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**Reaction Modelling in Computational Chemistry:
from DFT to High-Accuracy Methodology for
Improving Catalysis Knowledge**

Author:

EUGENIO ROMANO

Supervisor:

PROF. GIOVANNI TALARICO

Co-Supervisor:

PROF. VINCENZO BARONE

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Coordinator: **PROF. NADIA REGA**

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Abstract

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**Reaction Modelling in Computational Chemistry: from DFT to
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by EUGENIO ROMANO

This thesis has pursued a unified computational view of polymerization catalysis that connects α -olefin and cyclic esters through the common concepts of stereoselectivity, regioselectivity and mechanistic aspects, with an eye to sustainable materials design. The objectives have been to investigate the mechanisms and the stereoelectronic effects that govern mechanism itself and microstructure of the final polymers, to build a benchmarked quantum-chemical protocol that reproduces experimental trends, and to derive design rules that transfer across ligand families and monomer classes.

The methodology adopted combines density functional theory (DFT) with the Activation Strain Model and Natural Energy Decomposition (ASM-NEDA) to separate strain and interaction along the reaction coordinate. Steric maps based on buried volume quantify ligand congestion around the metal centre. For α -olefins, through DFT analysis the generally accepted Cossee mechanism has

been revisited, predicting for low-symmetry systems a chain-stationary mechanism, arising from two diastereotopic sites. The origin of this mechanism has been studied and seems to be system dependent across bridged metallocenes, salalen and pyridylamido complexes. Site epimerization and diastereotopic sites are central. Steric maps alone do not account for the calculated energy gap corresponding to the experimentally observed selectivity, which motivates for an explicit decomposition of strain and interaction terms, making the former the determinant factor.

Stereoselectivity is rationalized within the same picture, integrating two stereoerror pathways, one arising from a misoriented chain with *anti* insertion and one in which the preferred orientation of the growing chain is preserved while the monomer inserts *syn*. ASM–NEDA shows stereocontrol dominated by strain with the catalyst fragment as the principal discriminator, while the interaction term adds a secondary stabilization. On the same coordinates, regioselectivity is analysed, with primary 1,2 insertion favoured by interaction stabilization and strain factors stabilizing the secondary 2,1 insertion. The balance between steric and interaction terms sets the preferred regiochemistry.

A dedicated benchmark links theory and experiment on propene stereocontrol across representative metallocene and post-metallocene families. Experimental pentad distributions are converted to free energy gaps and directly compared with computed barriers. Performance depends strongly on the treatment of dispersion in the optimization step and on solvent model in single point calculations.

The same framework extends to cyclic esters. Achiral aluminium complexes control tacticity in *rac*-lactide through the monomer that determines the wrapping mode, creating local chirality at the active site. This aspect has been analysed through DFT, ASM-NEDA and buried volume analysis. A recently synthesised pyridylamido iron catalyst polymerizes δ and ϵ "challenging" lactones with high activity and narrow dispersity. Computations reproduce relative rates through a precise analysis of the mechanisms and support a picture in which different species, arising from the neutral precursor, can initiate the polymerization.

Overall, the study delivers a view that bridges the worlds of polyolefins and polyesters, comparing experiments and theory, suggesting possible guidelines that link the main features of catalysts, including ligand nature and symmetry, to selectivity and activity, also in support of a circular polymer strategy.

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Introduction

Designing catalysts that control polymer microstructures with precision while meeting sustainability goals requires a unified view of polymerization catalysis supported by computational analysis. The decisive features are stereoselectivity, regioselectivity and the balance between propagation and termination events that fixes molecular mass. These principles make a bridge between the chemistry of α -olefin and the chemistry of cyclic esters, creating a common language for material that range from commodity polyolefins to recyclable and more environmental-friendly polyesters.

Polyolefins remain central to the materials economy because they merge low production cost with chemical resilience and mechanical versatility. Indeed, the range of application spans from packaging to transportation to medical uses.¹ Industrial isotactic polypropylene production is dominated by multisite TiCl_4 supported on MgCl_2 in the presence of internal and/or external donors and an aluminium alkyl species as co-catalyst.² The introduction of homogenous single-site catalysts enabling the possibility of ligand variation and, thanks to computational analysis, to study in depth the origin of mechanisms of stereoselectivity, regioselectivity and termination reactions.³⁻⁹ The advance in homogenous catalysis introduced post-metallocene systems, enlarging the range of polymer microstructures, also at higher temperature.¹⁰⁻¹⁵

The mechanism that governs olefin polymerization is the Cossee chain migration mechanism.¹⁶ The olefin first coordinates at a vacant site, migratory insertion follows creating a new C-C and C-Metal bond and, eventually, the growing chain moves to reestablish a new vacant coordination site opposite to the first one. High symmetry catalyst such as C_2 -symmetric systems follow this mechanism to produces highly regular polymers. Lower symmetry systems could create non-equivalent diastereotopic sites and potentially follow a slightly different mechanism, in which the catalytic sites epimerize. In **Chapter 1**, DFT, coupled with Activation Strain Model – Natural Energy Decomposition Analysis¹⁷⁻¹⁹ (ASM-NEDA) and Buried Volume analysis^{20,21}

(% V_{Bur}), guides the comprehension and the origin of this difference, investigating steric and electronic effects occurring in depending on the different ligand framework.^{22–28}

Stereoselectivity is the first pillar in α -olefin polymerization catalysts. Two limiting pictures are representative for this aspect, the enantiomorphic site control (ESC) and chain end control (CEC). The former indicates that the monomer enantioface selection is dictated by the chiral environment around the metal centre, in the latter is the configuration of the last inserted unit to select the monomer enantioface. The Corradini model links high selectivity to a preferred orientation of the growing chain, often assisted by an α -agostic interaction involving the metal centre and the growing chain, with the insertion occurring always in an *anti* fashion.^{29–32} Stereoerrors can arise when the chain misorients or when the chain maintains its preferred orientation but the monomer approach in a *syn* fashion, and such features were reproduced both on heterogenous and homogeneous catalysts with the employment of DFT and earlier QM-MM studies.^{33–39} In literature important exceptions are documented such as pyridylamido hafnium complexes. These systems deliver highly isotactic polypropylene at elevated temperature, despite their lower symmetry (C_1 or C_s symmetry). Computational evaluation assigns stereocontrol to a direct steric interaction between monomer and ligand, since no preferred orientation of the chain is detected.^{11,40}

In **Chapter 1**, stereoselectivity is revisited through the combination of DFT, ASM-NEDA and Buried Volume (% V_{Bur}) analysis to shed light on the stereoelectronic factors determining the occurrence of the stereoerrors, depending on the different ligand framework.

Regioselectivity is the second pillar in α -olefin polymerization in determination of microstructure. Propagation usually proceeds through 1,2 primary insertion which sustains regioregularity, crystallinity and high melting point.⁴¹ 2,1 secondary insertion and its occasional occurrence introduces regiodefects that lower crystallinity and melting points.⁴² Notwithstanding this, many examples of catalyst propagating

through secondary insertion are reported in literature, producing syndiotactic polypropylene.^{43–49} Computational efforts have been made during the years to understand what is guiding the choice for primary or secondary insertion. For tetrahedral metallocene systems the disfavouring of secondary insertion is often derived by steric repulsion whereas in octahedral post-metallocenes electronic factors can dominate the preference for primary insertion.^{6,50–52} In **Chapter 1** these aspects will be disclosed by combining DFT, ASM-NEDA and Buried Volume ($\%V_{\text{Bur}}$) analysis, analysing different catalyst with different ligand frameworks.

Chapter 2 is proposed as a link between experiment and theory. Stereoregularity in α -olefin polymerization catalysis is determined by the percentage of isotactic [*mmmm*] pentads obtained by ^{13}C NMR.⁵³ In this chapter compares four prototype homogenous catalysts, delivering isotactic polypropylene through the two different mechanisms of stereoselection described above.

The main goal is a stringent benchmark. Experimental stereoselectivity from ^{13}C NMR are converted into experimental Gibbs free energy differences to correlate them to theoretical stereoselectivity obtained from the analysis of transition states. Multiple density functionals are tested together with dispersion corrections and solvation models in order to identify a protocol that performs consistently across tetrahedral metallocenes and octahedral or pseudo-octahedral post-metallocenes.

Sustainability and circularity are the motivation of **Chapter 3**. The environmental burden of mismanaged plastics and the spread of microplastic through ecosystems and into humans have made plastic sustainability a central priority.^{54–58} The transition favours renewable feedstocks and improved end-of-life options that include degradability, reuse and chemical recycling to monomer,^{56,59} and aliphatic polyesters are pivotal in this scenario.⁶⁰ Polylactide (PLA) already holds a significant market position through biocompatibility and biodegradability, although slow degradation under ambient conditions and intrinsic brittleness motivate new microstructures. Lactide (LA) has two stereogenic centres and exists as *L*-LA, *D*-LA and *meso*-LA. Stereocomplexes, formed by mixing PDLA and PLLA after their co-crystallization,

exhibit superior thermal and mechanical properties than each homopolymer.⁶¹ These observations raised interest in the polymerization of the racemic mixture of LA to obtain polymers with new microstructures.^{62,63} The primary route to obtain stereoregular PLA involves ring opening polymerization (ROP) with transition metal catalysts, following the pioneering work of Spassky.⁶⁴ Stereocontrol in LA ROP follows the same conceptualization as illustrated for α -olefin polymerization catalysis, ESC and CEC. Mechanistic rationalizations are relative scarce and have often emphasised ESC over CEC.^{65–69} In **Chapter 3** DFT, ASM-NEDA and Buried Volume ($\%V_{\text{Bur}}$) analysis are involved to address this gap, by analysing in depth the stereoselective ROP of *rac*-LA catalysed by achiral catalyst.

