyl styryldiazoacetate leading to the generation of the cyclopropane product in 98% *ee* (Scheme 2b) [13,71]. This result very well supported the proposed concept that the observed enantioselectivity of Rh_2(*S*-DOSP)$_4$ originates from an $\alpha,\beta,\alpha,\beta$-conformation adapted during catalysis. However, the use of Rh_2(*S*-biTISP)$_2$ catalyst preferentially resulted in the generation of the (1*S*,2*S*)-cyclopropane product (Scheme 2b) which was the opposite to that obtained with the Rh_2(*S*-DOSP)$_4$-catalysed reaction (Scheme 2a). The authors returned this difference in asymmetric induction to the different preferred staggered orientation for the carbene binding which causes different channels of the metal-carbene intermediate to be exposed to the approaching alkene [13].

In the same context, Rh_2(*R*-BTPCP)$_4$ was also reported as a catalyst that exhibited high enantioselectivity levels [73–75]. For example, the Rh_2(*R*-BTPCP)$_4$-catalyzed cyclopropanation of styrene with methyl styryldiazoacetate generated the cyclopropane product in 92% *ee* [73]. Based on its X-ray crystal structure, this enantioselectivity was again returned to the $\alpha,\beta,\alpha,\beta$-distribution of ligands around the dirhodium(II) core (Scheme 3) [73].



Scheme 3. Rh_2(*R*-BTPCP)$_4$-catalyzed cyclopropanation of styrene with methyl styryldiazoacetate and the D_2-symmetric structure of Rh_2(*R*-BTPCP)$_4$ according to its X-ray crystal structure [73].

This research was further extended and, very recently, Davies et al. reported its analogue, Rh_2(*R*-3,5-(*p*-*t*BuPh)TPCP)$_4$, as a very successful catalyst in achieving highly regio-, diastereo- and enantio-selective C-H functionalization at the inactivated C2 position of *n*-alkanes and terminally substituted *n*-alkyl compounds (Scheme 4) [52]. Again, X-ray crystallography along with computational studies showed that the catalyst disfavors the existence of two adjacent 3,5-di(*tert*-butylphenyl)phenyl groups on the same face of the catalyst. Hence the preferred orientation of ligands is $\alpha,\beta,\alpha,\beta$ around both catalyst's active sites (Scheme 4) [52].



Scheme 4. Rh_2(R-3,5-di(p-tBuPh)TPCP)$_4$-catalysed C-H functionalization of pentane and substituted *n*-alkanes and the D_2-symmetric structure of the catalyst according to its X-ray crystal structure. The two 3,5-di(p-tBuPh)C_6H_3-groups are highlighted in yellow. (X-ray crystal structure adapted with permission from Macmillan Publishers Ltd.: Liao, K.; Negretti, S.; Musaev, D.G.; Bacsa, J.; Davies, H.M.L. *Nature* **2016**, *533*, 230–234, Copyright 2017).

2.2. *α,α,β,β- and α,α,α,α-Conformations*

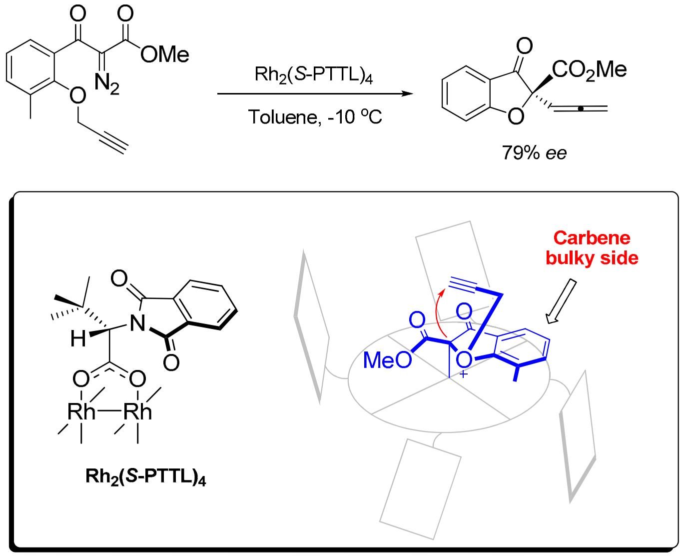
2.2.1. Global Catalyst Symmetry

The previous proposal that only catalysts with D_2- and C_2-symmetric structures are effective in terms of enantiocontrol [53] relied also on Hashimoto's reports for Rh_2(S-PTTL)$_4$. In 1993, Hashimoto, Ikegami and co-workers first reported their famous complex, Rh_2(S-PTTL)$_4$ [76,77], as a catalyst that manifested (along with its variants) high enantioselectivity levels in wide range of organic transformations [2,54,78–84]. For example, in enantioselective [2,3]-sigmatropic rearrangement of the cyclic propargylic oxonium ylide shown in Scheme 5a, Rh_2(S-PTTL)$_4$ provided the best enantioselectivity of 79% *ee* of the corresponding allenic bearing benzofuran-3-one product (Scheme 5a) [85].