The **Chapter 3** shows also an extension to challenging monomers that are relevant to chemical recycling. Polymerization of five and six membered rings are thermodynamically neutral, hence their synthesis relies on temperature management and/or phase separation to shift equilibria.⁷⁰ In this context, δ -alkyl δ -lactones are attractive because of their availability but the presence of side chains reduces their ring strain and complicate kinetics.^{71,72} Metal catalysed ROP remains scarce and often limited in molecular weight. Iron catalysts bearing pyridylamido ligand framework provide a sustainable platform to this purpose. The coordinated precursors show high activity and living character in the ROP of *L*-LA and ϵ -caprolactone (ϵCL)⁷³ and **Chapter 3** shows how DFT is helpful in identifying possible mechanisms across different monomers (δ -alkyl δ -lactones and ϵ -lactones) to rationalize the activity of the catalyst towards different challenging monomers.

In this work, computational is put at the core of the analysis. DFT provides the primary lens, while ASM-NEDA and Buried Volume ($\%V_{\text{Bur}}$) analysis acts as complementary supports to separate electronic and steric effects. **Chapter 1** sees DFT with ASM-NEDA and Buried Volume ($\%V_{\text{Bur}}$) analysis as means to revisit consolidated aspects of α -olefin polymerizations catalysis and expanding their comprehension. **Chapter 2** addresses the well-known variability of DFT outcomes. Different functionals, dispersion corrections and solvation models can shift barriers and selectivity and can

lead to misleading conclusion if no calibration is made. **Chapter 3** applies the same approach in **Chapter 1** for stereoselective ROP of *rac*-LA and looks at DFT as the main guide to rationalize catalyst experimental activity and shed lights on mechanistic aspects that would remain elusive without such approach.

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Chapter 1 -

Mechanism, Stereoselectivity and Regioselectivity in α -olefin polymerization catalysis: a DFT/ASM-NEDA/Buried Volume analysis combined approach to reveal the impact of stereoelectronic effects

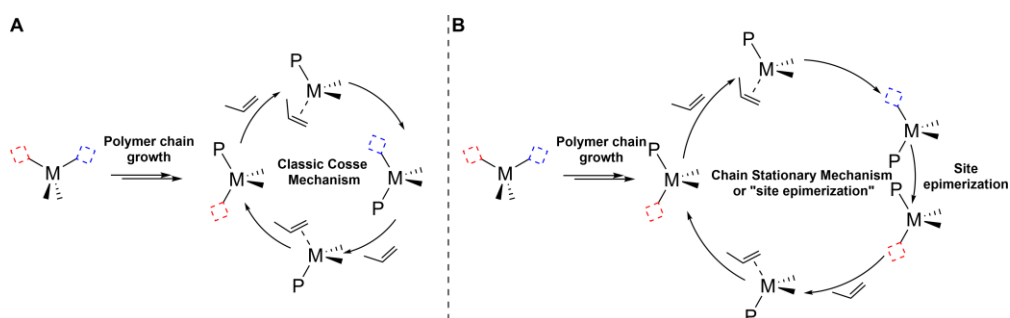
Abstract

A combined approach including DFT/ASM-NEDA/Buried Volume analysis is used to investigate the stereoelectronic effects involved in α -olefin polymerization catalysis, in order to reveal the impact of steric and electronic factors in guiding the mechanism, stereoselectivity and regioselectivity.

1.1 Introduction

Polyolefins (POs), principally polyethylene (PE) and polypropylene (PP), thanks to their low-cost production, chemical and mechanical properties, are the most versatile materials in the world, with a wide range of applications (from packaging, automotive industry, medical application and so on).¹ The industrial synthesis, particularly for isotactic PP (iPP) is dominated by Ziegler-Natta (ZN), an heterogeneous process involving a multi-site $\text{TiCl}_4/\text{MgCl}_2$ catalysts to which an internal and external Lewis bases are added, in combination with a cocatalyst (usually an aluminium-alkyl compound).² Higher fine tune of the PO microstructures has been achieved after the discovery of homogeneous, single site, catalysts, featuring a metallocene framework.³ Their employment, in synergy with computational chemistry, facilitated the through rationalization of the polymerization mechanism, including important aspects such stereoselectivity,^{3,4} regioselectivity⁵⁻⁷ and molecular weight^{8,9} in α -olefin polymerization catalysis. The insights gained on metallocene catalysts allowed the synthesis of a new class of catalysts, the non-metallocene (or post-metallocene) systems,¹⁰⁻¹² which enabled the possibility of enlarging the range of microstructure, and hence of applications, of polyolefins (reaching stereoregular block and multiblock copolymers) at higher temperature.¹³⁻¹⁵

Concerning the mechanistic pathway, the polymerization of α -olefin, such as propylene, notwithstanding different (and/or improved versions) proposed during the years,³ proceeds *via* the most accredited mechanism described by Cossee (“Chain Migration mechanism (CM)),¹⁶ which is the central for understanding the stereocontrol and kinetics of olefin polymerization. This mechanism occurs in two subsequent steps: (1) olefin coordination to a vacant coordination site of the metal centre, (2) Migratory insertion of the monomer into the metal-carbon bond of the growing chain and (3) migration of the polymer chain into the coordination site in which the olefin was previously coordinated (**Scheme 1.1A**). For highly symmetric catalysts, such as C_2 -symmetric metallocenes and post-metallocenes, the mechanism enables stereoregular insertion with high control, however, variation in the ligand framework, leading the reduced symmetric systems (*i.e.* C_1 -symmetry catalysts) could led to polymers with different microstructures and stereocontrol. Hence, for the latter, the presence of two diastereotopic active sites could induce a variation in the mechanism followed by the catalyst, deviating from the classical one to a “Chain Stationary mechanism” (CS) (**Scheme 1.1B**).

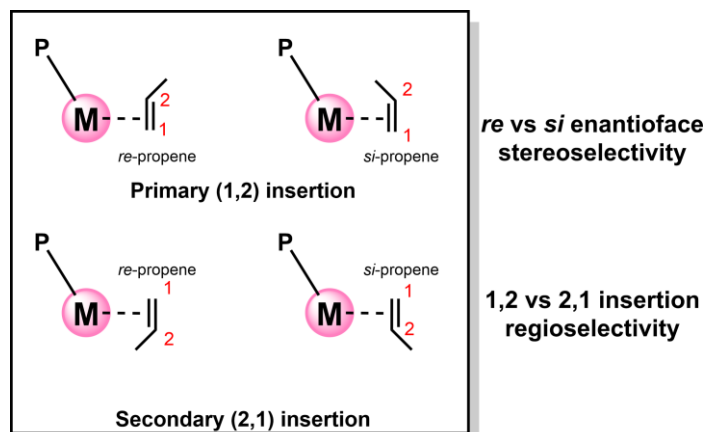


Scheme 1.1. Schematic comparison between the classic Cossee Mechanism (A) and Chain Stationary Mechanism (B) in α -olefin polymerization catalysis. In the classic mechanism, the polymer chain migrates after each insertion, in the chain stationary, the polymer chain “remains” fixed (after site epimerization).

Many examples of precise modification of the ligand framework, and hence their steric factors, are reported in literature, regarding both metallocene and post-

metallocene catalytic systems.^{17–24} Notwithstanding the large number of systems, the factors (steric and/or electronic) that determines this mechanism are not exactly clear. In this *scenario*, DFT, in combination with Activation Strain Model - Natural Energy Decomposition Analysis (ASM-NEDA) and Buried Volume analysis ($\%V_{\text{Bur}}$) (for more information, see **Section 1.2 Computational Details**), could help to shed lights on these aspects and the results are presented in **Section 1.3 Polymerization Mechanism Analysis**.

The microstructure of α -olefin based materials is the primary factor determining their final properties. Because of the prochirality of α -olefins, several enchainment of the monomer units is possible due to the stereochemistry and regiochemistry of the insertion, as illustrated in **Scheme 1.2** for propene monomer.

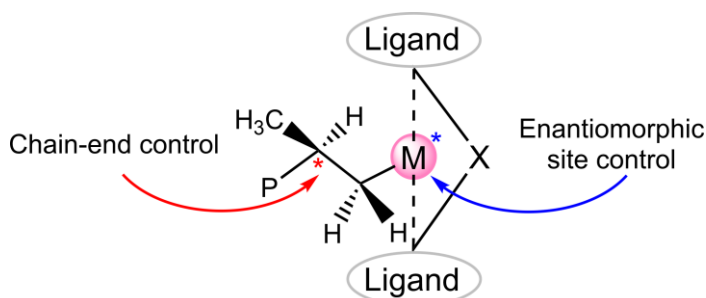


Scheme 1.2. Potential enchainment of propene monomers into metal-carbon bond.

The stereoregularity of the resulting polymer, *i.e.* the spatial arrangement of substituent groups (for example, methyl groups for propylene) dictates its thermal, mechanical and crystallization properties, making the stereoselectivity a crucial aspect for catalysts in α -olefin polymerization catalysis to tailoring the performance and application range of polyolefins.

In stereoselectivity α -olefin polymerization catalysis, two limiting models are invoked for enantioface discrimination at each propagation step, namely enantiomorphous site

control (ESC), where a chiral active site (chirality related to the metal and /or the ligand framework) selects the monomer enantioface independently on the previous insertion, and chain-end control (CEC), where the configuration of the last inserted unit influences the approach of the incoming monomer. Most classical Ziegler-Natta and many homogenous systems are dominated by ESC, while specific catalyst (those favouring 2,1 insertion or featuring fluxional sites) can exhibit CEC contributions.

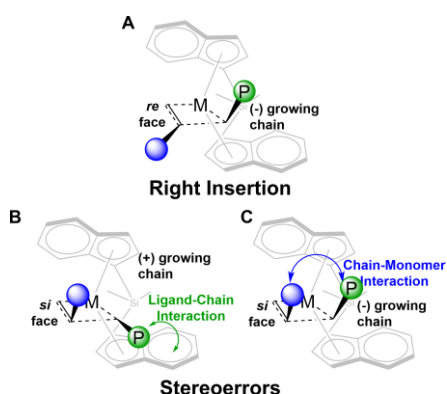


Scheme 1.3. Enantiomorphic site control (ESC) and Chain-end control (CEC) schematic representation.

The accepted model for the stereoselectivity, the so called “chiral control of the growing chain”, has been formulated after the intuition of Corradini,^{25–27} for which the chiral orientation of the growing chain, induced by the chirality of the active sites and supported by an α -agostic interaction with the metal centre,²⁸ selects the monomer enantioface rather than any other interaction involving the monomer and catalytic pocket. More in depth, the growing chain can adopt two possible configurations, (+) or (-), in order to avoid steric interactions with the ligand framework of the active site.²⁹ The incoming monomer inserts in the metal-carbon of the chain bond in an *anti* fashion avoiding steric interactions between the methyl group of propene (or alkyl group for higher α -olefins) and the growing chain (**Scheme 1.4A**) Accordingly to this picture, stereoerrors could occurs due to a misorientation of the growing chain while monomer still inserting in *anti* fashion (**Scheme 1.4B**, which is going to be called S1). This model, firstly explained through molecular mechanics calculations on

heterogeneous systems,^{25–27} has been extended to homogenous systems (metallocene and post-metallocene) by employing first a combined quantum mechanics/molecular mechanics (QM/MM) approach and then DFT calculations, using the octahedral homogenous systems to validate the model for classic heterogeneous ZN catalysts.^{30–32,3,4}

Subsequently, Morokuma, Rappè and co-workers reported, through computational analysis, the possibility of a non-classical stereoerror, in which the growing polymer chain maintains its preferred orientation and the monomer inserts in a *syn* fashion into the first C-C bond of the growing polymer chain (**Scheme 1.4C**, that is going to be named as S2).^{33–36}



Scheme 1.4. General representation of transition states (TSs) for olefin insertion: (A) for regular insertion, (B) and (C) for two sources of stereoerrors for a C_2 -symmetryc homogenous metallocene systems.

It is clear that the combination of computational and experimental efforts provided a unified model for stereoselectivity in α -olefin polymerization catalysis field, speeding up the ligand design process and its effect on the material proprieties.³⁷ However, exceptions to this model exist and are represented by a new class of catalysts base on Hafnium bearing a pyridyl amido ligand skeleton, which is able to produce polymers with high isoselectivity, at high temperature, despite the C_1 or C_s symmetry of the

catalytic precursors.¹¹

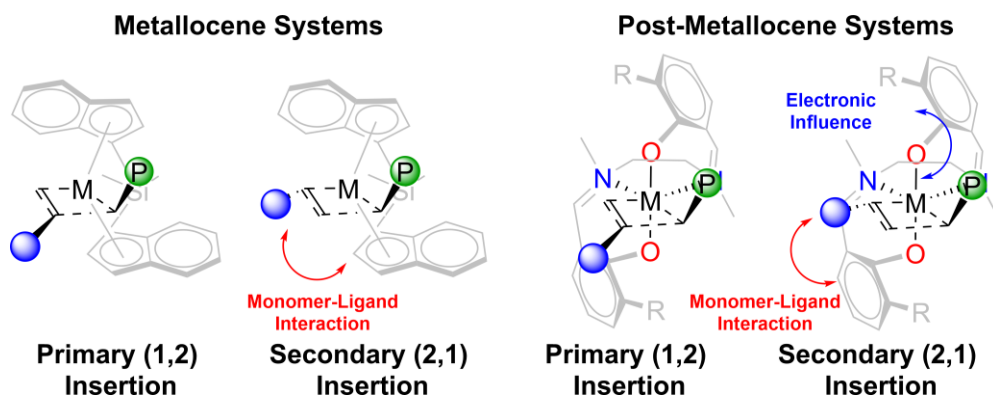
Indeed, computational analysis was able to predict that pyridylamido-based catalysts are one of those classes of catalysts that does not follow the classic chain migratory proposed by Cossee, as mentioned above, and, making one of the two diastereotopic sites the preferred one for the insertion.³⁸ Additionally, the stereoselectivity is determined by direct interactions between the ligand framework (aniline moiety in particular) and the monomer itself, since the growing chain does not adopt a chiral orientation as proposed in the classic Corradini's model for stereoselectivity.³⁸

As it can be inferred, it is generally accepted that stereoselectivity is determined by steric factors, that is mostly correct for the description of stereoerror insertions for a single catalyst class. However, it remains important understanding and comparing catalysts of different classes to give a more detailed picture of the bonding also in terms of electronic contributions, and this is the objective of the analysis that will be presented in **Section 1.4 Stereoselectivity Analysis**, in which DFT, ASM-NEDA and buried volume analysis have been combined to pursue this aim.

The polymerization of α -olefin proceeds predominantly through successive 1,2-primary insertions,³⁹ ensuring high regioregularity, which is essential for achieving desirable material proprieties such as high crystallinity and elevated melting temperatures. However, the sporadic occurrence of 2,1-secondary insertions, often referred to as regiodefects, can significantly affect polymer microstructures, leading to a decrease in both degree of crystallinity and melting point.⁴⁰

This mechanistic behaviour is observed in both heterogeneous catalysts (TiCl_3 and TiCl_4 supported on MgCl_2)³⁹ and for homogeneous metallocene systems.³ While most known catalysts favour 1,2-insertions, two notable exceptions, leading to the formation of syndiotactic polypropylene (sPP), are known for their preference for 2,1-secondary insertions, *i.e.* the vanadium-based systems^{41,42} and the more recent bis(phenoxy-imine) TiCl_2 complexes^{43–48}. The development of these catalysts has triggered growing interest in understanding the fundamental determinants of regioselectivity in the polymerization of α -olefins.

Several computational studies have attempted to elucidate the origins of regioselectivity.^{49–51,6} Both steric and electronic factors have been proposed as governing elements, strongly dependent on the ligand environment surrounding the metal centre. From a steric perspective, the 2,1-secondary insertion is generally disfavoured due to the repulsive interaction between the methyl group (or the alkyl group of higher α -olefins) of the propene monomer and the substituent of the ligand skeleton. These steric constraints are particularly relevant for metallocene systems. Electronic contributions seem to play a more prominent role in octahedral post-metallocene systems. In this case, orbital interactions between the heteroatoms coordinated to the metal centre and the metal centre itself, *via* trans effect, could modulate the stabilization of the primary or secondary insertion, by selectively stabilizing or destabilizing specific insertion pathway. Additionally, studies carried out on model catalyst systems have highlighted the importance of electrostatic interactions in determining regioselectivity (**Scheme 1.5**).



Scheme 1.5. Steric and electronic effects occurring in regulation of regioselectivity, for metallocene and post-metallocene catalytic systems.

These results underline the multifaceted nature of regioselectivity, which appears to arise from delicate interplay of steric and electronics effects, each differently weighted on the catalyst class. In general, tetrahedral metallocene and octahedral post-

metallocene catalysts exhibit regioselectivity that appears to stem from distinct origins. Consequently, a systematic and comparative investigation across different catalyst types is essential to develop a unified understanding of regioselectivity in α -olefin polymerization catalysis.

Once again, this objective has been addressed by integrating DFT methods with ASM-NEDA and buried volume analysis, and the results are showed **Section 1.5 Regioselectivity Analysis**.

1.2 Computational Details

All DFT calculations have been performed with the Gaussian09⁵² and Gaussian16⁵³ set of programs, using the B3LYP hybrid GGA functional^{54,55} in conjunction with the polarized split-valence basis set (SVP)⁵⁶ of Ahlrichs and co-workers for H, C, N, O, Si, F and LANL2DZ pseudopotentials and basis sets⁵⁷ were employed for Zr, Hf and I atoms in the optimization steps. The choice of B3LYP is due to its wide application in the field of polymerization catalysis, as reported in the literature within the Chapter, for its good compromise between accuracy and time. Stationary points were characterized using vibrational analyses, and these analyses were also used to calculate zero-point energies and thermal (enthalpy and entropy) corrections (298.15 K, 1 bar). Improved electronic energies were obtained from single-point calculations using the TZVP basis set for H and second-row atoms⁵⁸ together with the SDD basis and pseudopotentials for metals and I (a f function with exponent 0.5 was added for Zr and Hf).⁵⁹ Dispersion corrections^{60,61} by Grimme (using EmpiricalDispersion=D3 keyword in Gaussian packages) were also added. The Gibbs free energies issued from these improved electronic energies and SVP thermal corrections are labelled $\Delta G(\text{B3/TZVP})$. Bulk solvent effects were taken into account by using the polarizable continuum model (PCM),⁶² leading to $\Delta G(\text{B3/D3/TZVP/PCM})$, considering toluene as solvent. The ASM-EDA model proposed by Bickelhaupt,⁶³ allows the decomposition of the reaction energy profile into two contributions along the reaction coordinate:

$$\Delta E_{\text{Tot}} = \Delta E_{\text{Strain}} + \Delta E_{\text{Int}}$$

ΔE_{Strain} is the energy related to the reactant deformation needed to reach the geometries required to react and ΔE_{Int} is the energy related to the strength of their mutual interactions. The former term is the sum of the strain related to each reactant: $\Delta E_{\text{Strain}} = \Delta E_{\text{Strain,frag1}} + \Delta E_{\text{Strain,frag2}}$.