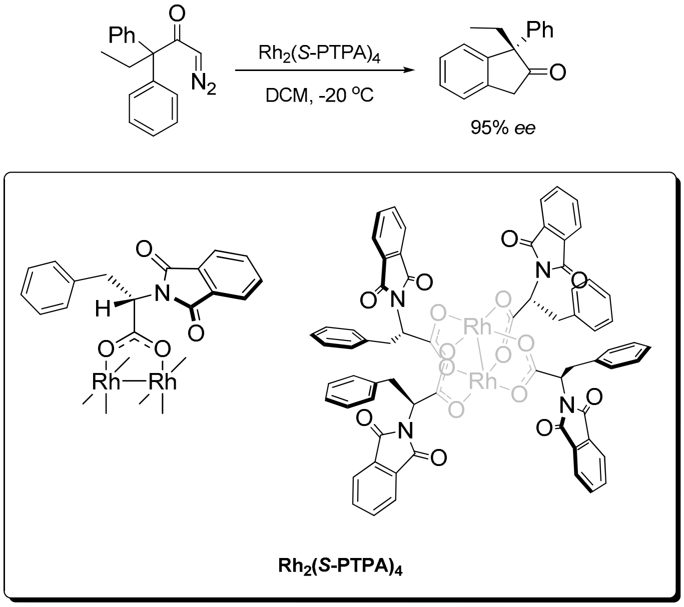
Hashimoto et al. initially proposed that Rh_2(S-PTTL)$_4$ favors the *α,α,β,β*-conformation during catalysis. This assumption was based on the X-ray crystal structure of its analogue, Rh_2(S-PTPA)$_4$, which also showed moderate to good enantioselectivity in some asymmetric transformations [76,79,85,86]. For example, in aromatic C-H insertion of *α*-diazoketones, Rh_2(S-PTPA)$_4$ resulted into the formation of the corresponding 1-alkyl-1-phenyl-2-indanones in up to 95% *ee* (Scheme 5b) [86]. The X-ray crystal structure of Rh_2(*S*-PTPA)$_4$ showed that the catalyst is adapting the *α*,*α*,*β*,*β*-conformation in solid state (Scheme 5b) [76,85–87].

Based on Hashimoto's hypothesis, a general model was proposed to account for the observed enantioselectivity with Rh_2(*S*-PTTL)$_4$ [85,86,88,89]. In this model, it was proposed that Rh_2(*S*-PTTL)$_4$ preferentially adapts the *α*,*α*,*β*,*β*-conformation during catalysis. The carbene orients itself at which, its bulky side is directed away from the catalyst walls (Scheme 5a). The substrate approaches from the *re*-face to generate the product in the observed absolute configuration.

a) Rh_2(*S*-PTTL)$_4$

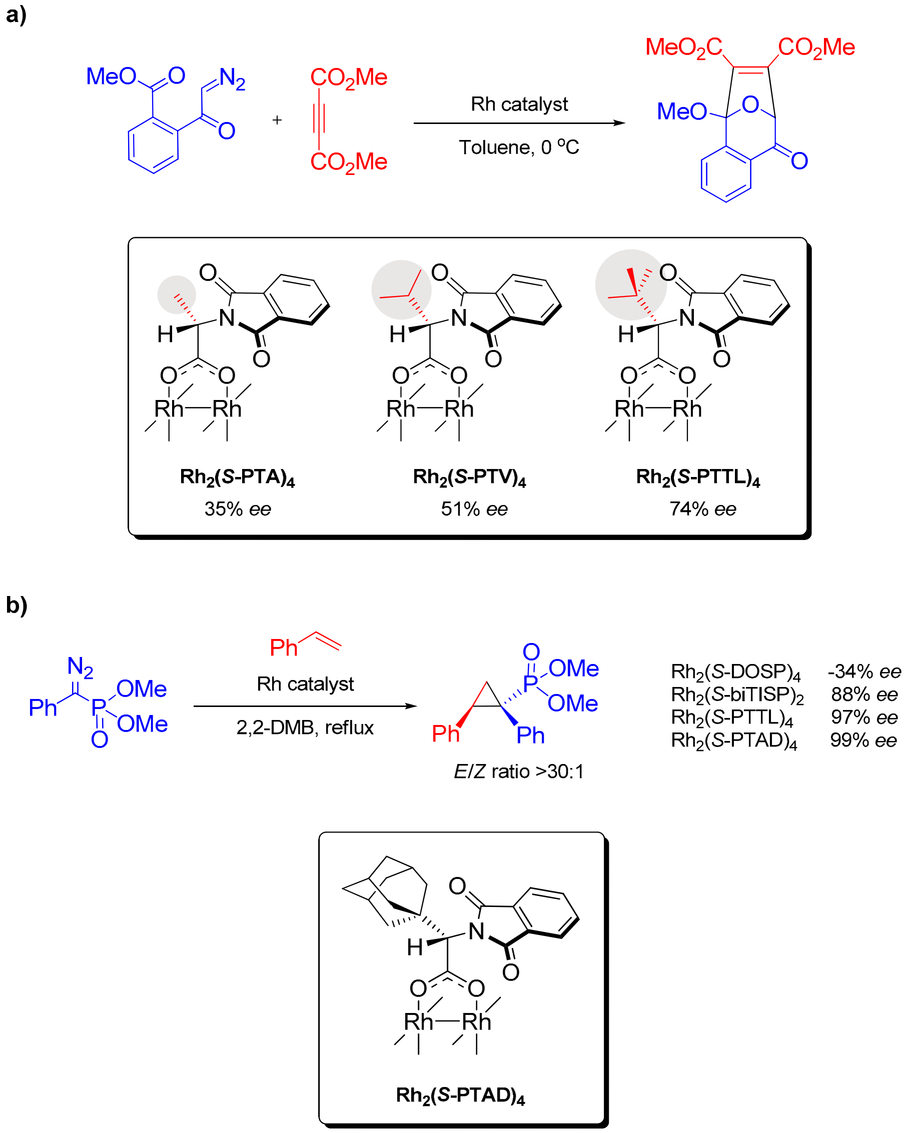


b) Rh_2(*S*-PTPA)$_4$



Scheme 5. (**a**) Rh_2(*S*-PTTL)$_4$-catalyzed enantioselective tandem propargylic oxonium ylide formation/[2,3]-sigmatropic rearrangement (Facial selectivity of the Rh_2(*S*-PTTL)$_4$-stabilized carbene according to the model proposed by Hashimoto et al. [85]); (**b**) Rh_2(*S*-PTPA)$_4$-catalyzed enantioselective aromatic C-H insertion reaction and the C_2-symmetric structure of the catalyst according to its reported X-ray crystal structure [76,85–87].

Later, Davies et al. noticed that, in some reactions, the steric bulk of the ligand affects the enantioselectivity of the catalyst at which the enantioselectivity increased by increasing the steric bulk at the α-carbon of the ligands. For example, in dirhodium(II)-catalyzed enantioselective tandem carbonyl ylide formation/intermolecular 1,3-dipolar cycloaddition of α-diazoketones, the best enantioselectivity was observed when Rh_2(*S*-PTTL)$_4$ was used as a catalyst (74% *ee*), followed by Rh_2(*S*-PTV)$_4$ (51% *ee*) and Rh_2(*S*-PTA)$_4$ (35% *ee*) [90] (Scheme 6a). As a consequence, Davies et al. suggested that the logical way to further develop the Rh_2(*S*-PTTL)$_4$ catalyst is to substitute the *tert*-butyl group connected to the α-carbon with a much bulkier hydrocarbon group. Accordingly, they introduced Rh_2(*S*-PTAD)$_4$ catalyst which is derived from L-adamantylglycine ligands (Scheme 6b) [37]. As expected, this catalyst succeeded to afford enantioselectivity levels superior to Rh_2(*S*-PTTL)$_4$ in different asymmetric transformations [37,88,91–95]. For example, Rh_2(*S*-PTAD)$_4$-catalyzed cyclopropanation of styrene with α-diazobenzylphosphonate resulted into the generation of the corresponding cyclopropylphosphonate product in high levels of enantioselectivity (99% *ee*) compared to Rh_2(*S*-DOSP)$_4$ (34% *ee*), Rh_2(*S*-biTISP)$_2$ (88% *ee*) and Rh_2(*S*-PTTL)$_4$ (97% *ee*) (Scheme 6b) [37].



Scheme 6. (**a**) Dirhodium(II)-catalyzed enantioselective tandem carbonyl ylide formation/intermolecular 1,3-dipolar cycloaddition of α-diazoketones [90]; (**b**) Rh_2(*S*-PTAD)$_4$-catalyzed enantioselective synthesis of dimethyl 1,2-diphenylcyclopropylphosphonate [37].

Up to this point, Hansen and Davies theoretical assumption that only catalysts with $\alpha,\alpha,\beta,\beta$- and $\alpha,\beta,\alpha,\beta$-arrangements results in high enantioselectivity and not the others [53] was very well supported by scientific evidence. Nevertheless in 2009, Fox et al. were able to capture an X-ray crystal structure for Rh_2(*S*-PTTL)$_4$ [78,87]. Surprisingly, the obtained structure revealed that the catalyst is adapting the $\alpha,\alpha,\alpha,\alpha$-conformation in solid state and not the expected $\alpha,\alpha,\beta,\beta$-conformation (Figure 2). Furthermore, the structure showed that the catalyst is having a rectangular chiral cavity (C_2- rather than C_4-symmetry) with only one ethyl acetate axial ligand coordinated to the rhodium atom from the cavity face.

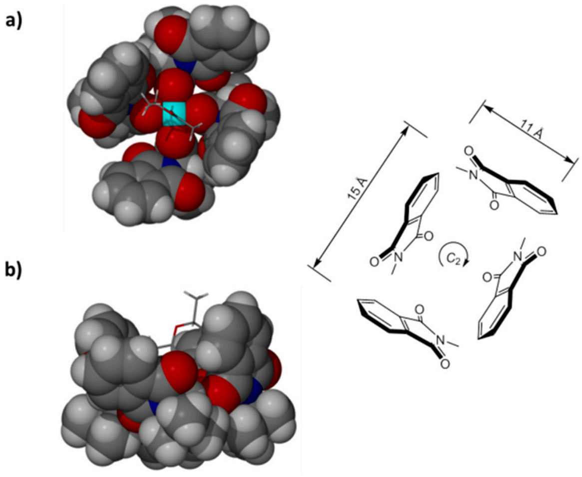
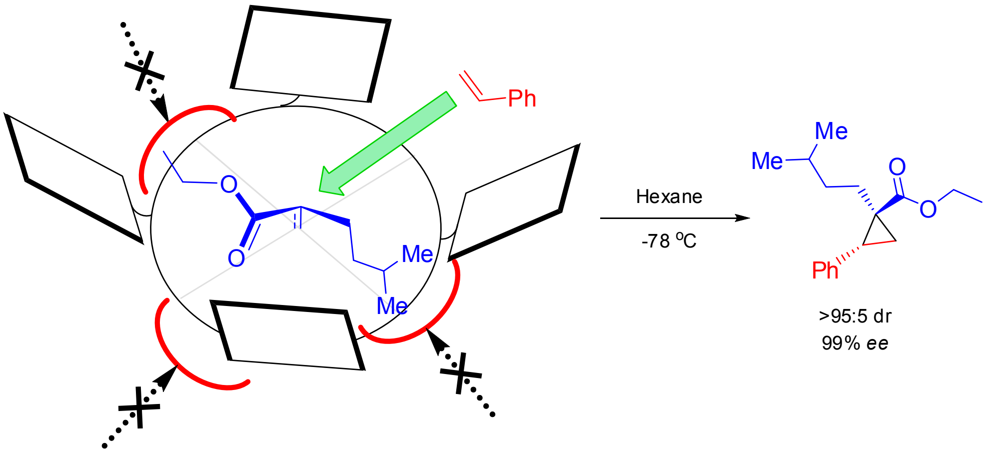