In this work, the fragment 1 corresponds to the cationic active species plus the growing polymer chain ($\Delta E_{\text{Strain(Cat)}}$), whereas fragment 2 corresponds to the monomer ($\Delta E_{\text{Strain(C3H6)}}$) for the insertion reactions, with each strain energy being calculated with respect to the equilibrium geometry of the pertinent fragments.

The ΔE_{Int} term has been decomposed using the NEDA (Natural Energy Decomposition Analysis),⁶⁴ which already includes the counterpoise correction for the Basis Set Superposition Error as proposed by Boys and Bernardi.⁶⁵ For this approach, no solvent correction could not be considered, hence the values reported will be referred to the electronic energy correct only for the dispersion term. At each point along the intrinsic reaction coordinate (IRC) $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ have been obtained from the ASM by subtracting the energy of the minimum equilibrium geometry from the energy of the respective fragment. For the same points, the NEDA has been performed using the NBO version 7 software linked to Gaussian16 (in conjunction with the TZVP basis set for H, C, N, O and the SDD basis and pseudopotential for the metal).⁶⁶ This permits to obtain ΔE_{Int} and all its components, namely electrostatic, polarization, charge transfer, exchange and deformation components: $\Delta E_{\text{Int}} = \text{ES} + \text{POL} + \text{CT} + \text{XC} + \text{DEF}$ where ES = classical electrostatic interaction; POL = polarization interaction; CT = charge transfer based on interaction between filled and empty orbitals; XC = exchange-correlation interaction; DEF = the energy cost to distort a fragment wavefunctions in the field of all other fragments of the complex. Dispersion contributions have been also estimated by the D3 model of Grimme.

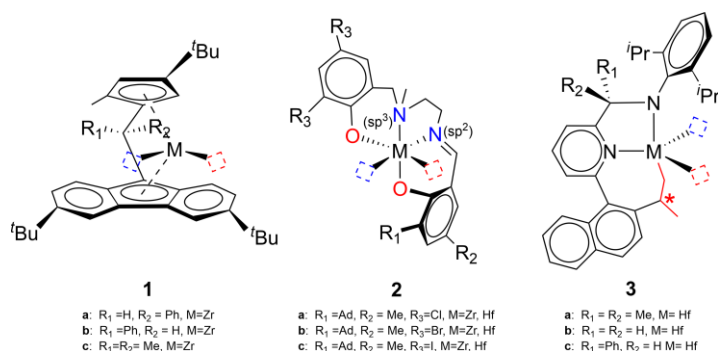
The analysis of ES, POL, CORE and CT contributions has been performed by the NEDA protocol by NBO07.⁶⁶ The ES and POL(+SE) terms are examined using

Natural Charges and induce and relaxed dipoles provided by NBO and NEDA analysis, respectively. The CORE term is a pure quantum-mechanic term which considers interactions between occupied orbitals, whilst the CT takes into account interactions between unfilled and filled orbitals. To gain further information on the CORE term, the overlap matrix of the NBOs of the highest occupied NBOs for fragment 1 and fragment 2 provided by NBO07 can be analysed by considering their overlap integral values (ij^{th} element matrix). The magnitude of S_{ij} values is indicative of the overlap of the considered filled NBOs and the higher is the value, the higher the destabilization. The differences in CT terms can be analysed with through the second-order perturbative analysis of the donor-acceptor interactions based on the NBO approach. The images have been made using Jmol program.⁶⁷

Buried volume analysis ($\%V_{\text{Bur}}$) has been carried out to quantify the steric impact of the ligand environment around the metal centre.⁶⁸ This approach evaluates the percentage of buried volume, defined as the fraction of a spherical volume centred on the metal that is occupied by the ligand atoms within a given radius. The analysis provides a quantitative measure of the steric hindrance exerted by ligands in the coordination sphere. It has been performed using the SambVca 2.1 tool⁶⁹, on DFT optimized geometry, with the aim to rationalize the results obtained with different catalytic systems and correlated with DFT and ASM-NEDA.

1.3 Polymerization Mechanism Analysis

Concerning the analysis of the polymerization mechanism, three different systems have been considered and showed in **Scheme 1.6**. Blue and red dashed boxes indicate two diastereotopic sites available for the polymerization.



Scheme 1.6. C_1 -symmetric active species employed for the analysis of polymerization mechanism.

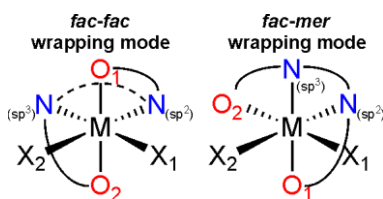
The three catalyst families considered here operate have been proposed to operate through CS mechanisms, yet they differ in the structural feature, enforcing this behaviour:

- 1) System **1**, isoselective *ansa*-metallocene: combined theoretical and experimental studies have already proven that these classical bridged C_1 metallocenes propagate *via* CS mechanism.²⁴
- 2) System **2**, isoselective post-metallocene salalen systems: synthesized by Kol and co-workers,²³ these complexes are characterized by an intrinsic electronic asymmetry arising from the ligand wrapping mode. The unequal trans influence of the coordination atoms around the metal centre has been identified as the key factor favouring the CS mechanism.
- 3) System **3**, pyridylamido-Hf complexes: isoselective systems and can produce high molecular weight polymers, even at temperature above 100°C. DFT analyses indicate their tendency to follow a CS mechanism.³⁸

In all these cases, the metal centre presents two diastereotopic coordination sites, either of which can be involved in the polymerization of α -olefins. The starting point of the discussion is the DFT analysis for all the systems in **Scheme 1.6**.

For the *ansa*-metallocene systems, for sake of simplicity, a simply notation was used to define the two diastereotopic active sites, labelled as inward the TS structure having the propene monomer inserted in the more crowded zone, the one with 'Bu substituent in position 3 of the Cp ligand (red box in **Scheme 1.6**) and as outward the TS structure in which the propene monomer inserts in less crowded zone (blue box in **Scheme 1.6**, see **Figure 1.1A and B**, system **1c**, for better representation). Additionally, both chirality, respectively *R* and *S*, have been considered for system **1a** and **1b** and in system **1c** the stereogenic centre has been removed by replacing H and Ph groups with two methyl substituents.

Concerning post-metallocene salalen **systems 2**, because of the ligand topology, two different wrapping modes, namely *fac-fac* (FF) and *fac-mer* (FM), are accessible and represented in **Scheme 1.7**.



Scheme 1.7. Schematic representation of ligand wrapping modes around metal centre. *Fac-fac*: O₁-N(sp²)-N(sp³) and N(sp²)-N(sp³)-O₂ occupy facial sets; *fac-mer*: O₁-N(sp²)-N(sp³) occupy a meridional set and N(sp²)-N(sp³)-O₂ occupy a facial set. X₁ and X₂ are two diastereotopic sites available.

The ligand coordination mode of the active species was found to correspond to FM wrapping arrangement, determined through experimental analysis on solid state neutral catalyst,²³ reproduced by DFT, albeit with a slight distortion.⁷⁰ Based on this

assumption, X₁ has been labelled as “site 1” (red box in **Scheme 1.6**) corresponds to olefin inserting at X₁ with the growing chain located at X₂, for both FF and FM wrapping mode (see **Figure 1.1C** and **D** for FM).

Pyridylamido systems **3** shows to relevant geometries for the active species: at one site, the chain-end sp³ carbon of the growing chain lies *trans* to the pyridyl nitrogen, giving a square-pyramidal coordination environment, denoting this site as PS (**Figure 1.1E**). At the opposite site, the sp² carbon of the inserting propene monomer occupies the position *trans* to the pyridyl N atom, resulting in a (strongly) distorted trigonal bipyramid and this site has been labelled as TBP (**Figure 1.1F**).

Based on this premises, DFT analysis has been carried out in order to reveal the favourite site for the insertion of propene in M-C(growing chain) bond, the results are showed in **Table 1.1**, and for sake of simplicity, only low-lying TS structures for system **1a** (*R* isomer), **2a** (Zr metal centre) and **3a** have been reported in **Figure 1.1** and all the results will be discussed on them.

Table 1.1. Gibbs free energy at DFT level (kcal/mol) for propene insertion TSs for systems 1, 2 and 3. Positive values indicate preference for site 1.

Sys.	1a	1b	1c	2a-Zr	2b-Zr	2c-Zr	2a-Hf	2b-Hf	2c-Hf	3a	3b	3c
ΔG	2.6	4.1	2.2	4.2	4.2	4.1	3.8	5.1	4.1	6.0	6.2	8.1

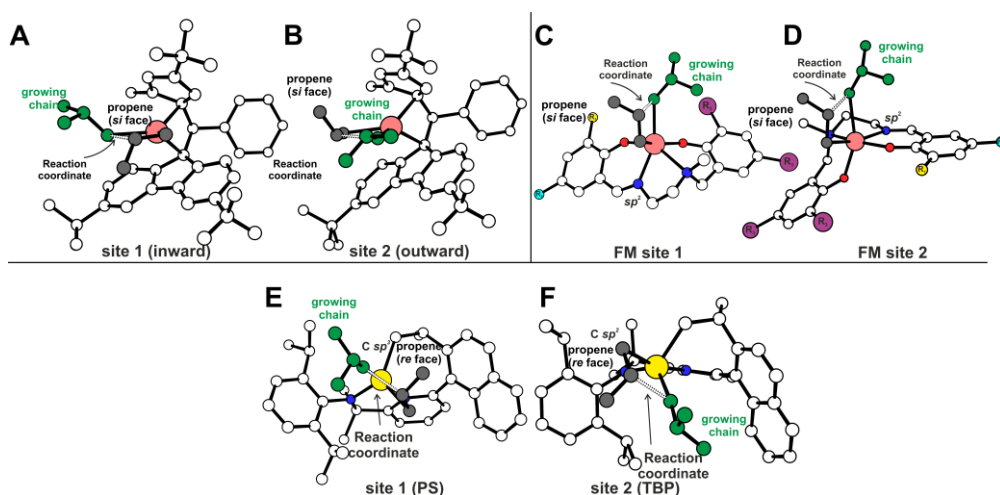


Figure 1.1. DFT optimized geometries for propene insertion TSs promoted by system 1a, system 2c and system 3a: site 1 (A, C and E) and site 2 (B, D and F). H atoms omitted for clarity.