Figure 2. (**a**) Space filling structure of mono(EtOAc) adduct of Rh_2(*S*-PTTL)$_4$ (top view); Schematic illustration of the rectangular binding pocket of Rh_2(*S*-PTTL)$_4$; (**b**) Space filling structure of mono(EtOAc) adduct of Rh_2(*S*-PTTL)$_4$ (side view). (Adapted from Adly, F.G.; Gardiner, M.G.; Ghanem, A. *Chem. Eur. J.* **2016**, *22*, 3447, Copyright 2017, with permission from John Wiley and Sons).

Based on the new information, Fox et al. introduced a new model to account for the enantioselectivity exhibited by Rh_2(*S*-PTTL)$_4$ in enantioselective cyclopropanation of styrene with α-alkyldiazoesters (Scheme 7) [78,87]. In this model, Rh_2(*S*-PTTL)$_4$ was proposed to keep its $\alpha,\alpha,\alpha,\alpha$-conformation during catalysis and the carbene is anticipated to align itself within the wide dimension of the catalyst's rectangular cavity leaving its *si*-face accessible by the substrate. Also according to Fox model, the *tert*-butyl groups are crucial to restrict the reactivity to the chiral cavity face of the catalyst and limit the racemic background reaction.



Scheme 7. Facial selectivity of the Rh_2(*S*-PTTL)$_4$-stabilized carbene according to the model proposed by Fox et al. [78,87].

Fox model was very well supported by the results obtained earlier for $Rh_2(S\text{-PTAD})_4$ by being more enantioselective than $Rh_2(S\text{-PTTL})_4$ [37,91–93,95,96]. The results were very relevant as the much bulkier adamantyl groups would more efficiently block the carbene ligands from coordinating to the achiral rhodium face (shrouded by the adamantly groups) compared to the *tert*-butyl groups of $Rh_2(S\text{-PTTL})_4$ leading to the observed more enantioselective outcome. Moreover, Fürstner et al. recently succeeded in capturing an X-ray crystal structure of the $Rh_2(S\text{-PTTL})_4{=}C(MeOC_6H_4)CO_2Me$ intermediate (Figure 3) [97]. The obtained structure showed that the entire carbene resides within a long narrow pocket formed by the four *N*-phthalimido groups of $Rh_2(S\text{-PTTL})_4$, that adapt an $\alpha,\alpha,\alpha,\alpha$-arrangement ($C_2$-symmetric). The overall situation looked, therefore, in good agreement with the model proposed by Fox. But, low temperature NMR data for this intermediate returned a single set of signals for the four chiral carboxylate ligands [97]. This observation was not in a good accord with a C_2-symmetric binding site as proposed by the Fox model.

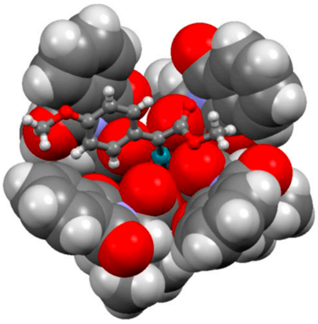


Figure 3. Space-filling model of the $Rh_2(S\text{-PTTL})_4 = C(MeOC_6H_4)CO_2Me$ unit (top view). (Reprinted from Werlé, C.; Goddard, R.; Philipps, P.; Farès, C.; Fürstner, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 10760, Copyright 2017, with permission from John Wiley and Sons).

Fox proposal was also challenged by data reported from different research groups. Adly, Ghanem and co-workers reported the X-ray crystal structure of $Rh_2(S\text{-PTAD})_4$ [98]. Similar to $Rh_2(S\text{-PTTL})_4$, the obtained structure showed that the catalyst is adapting the $\alpha,\alpha,\alpha,\alpha$-conformation in solid state, however, the catalyst was observed to form a bis(EtOAc) adduct when crystalized from ethyl acetate/*n*-hexane (Figure 4). This observation contradicted with the assumption proposed by Fox et al. in their model and confirmed that the adamantyl groups are not completely blocking the "achiral" catalyst face. In other words, there is still enough room for a Lewis basic ligand to coordinate to the achiral axial rhodium site. This observation provided direct evidence that both Rh atoms are still accessible by the diazo substrates even after the introduction of the bulkier adamantyl groups [98]. In addition, results have shown that complexes with *tert*-butyl groups at their α-carbon produced enantioselectivity levels similar and sometimes higher than $Rh_2(S\text{-PTAD})_4$ which carries the bulkier adamantyl groups [98].