DFT results show a marked preference for the insertion to occur at site 1 (inward and PS for systems **1** and **3**). For systems **1**, the growing chain occupies the more accessible site and the olefin coordinates and inserts at the more hindered side (inward) of the catalysts, independently on the chirality of the C-bridge. Systems **2** prefer having the growing chain *trans* to the N_{imine} (sp^2), giving more validity to the proposed idea of Kol *et al.* regarding electronic *trans* effects, as a consequence of the FM wrapping mode (more evident than the FF coordination)⁷⁰, in controlling chain direction.²³ Systems **3** show substantial Gibbs energy values (> 5.0 kcal/mol) and essentially insensitive to the nature of R_1 and R_2 substituents on the pyridylamido skeleton. These results enforce the idea of a CS mechanism but, despite the magnitude of the site preference, no rational has been established in literature.

Apparently, systems **1** and **3** exhibit CS mechanism arising from ligand-based steric effects (steric congestion due to the asymmetry of the ligand in systems **1** and PS vs. TBP preference in systems **3**), governing the chain direction. To quantitatively test

this steric hypothesis, buried volume analysis ($\%V_{\text{Bur}}$) has been carried out and showed in **Figure 1.2**.

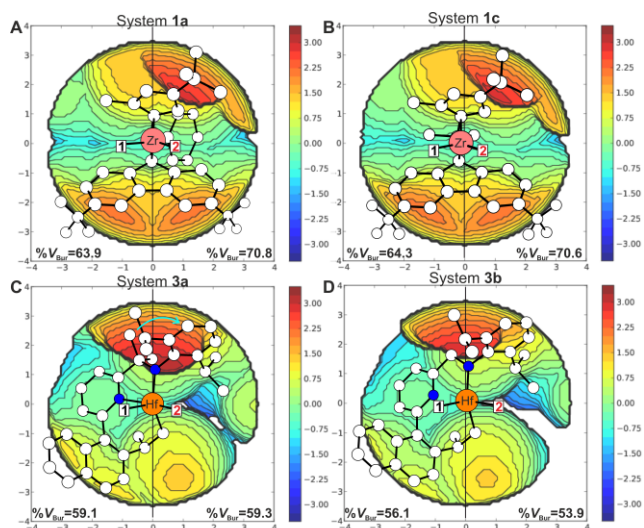


Figure 1.2. Steric maps of neutral precursors for systems 1a (A) and 1c (B) and systems 3a (C) and 3b (D) with the $\%V_{\text{Bur}}$ values obtained for the left and right quadrants.

$\%V_{\text{Bur}}$ analysis, and the steric map of *ansa*-metallocene **1a** (**Figure 1.2A**), reveals a clear inward/outward asymmetry: the outward side is more crowded than the inward side (70.8% vs. 63.9%), consistent with the presence of *t*Bu substituent. This steric pattern is preserved moving from system to system. Regarding systems **3**, a plausible reading of the values reported in Table 1.1 could be related to the different steric hindrance at the PS and TBP sites. The analysis carried out on the neutral mono-inserted product shows similarities between the two sites for systems **3a** (59.1% vs 59.3%, **Figure 1.2C**) that persist upon modifying the ligand framework (system **3b**, **Figure 1.2D**). By comparing two system steric maps, it emerges that the variation of R_1 and R_2 substituents increases the bulkiness of the catalytic pocket by pushing the *i*Pr groups on the phenyl ring toward the coordination site, that is evident by comparing the right quadrants in **Figure 1.2C** and **2D** (59.3% vs. 53.9%); this is the

“buttressing effect”.³⁸

Considering the possibility of a combination of steric and electronic effects, a quantitative interpretation of the DFT results showed above could be obtained through the ASM-NEDA analysis, as described in **Section 1.2 Computational Details**. For sake of simplicity, only systems **1a**, **2a** and **3a** will be analysed.

In **Figure 1.3**, the Activation Strain Diagram are reported for the three systems under analysis, in which ΔE , ΔE_{Strain} and ΔE_{Int} are reported as function of the reaction coordinate (the distance between two C atoms involved in the insertion reaction).

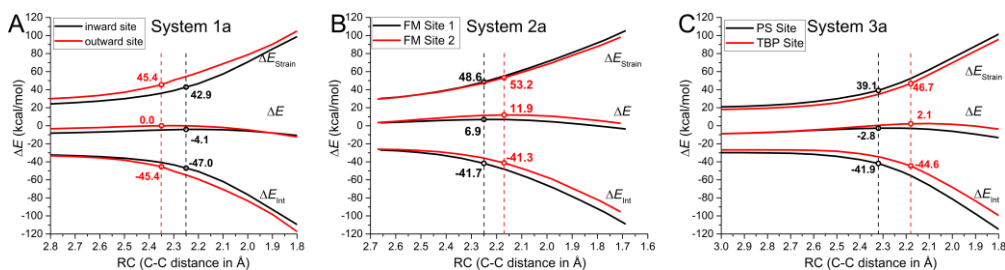


Figure 1.3. ASM analysis of the propene insertion at inward, site 1, PS site (black) and outward, site2 and TBP (red) of systems 1a, 2a and 3a as a function of the reaction coordinate. With circles are reported the values (kcal/mol) calculated at the two TS structures.

Concerning system **1a**, both ΔE_{Strain} and ΔE_{Int} contribute to the preference for the insertion to occur at the inward site (**Figure 1.3A**), with the former playing a dominant role. Consistently with $\%V_{\text{Bur}}$ analysis, the outward site is more congested and thus more destabilized by the deformation. In line with this picture, $\Delta E_{\text{Strain}(\text{Cat})}$ favours inward insertion (black curve), while $\Delta E_{\text{Strain}(\text{C}_3\text{H}_6)}$ shows a slight counter-preference for the outward insertion (red curve) (**Figure 1.4A and B**). The results of ΔE_{Int} decomposition accounts also for a further stabilization due to the charge transfer (CT) terms, which involves interaction between filled and unfilled orbitals and the main contributions to it are reported in **Table 1.2** and **Figure 1.5**.

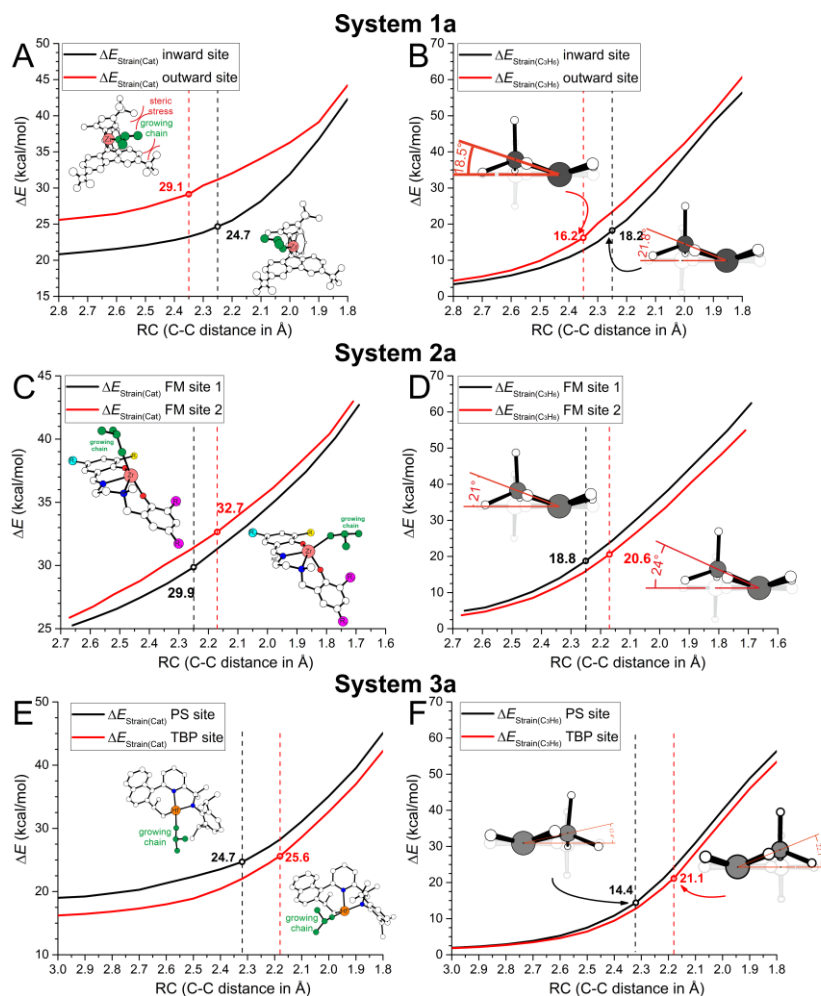


Figure 1.4. ASM-NEDA analysis of the ΔE_{Strain} decomposed into $\Delta E_{\text{Strain(Cat)}}$ (A, C and E for systems 1a, 2a and 3c) and $\Delta E_{\text{Strain(C3H6)}}$ (B, D and F for systems 1a, 2a and 3c) for propene insertion at the two different sites (black for inward, FM site 1 and PS and red for outward, FM site 2 and TBP) as a function of the reaction coordinate. Values in kcal/mol and with circle are reported the values calculated at the TS structures. The olefin deformation is reported with respect to the free optimized olefin (light grey).

The activation strain diagram for system **2a** mainly account the 5 kcal/mol of difference to ΔE_{Strain} and not ΔE_{Int} , contrary to electronic *trans* influence expectation

(**Figure 1.3B**). Additionally, inspecting **Figure 1.1**, it appears that there are no differences in the distances involving metal centre and terminal C atom of the growing chain (2.43 Å vs. 2.49 Å). Going further into the analysis, the insertion at site 1 occurs at higher distances than site 2 (2.25 Å vs. 2.17 Å), forcing higher deformation at site 2 than site 1. Indeed, $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C}_3\text{H}_6)}}$ (**Figure 1.4C and D**) are lower at site 1 and, in particular, although for equal C-C distances the olefin deformation appears larger at site 1 than site 2, the TS deformation penalty is smaller at site 1 than site 2, with a visibly less pronounced methyl deformation at site 1.

Finally, the ΔE gap between PS and TBP sites for system **3a** is mainly driven by a larger ΔE_{Strain} at TBP site (46.7 vs. 39.1 kcal/mol), only partially compensated by ΔE_{Int} . The latter profile is lower (hence more stabilizing) at PS site than TBP site along all the reaction coordinate, inducing the olefin to approach closer (2.32 Å, black dotted line for PS and 2.18 Å, red dotted line for TBP) to reach comparable electronic stabilization at the cost of higher steric deformation. The further decomposition of ΔE_{Strain} reveals that $\Delta E_{\text{Strain(Cat)}}$ is similar at both sites (**Figure 1.4E**), since both geometries prefer to place to growing chain *trans* to N atoms (pyridinic N for PS site and amido N for TBP site). Conversely, $\Delta E_{\text{Strain(C}_3\text{H}_6)}}$ terms show a noticeable difference (14.4 vs 21.1 kcal/mol, **Figure 1.4F**). By inspecting **Figure 1.4F**, the olefin undergoes a larger methyl deformation to insert at TBP site (red curve) than the PS site (black curve). This also explain why the % V_{Bur} analysis on the mono-inserted specie (**Figure 1.2C and 2D**) do not shows any clear asymmetry of the ligand.

Before concluding, for system **1a** a notable contribution from ΔE_{Int} was detected. Indeed, the NEDA analysis highlighted a difference of about 20 kcal/mol on the CT contribution between propene insertion TSs at the inward and outward sites of system **1a**. The origin of this difference can be analysed with the help of a second-order perturbative analysis of the donor-acceptor interactions based on the NBO approach. In Table 1.2 are reported:

1) the main donor-acceptor interactions from the Zr centre to the olefin, namely from the bonding orbital (BD) between Zr and C α of the growing chain toward the antibonding p orbital (BD*) of the olefin.

2) the σ -donation from the BD of the olefin toward empty valence nonbonding orbitals (of "lone vacancy", LV type) of Zr, with a strong d_z^2 character.

3) the stabilizing interactions between the Zr and the cyclopentadienyl (Cp) ligand. Here the electron-donor LPs are localized on different C atoms of the Cp ring, (C5 and C2 for inward and outward sites, respectively). The electron-donor LVs, localized on Zr centre, differ principally in the f character of the orbital, which is higher for LV (2) in inward TS.

The $E^{(2)}$ values indicate the stabilization derived from the interaction between the electron-donors and electron-acceptors (the greater the $E^{(2)}$ values, the higher the stabilization). With the capital letters A-F in **Table 1.2** are reported the structures visualized in **Figure 1.5** by using the PNBO ("pre-orthogonalized" NBO) where the donors are reported in blue and red and the acceptors in yellow and green by using the Jmol program⁶⁷.

Table 1.2. Main interactions between donors and acceptors computed by NBO analysis for the propene TSs at the inward and outward sites of system 1a.

	inward (A)	outward (B)	inward (C)	outward (D)	inward (E)	outward (F)
Donor	BD Zr-C α		BD Olefin		LP C(5)	LP C(2)
Acceptor	BD* Olefin		LV (1) Zr		LV (2) Zr	LV (1) Zr
$E^{(2)}$ (kcal/mol)	71.6	55.8	66.0	40.4	90.5	63.2
$\Delta E^{(2)}$ (kcal/mol)	15.8		25.6		27.3	

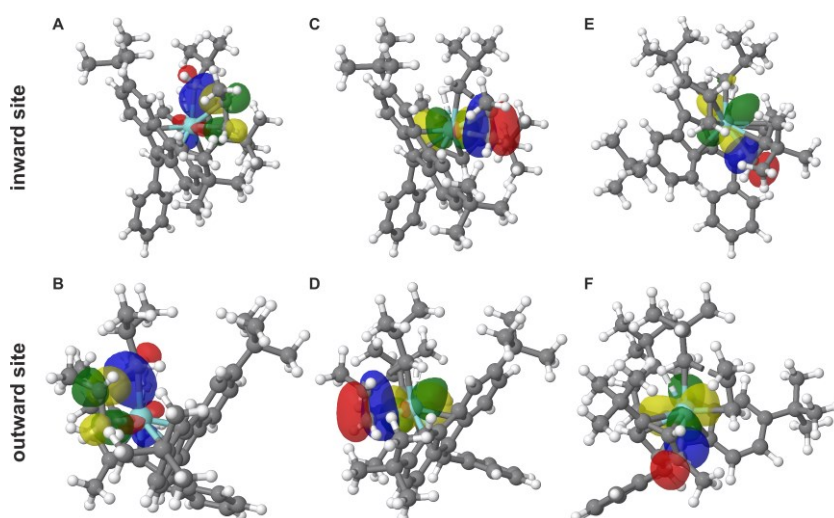


Figure 1.5. Main interactions between the electron-donors and electron-acceptors for the inward (left) and outward (right) TS structures for the system 1a. Capital letters label the couple of donor and acceptors reported in Table 1.2.

In conclusion, the results obtained by combining DFT evaluations with ASM-NEDA and Buried Volume ($\%V_{\text{Bur}}$) analysis show that across systems **1-3** the observed site preferences stem from subtle balances between strain and interaction terms: the family of system **1** is mainly governed by catalyst strain (with a minor, oppositely olefin term) and, as showed above, by a not-negligible interaction contribution (CT specifically); for system **2** the key factor is the strain one that prevails on the expected electronic *trans* influence; system **3** preference for PS site is rooted in olefin deformation at TS.

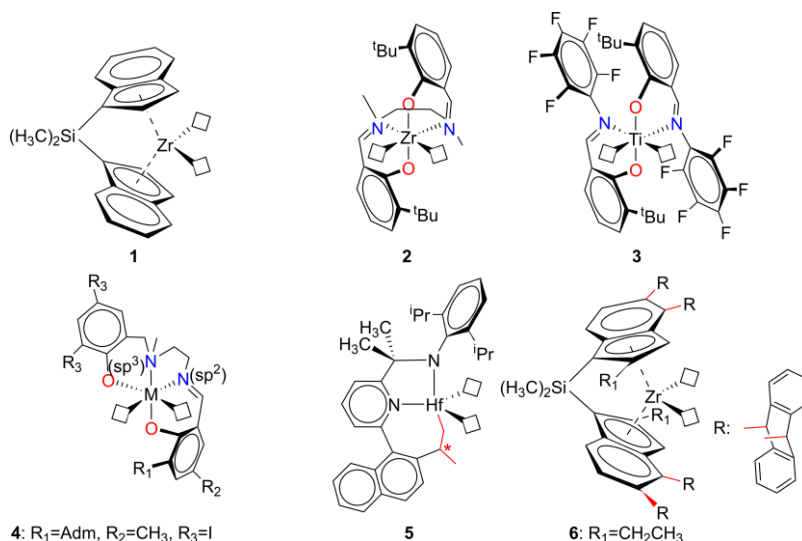
Overall, the DFT results are consistent with a CS mechanism, which is controlled by the ligand framework, directing the chain direction. In this *scenario*, ASM-NEDA and $\%V_{\text{Bur}}$ analysis provide decisive insights into its origin.

1.4 Stereoselectivity Analysis

Stereoregulation in PP polymerization is not a merely matter of selecting *re* or *si* enantioface of the prochiral propene (or α -olefin in general). Many systems exhibit additional factors governing the tacticity and the occurrence of stereoerrors.

In order to treat these aspects coherently in this Section, the analysis of stereoselectivity mechanism will be held adopting a unified framework. Firstly DFT, which is used to map the relevant propagation pathways and the associated stereoerror(s) (SE) across a representative set of catalysts, showed in **Scheme 1.8**. For a rapier and qualitatively interpretation of steric effects, a quadrant representation has been employed, with white and grey sectors indicating free and occupied zones of the ligand framework, respectively.

As can be inferred from the **Scheme 1.8**, the catalyst set spans three families: two C_2 -symmetric ansa-metallocene active species of (system **1** and **6**)^{3,71}, two C_2 -symmetric non-metallocene systems (system **2** and **3**)^{72,73} and two C_1 -symmetric catalysts (system **4** and **5**)^{11,23}. Within this series, system **3** is the only catalyst producing syndiotactic PP (sPP), whereas the remaining systems yield isotactic PP (iPP).



Scheme 1.8. Active catalytic species of selected systems for the of stereoselectivity re-analysis.