Also, different reported observations confirmed the flexibility of the PTTL ligands around the rhodium active center, especially in solution and emphasized the effect of the shape and size of the axial ligand on the overall structure of the dirhodium(II)-carbene intermediate. For example, 2D heteronuclear NOESY data reported by the groups of Charette [54] and Duddeck [99], independently, confirmed that $Rh_2(S\text{-PTTL})_4$ and analogues have a mobile conformation in solution. This confirms the existence of other conformers with at least one *N*-phthalimido group is flipped downward. Further and based on X-ray crystallographic data, $Rh_2(S\text{-PTTL})_4(NC\text{-}C_6H_4\text{-}CN)$ adduct was found to adapt a conformation in which one of the ligands is twisted by only about 80° in solid state [87]. In other words, the ligand's blocking group lies in the periphery of the catalyst, the case that was originally supposed to be problematic due to steric constraints [36,53]. Gardiner and Ghanem [2,100] also succeeded to grow crystals of $Rh_2(S\text{-PTPA})_4(EtOAc)_2$ and $Rh_2(S\text{-PTPA})_4(MeOH)(H_2O)$ and they found that different conformations exist for each of these adducts at which, all of them feature inequivalent axial coordination sites unlike its original $\alpha,\alpha,\beta,\beta$-structure previously reported by Hashimoto [76,85–87]. The Rh_2(*S*-PTPA)$_4$(EtOAc)$_2$ adduct exhibited an $\alpha,\alpha,\alpha,\beta$-conformation, while Rh_2(*S*-PTPA)$_4$(MeOH)(H_2O) adduct exhibited an $\alpha,\alpha,\alpha,\alpha$-conformation in solid state.

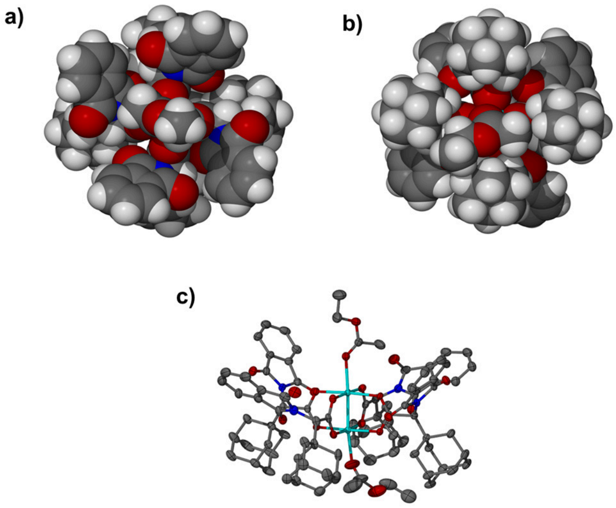


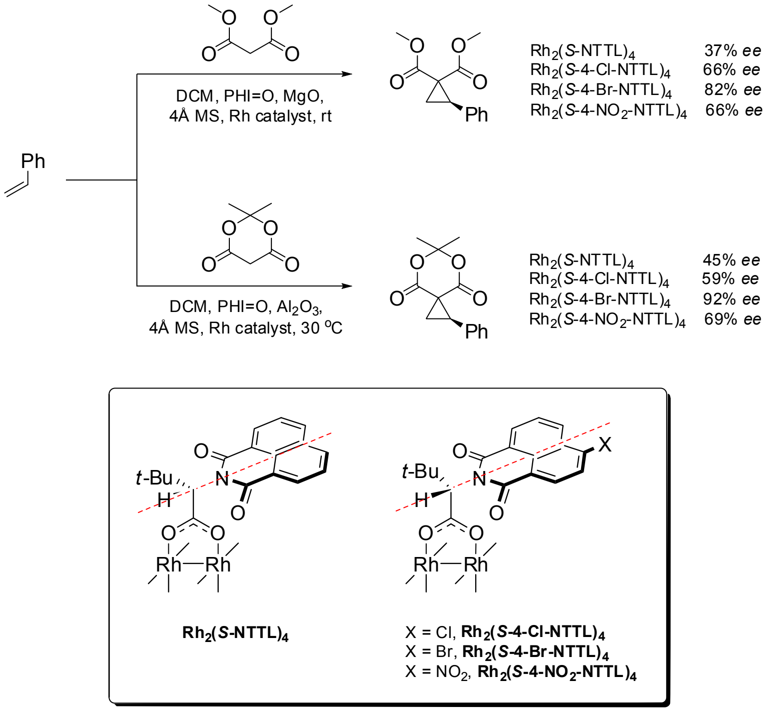
Figure 4. Space filling structure of bis(EtOAc) adduct of Rh_2(*S*-PTAD)$_4$ viewed along the Rh-Rh axis (**a**) into the chiral crown cavity, (**b**) onto the achiral Rh coordination site shrouded by the adamantyl groups. (**c**) Side view of bis(EtOAc) adduct of Rh_2(*S*-PTAD)$_4$. (Adapted from Adly, F.G.; Gardiner, M.G.; Ghanem, A. *Chem. Eur. J.* **2016**, *22*, 3447, Copyright 2017, with permission from John Wiley and Sons).

2.2.2. Local Ligand Symmetry

Following the classical way of catalyst design, all reported chiral dirhodium(II) carboxylate complexes derived from L-amino acid ligands were designed to have a symmetric *N*-protecting groups for the construction of the chiral ligands [4,53]. However in 2004, Müller and Ghanem reported several Rh_2(*S*-NTTL)$_4$ analogues at which, one hydrogen on the *N*-protecting group is substituted to generate catalysts carrying asymmetric *N*-protecting groups for asymmetric cyclopropanation of styrene with dimethyl malonate [101] and Meldrum's acid [102] (Scheme 8). The authors were surprised when screening results revealed that Rh_2(*S*-4-Br-NTTL)$_4$-catalyzed cyclopropanation proceeded with far improved levels of enantioselectivity compared to Rh_2(*S*-NTTL)$_4$.

Unfortunately, the authors had no success in growing X-ray quality crystals for Rh_2(*S*-4-Br-NTTL)$_4$. Instead, the X-ray crystal structure of Rh_2(*S*-NTTL)$_4$ (Figure 5) was used as a model to account for the enhanced enantioselectivity that accompanied Rh_2(*S*-4-Br-NTTL)$_4$ [102]. The authors proposed that, if Rh_2(*S*-4-Br-NTTL)$_4$ is retaining a similar structure to Rh_2(*S*-NTTL)$_4$ during catalysis (following Fox et al. proposal), the bromo-substituents would be situated at the cavity rim and are likely to exert a strong influence on the enantiofacial discrimination of the approaching substrate leading to the observed enhanced enantioselectivity. The authors also returned the improved performance of the 4-Br substituted catalyst over the 4-Cl analogue to the size of the substituents. The larger bromo-substituents are expected to exert more influence at the cavity rim leading to higher enantioselectivity in the case of Rh_2(*S*-4-Br-NTTL)$_4$.

Later, Adly and Ghanem investigated this further and they introduced a new approach for the design of dirhodium(II) carboxylate complexes. This approach is through the reduction of the *N*-protecting group symmetry by the inclusion of a bulky substituent at the catalyst's cavity rim. By the application of their new approach, the authors were able to introduce their catalyst, Rh_2(*S*-^{tert}PTTL)$_4$ (Scheme 9) [89,98,103]. For this catalyst, the planarity of the *N*-phthalimido groups is maintained but the local symmetry of the *N*-protecting group was reduced from C_{2v} to C_s by virtue of the substituents. Screening of Rh_2(*S*-^{tert}PTTL)$_4$ in different enantioselective cyclopropanation reactions demonstrated that, generally, $Rh_2(S\text{-}^{tert}PTTL)_4$ is more enantioselective than $Rh_2(S\text{-PTTL})_4$, while returning comparable enantioselectivity to $Rh_2(S\text{-PTAD})_4$ (Scheme 9) [98].



Scheme 8. Dirhodium(II)-catalyzed enantioselective cyclopropanation of styrene with dimethyl malonate [101] and Meldrum's acid [102].

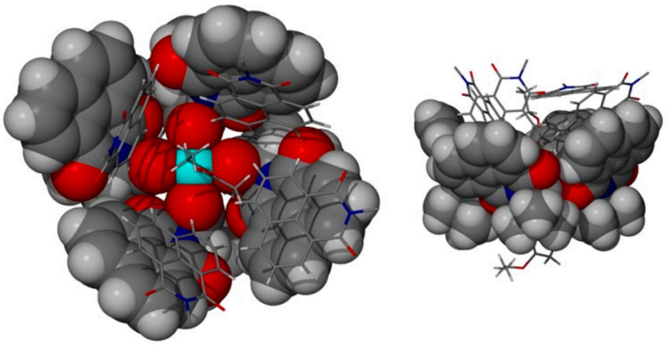
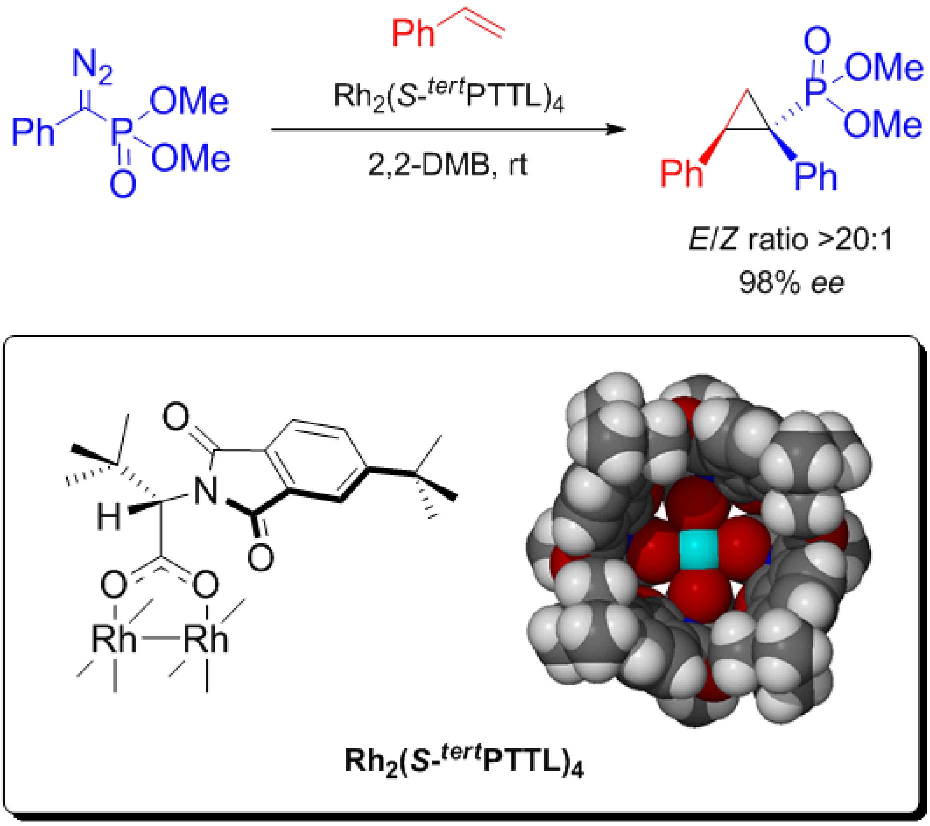


Figure 5. Space filling structure of bis(EtOAc) adduct of $Rh_2(S\text{-NTTL})_4$ (top and side view). (Reprinted from Ghanem, A.; Gardiner, M.G.; Williamson, R.M.; Müller, P. *Chem. Eur. J.* **2010**, *16*, 3291, Copyright 2017, with permission from John Wiley and Sons).