DFT analysis starts from system **1** and **2**, *ansa*-metallocene and salan systems respectively, bot producing iPP *via* 1,2 (primary) insertion. The two complexes exhibit two different coordination environment, tetrahedral and octahedral, respectively. Stereocontrol mechanism is visualized in an intuitive quadrant

representation (**Figure 1.6**, as insets).

As already noted, the C_2 -symmetric *ansa*-metallocene **1** fixed a chiral pocket for the growing chain (**Figure 1.6A**), with the *ortho*-substituents on the salan framework playing the same role in system **2** (**Figure 1.6A'**). Stereoerrors arise from two different pathways, as declared in the **Introduction**: the first one (S1 or chain misorientation, CMO) presents the growing chain in its non-preferred chiral orientation, thus selecting the opposite monomer enantioface to retain the *anti* chain-monomer motif while in the second path (S2 or monomer misorientation, MMO) chain maintains its preferred orientation with the monomer inserting *syn* to the chain

itself. Both SE transition states are close in energy (about 1 kcal/mol, as reported in Table 1.3).

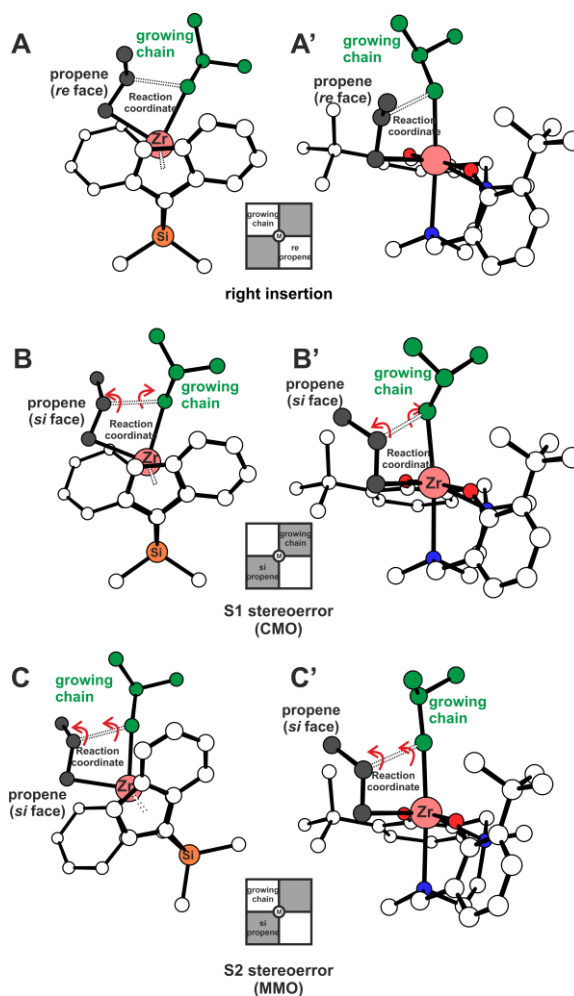


Figure 1.6. DFT optimized TSs for 1,2-primary propene insertion: system 1 (top row) and system 2 (bottom row). A/A': regular insertion; B/B': S1 stereoerror (CMO); C/C': S2 stereoerror (MMO). Hydrogen atoms omitted for clarity. Red arrows denote the relative orientation of the monomer and growing chain. Insets: quadrant representations.

Table 1.3 Relative DFT electronic energies (ΔE) and Gibbs (ΔG) energies in kcal/mol for the two SE paths (S1 and S2), referenced to the regular propene insertion TS ($\Delta E(\Delta G)_{\text{Stereo1}}$ and $\Delta E(\Delta G)_{\text{Stereo2}}$) for systems **1-6**.

System	$\Delta E(\Delta G)_{\text{Stereo1}}^{\text{a)}$	$\Delta E(\Delta G)_{\text{Stereo2}}^{\text{a)}$	$\Delta E(\Delta G)_{\text{Stereo1}}^{\text{b)}$	$\Delta E(\Delta G)_{\text{Stereo2}}^{\text{b)}$
1	4.0 (4.3)	4.2 (3.4)	4.0 (4.4)	4.3 (3.6)
2	3.2 (3.6)	2.1 (1.9)	2.5 (3.0)	3.4 (3.2)
3	3.1 (4.1)	3.0 (3.6)	4.0 (5.0)	2.9 (3.5)
4	2.2 (2.0)	3.4 (4.0)	1.7 (1.4)	3.7 (4.3)
5	4.0 (3.1)	/	3.6 (2.8)	/
6	9.4 (8.8)	9.2 (8.6)	9.3 (8.8)	9.1 (8.4)

^{a)} DFT energies include dispersion and solvent correction (PCM model). ^{b)} DFT energies including only dispersion correction (no solvent).

In the quadrant view (**Figure 1.6**, as insets), regular insertions place the growing chain and monomer in a free sectors of the pocket (white zones), while in S1/CMO (panels **B/B'**), both growing chain and monomer point at the zone occupied by the ligand and in S2/MMO (panels **C/C'**), the *syn* alignment of the methyl group of propene and the chain end leads to mutual steric interactions.

Phenoxyimine system **3** (**Scheme 1.8**) is C_2 -symmetric catalyst, like systems **1** and **2**, yet yielding sPP rather than iPP, through a sort of chain-end control by secondary (2,1) insertion.^{44,73} Indeed, after each insertion, its backbone undergoes to a site inversion (from Δ to Λ and *viceversa*). The two stereoerror pathways (**Figure 1.7B** and **C**) are quite different from those seen for systems **1** and **2**. S1 (MMO) stereoerror resembles that in the previous cases, whereas the alternative S2 stereoerror arises from an occasional skip of the site inversion (SSI) rather than a CMO event. The computed barriers for the two SE are reported in **Table 1.3** and are small. An alternative *scenario*, in which the syndiotactic propagation is preserved could be depicted by the insertion of *si*-propene into a *re*-ending growing chain at the Δ -site (**Figure 1.7D**) but it is ruled out due to the high TS Gibbs energy (calculated as 7.0 kcal/mol).

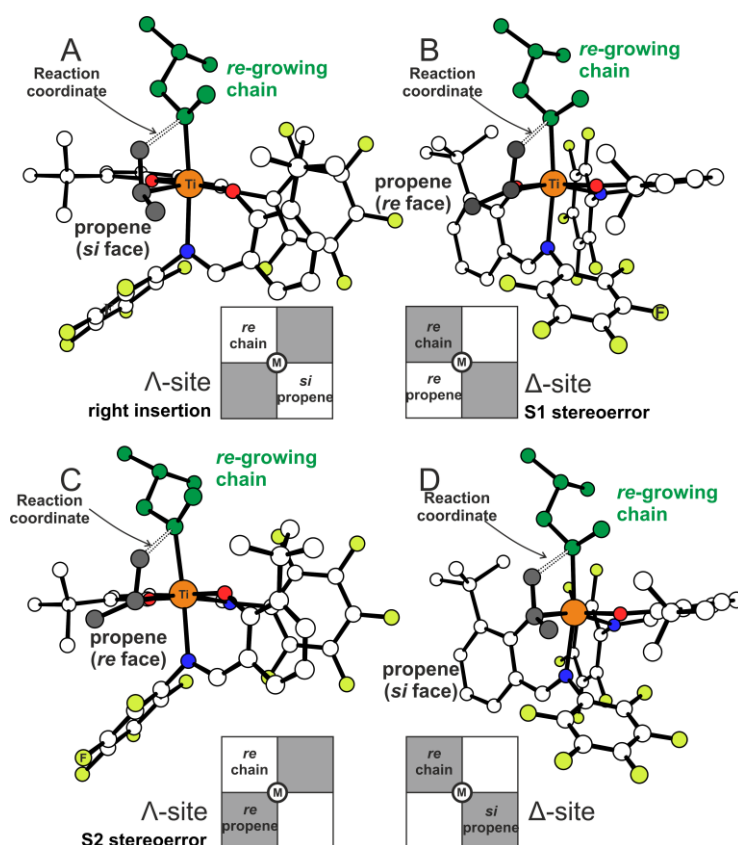
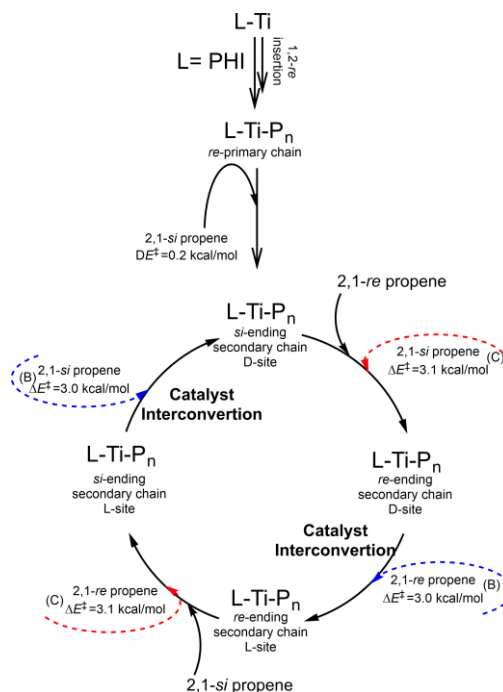


Figure 1.7. DFT optimized TSs for 2,1-secondary propene insertion into a *re*-ending secondary chain for system 3, with corresponding quadrant representations.

Also, in this case the quadrant representation is informative: as before, during regular propagation, both growing chain and monomer occupy free zones, but after the insertion the chain is displaced into a congested region. A rapid subsequent insertion would generate an SSI-type stereoerror, in a sPP sequence (**Figure 1.7C**). For a normal propagation, the site inverts after each insertion, being ready for the next one; at this point an MMO stereoerror could occur (**Figure 1.7B**). For this type of system, it can be inferred that the stereoerror mechanism is governed by the kinetic competition between inversion and insertion. A schematic representation of the elementary steps for the polymerization mechanism is depicted in **Scheme 1.9**.