The X-ray crystal structure of $Rh_2(S\text{-}^{tert}PTTL)_4$ showed that the catalyst is adapting the $\alpha,\alpha,\alpha,\alpha$-conformation in solid state (Scheme 9) featuring the *tert*-butyl substituents similarly disposed towards the "corner" of the nearly square-shaped cavity. The cavity is approximately square if compared to the reported structure of $Rh_2(S\text{-PTTL})_4$. The authors claimed that the added *tert*-butyl substituent on the *N*-phthalimido group in $Rh_2(S\text{-}^{tert}PTTL)_4$ reinforced the overall chiral twist of the cavity, while, at the same time, not placing added steric hindrance to the binding of axial carbene ligand [98]. The authors proposed that, if this geometry is relevant during catalysis, it is likely to be the reason for the observed enhanced enantioselectivity relative to its parent, $Rh_2(S\text{-PTTL})_4$.

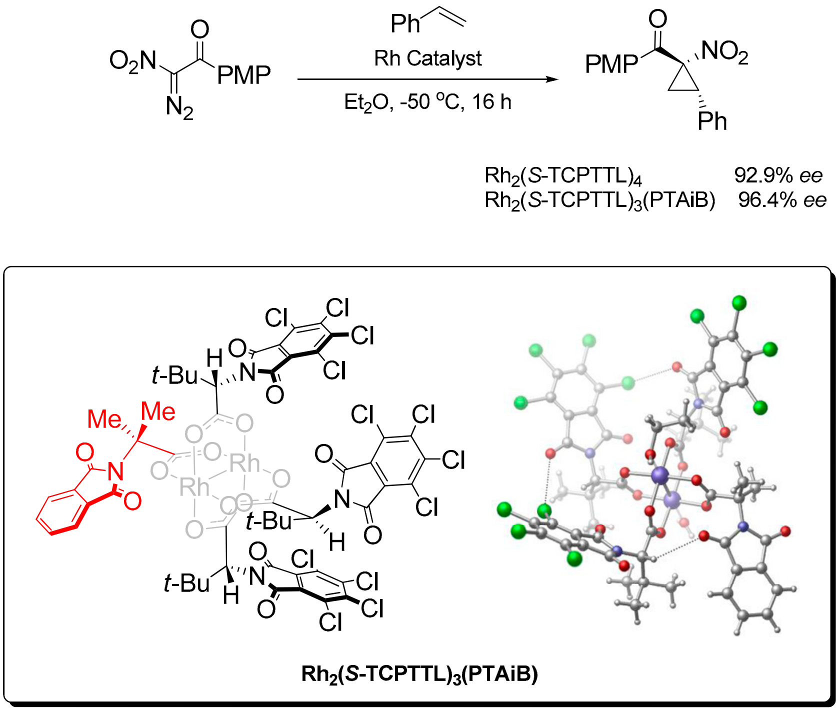


Scheme 9. Rh_2(*S*-^{tert}PTTL)$_4$-catalyzed enantioselective synthesis of dimethyl 1,2-diphenylcyclopropylphosphonate and X-ray crystal structure of Rh_2(*S*-^{tert}PTTL)$_4$ (top view). (X-ray crystal structure adapted from Adly, F.G.; Gardiner, M.G.; Ghanem, A. *Chem. Eur. J.* **2016**, *22*, 3447, Copyright 2017, with permission from John Wiley and Sons).

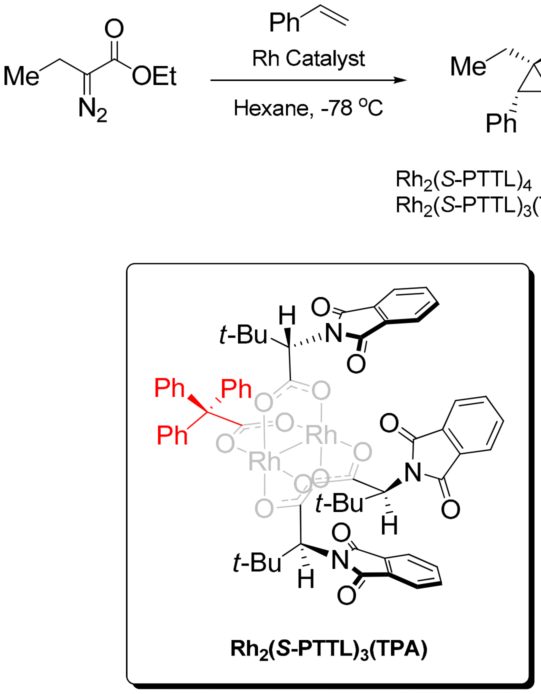
2.3. *α,α,α,β-Conformation*

In 2012, Charette et al. explored the replacement of one of the ligands of Rh_2(*S*-TCPTTL)$_4$ (the chlorinated version of Rh_2(*S*-PTTL)$_4$) with *N*-phthalimido-2-aminoisobutyric acid ligand (PTAiB). This led to the generation of the lower symmetry heteroleptic complex, Rh_2(*S*-TCPTTL)$_3$(PTAiB) [104]. The X-ray crystal structure of this complex revealed that it is adapting the *α,α,α,β*-conformation in solid state (Scheme 10). Surprisingly, screening results demonstrated that lowering the global symmetry of the catalyst had a beneficial impact on its enantioselectivity. In the cyclopropanation reaction of alkenes with *α*-nitro diazoacetophenones, Rh_2(*S*-TCPTTL)$_3$(PTAiB) resulted into the formation of the cyclopropane product in 96.4% *ee* which was higher compared to its parent Rh_2(*S*-TCPTTL)$_4$ (92.4% *ee*) (Scheme 10).

Also in the same year, Fox et al. reported the mixed ligated complex, Rh_2(*S*-PTTL)$_3$(TPA) (Scheme 11) [105]. The X-ray crystal structure of this complex showed that all of the *N*-phthalimido groups are on one face of the complex in a structural similarity to Rh_2(*S*-PTTL)$_4$ but with an incomplete chiral pocket (analogous to an *α,α,α,β*-arrangement). Rh_2(*S*-PTTL)$_3$(TPA) returned its best enantioselectivity in the cyclopropanation of styrene with ethyl *α*-diazobutanoate (88% *ee*) which was higher than the observed enantioselectivity with Rh_2(*S*-PTTL)$_4$ in the same reaction (79% *ee*) (Scheme 11). The scope of this catalyst was expanded to include other substrate classes, namely aliphatic alkynes, silylacetylenes and *α*-olefins, that were particularly challenging in intermolecular cyclopropanations with *α*-alkyl-*α*-diazoesters. Generally, Rh_2(*S*-PTTL)$_3$(TPA) was able to catalyze enantioselective cyclopropanations returning yields and enantioselectivities comparable and sometimes higher than Rh_2(*S*-PTTL)$_4$ [105].



Scheme 10. Enantioselective cyclopropanation reaction of alkenes with α-nitro diazoacetophenones and X-ray crystal structure of Rh_2(*S*-TCPTTL)$_3$(PTAiB). (X-ray crystal structure adapted with permission from Lindsay, V.N.G.; Charette, A.B. *ACS Catal.* **2012**, *2*, 1221. Copyright 2017 American Chemical Society).



Scheme 11. Enantioselective cyclopropanation of styrene with ethyl α-diazobutanoate and structure of Rh_2(*S*-PTTL)$_3$(TPA) according to its X-ray crystal structure [105].

3. Conclusions

From the above demonstration, all models proposed to account for the enantioselectivity observed with different dirhodium(II) carboxylate catalysts relied mainly on the obtained X-ray crystal structures of these catalysts (except for Rh_2(*S*-DOSP)$_4$ and related prolinate-based complexes). However, due to crystal packing, π-stacking and/or existence of axial and lattice solvent molecules within the crystal unit cell, the static pose of a catalyst and its chiral ligands portrayed in its X-ray crystal structure does not validate the adaption of the catalyst to the same conformation in solution and during catalysis. In other words, based on the size and the shape of the axial carbene ligand, as well as the reaction solvent used, the metal-carbene intermediate may adapt a different conformation during catalysis to the one observed in its X-ray crystal structure.

In fact, carboxylate ligands contain conformationally mobile units [13,54,87,98,99] which might give the ability to the dirhodium(II) catalyst to adapt its conformation to the particular substrate undergoing the reaction. Then enantioselection mechanisms can mainly originate from the different preferred reaction channels as a function of the different steric interactions taking place between the approaching substrate and the formed dirhodium(II)-carbene complex. This can explain the compatibility of a particular dirhodium(II) carboxylate catalyst with a particular substrate returning high levels of enantioselectivity, while the same catalyst might not retain the same level of enantioselectivity after switching to a different substrate. As a result, catalyst optimization is always necessary in method development to find the optimum catalyst that can return the highest possible level of enantioselectivity with the particular substrate undergoing the reaction. Based on that, researchers must not only limit their focus on the four main conformations of dirhodium(II) carboxylate complexes and an expansion in the considered conformational space is essential.

Even by relying on the catalyst X-ray crystal structures alone to justify the observed enantioselectivity, it is obvious from the demonstration above that dirhodium(II) carboxylate catalysts with $\alpha,\alpha,\alpha,\alpha$-, $\alpha,\alpha,\alpha,\beta$-, $\alpha,\alpha,\beta,\beta$- and $\alpha,\beta,\alpha,\beta$-ligand arrangements were all reported to lead to high levels of enantioselectivity. As a consequence, the original proposal that catalysts with $\alpha,\alpha,\beta,\beta$- and $\alpha,\beta,\alpha,\beta$-geometries will only result in high enantioselectivity [53] can no longer be considered as valid. In other words, symmetry of the catalyst is not a mandatory prerequisite for achieving high levels of enantioselectivity. Subsequently, the use of high symmetry ligands as the traditional way to produce high symmetry catalysts [53] may not be as essential as previously thought.

All in all, although the knowledge around the structure of dirhodium(II) carboxylate complexes has been expanded dramatically in the last decade, the topic is still in its infancy. With the fast development in X-ray crystallography, computational chemistry and NMR spectroscopy, researchers may prosper in solving the mystery behind this topic. This, in turn, will aid to a great extent in the design of highly stereoselective chiral dirhodium(II) catalysts in the future.

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