Scheme 1.9. Catalytic cycle for system 3. Capital letters in parenthesis correspond to the stereoerror in Figure 1.6.

System **4** is a C_1 -symmetric species producing iPP. It is another example of catalyst able to invert its ligand wrapping mode during the polymerization. DFT results suggest that the propagation mainly occurs in the *fac-mer* (FM) geometry (**Figure 1.8A**) whereas the lowest-energy stereoerror appears only after a change in the wrapping mode from a FM geometry to *fac-fac* (FF) geometry around the metal atom (S1 stereoerror, in **Figure 1.8B**). For FM and FF representations, refer to **Scheme 1.7**. The alternative CMO-type stereoerror (S2, **Figure 1.8C**), featuring a *syn* arrangement of growing chain (forced by the bulky adamantyl substituent as in the regular insertion) and inserting monomer, results in a more disfavoured situation than S1. The DFT energetics are reported in **Table 1.3** and match the experimental stereoselectivity of this system.²³ These results imply that in absence of a ligand wrapping mode

interconversion the catalysis would be substantially more isoselectivity than the expected. In practice, propagation happens in FM mode and the dominant (or lower) stereoerror occurs in FF one. The interpretation of the quadrant representations (**Figure 1.8**, insets) indicates that, even in S1 stereoerror in FF wrapping mode of the ligand framework, both growing chain and inserting monomer resides in free zone.

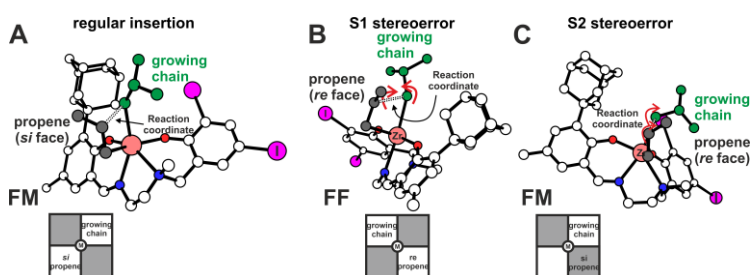


Figure 1.8. DFT optimized TSs for 1,2-primary propene insertion for system 4, with corresponding quadrant representations.

System 5, belonging to the pyridylamido-Hf family of catalysts, shows distinctive stereochemical features. The active species is generated *in situ* by the first monomer insertion into the Hf-C_{aryl} bond, “defining” the ligand and the catalytic pocket (the active species is represented in **Scheme 1.8**, in red the first inserted olefin).^{74–76} As showed above and from literature, as a consequence of this structural evolution, this system (and the family of catalyst to which it belongs) propagates through a CS mechanism on PS geometry, so only at one site.³⁸ Additionally, this catalyst family does not follow the classical Corradini model for stereoselectivity²⁵. Indeed, its stereoselectivity arises from direct monomer-ligand steric interactions within the catalytic pocket. The *ortho*-substituents on the aniline ring play a crucial role in determining the stereocontrol, while the remote substituent groups on the bridge linking the pyridine and N-aryl fragments enhance enantioselectivity *via* a “buttressing effect”, that pushes the N-aryl ring, and its *ortho* substituents, toward the catalytic pocket. In other words, the ligand imposes the enantioselectivity and not the

chirality of the growing chain. The calculated stereoselectivity for system **5** is showed in **Table 1.3** and the TSs structures, showing the buttressing effect, are reported in **Figure 1.9**.

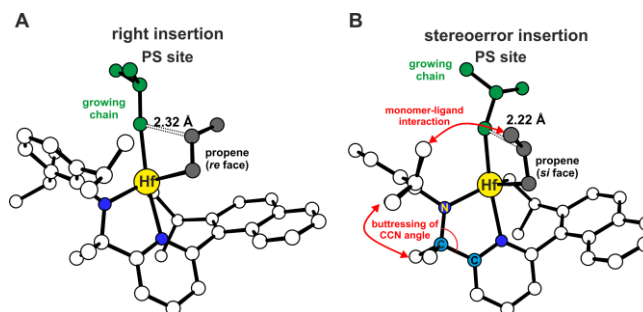


Figure 1.9. DFT optimized TSs for 1,2-primary propene insertion for system **5**. Red arrows indicate the buttressing effect.

System **6**, a cyclopenta[*a*]tritycil *ansa*-metallocene, was identified through an integrated high-throughput experimentation/quantitative structure-activity relationships (HTE/QSAR) approach.⁷¹ Experimentally, it exhibits exceptional isoselectivity, on the order of one stereoerror per 4000 insertions at room temperature and 1 per 4000 at 120°C, maintaining high activity under both conditions. DFT energetics are reported in **Table 1.3**, corroborating this behaviour. Analysis of DFT structures confirms the CMO and MMO stereoerror TSs, which are remarkably high in energy, consistently with the scarce formation of stereoerror (**Figure 1.10**). The evaluations concerning the quadrant representation made for system **1** can be extended to system **6**.

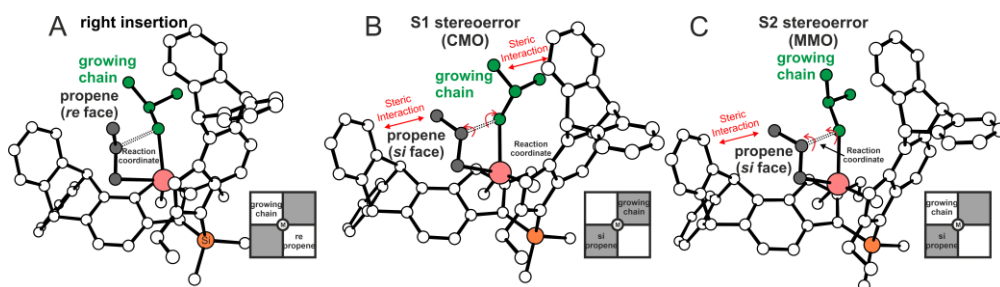


Figure 1.10. DFT optimized TSs for 1,2-primary propene insertion: system 6. In A, regular insertion, in B S1 stereoerror (CMO) and in C/C', S2 stereoerror (MMO). Hydrogen atoms omitted for clarity. Red arrows denote the relative orientation of the monomer and growing chain. Insets: quadrant representations.

Buried volume analysis has been made for all the systems and showed in **Figure 1.11**, with total buried volume $\%V_{\text{Bur}}$ values reported on top and the values for each quadrant reported inside the map. Indeed, by analysing the values in the quadrants, it is possible to note the influence of the ligand skeleton, for systems **1-4** and **6**, in orienting the growing chain for the regular insertion (NE quadrant). Conversely, NE quadrant for system **5** results to be the lowest occupied reinforcing the concept of no chiral orientation of the growing chain, that has been to be said peculiar of this class of catalyst.³⁸ Additionally, correlation of the experimental and calculated stereoselectivity and total $\%V_{\text{Bur}}$ values shows how the ligand modification, and hence the occupied volume, impact markedly on the stereoselectivity (**Figure 1.11**).

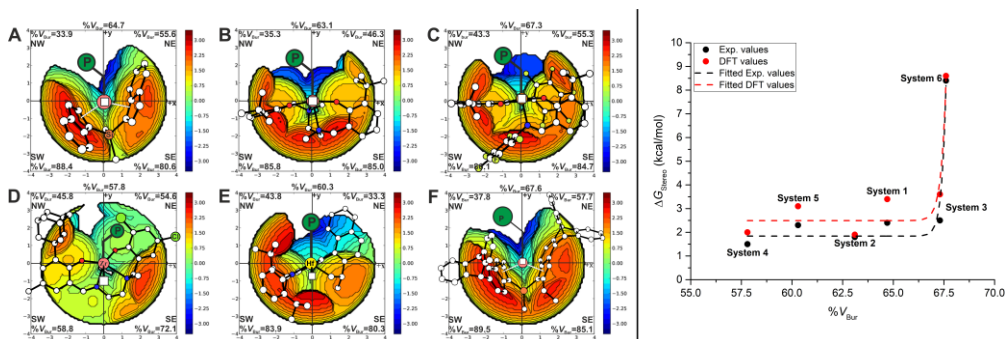


Figure 1.11. Steric maps of neutral precursor of system 1 to 6 (from A to F respectively). Total

and quadrant % V_{Bur} are reported. The white box represents the available site for the incoming monomer and the green circle with P inside represents the growing chain in its favoured orientation. Correlation graph of experimental and calculated stereoselectivity and total % V_{Bur} on the right panel.

ASM-NEDA approach has been applied to dissect the factors governing stereoselectivity. The DFT analysis order will be maintained. **Figure 1.12A** and **B** reports ΔE_{Tot} decomposition in ΔE_{Strain} and ΔE_{Int} , projected onto $C_{\text{olefin}}-C_{\text{chain}}$ distance (TSs marked as circles).

For system **1**, the three TSs lie within a narrow RC window (2.24 Å for regular, 2.28 Å for S1/CMO and 2.25 Å for S2/MMO). Stereoselectivity seems to arise primarily from ΔE_{Strain} for both SE pathways, CMO stereoerror resulting in the smaller ΔE_{Strain} (about 2.6 kcal/mol lower than MMO), while MMO exhibiting higher ΔE_{Int} stabilization (**Figure 1.12A**). For system **2** (**Figure 1.12B**), the regular and CMO TSs occur at similar RC (2.19 and 2.21 Å), while MMO is earlier (2.33 Å). As for system **1**, the strain term seems to be the main discriminator.

ΔE_{Strain} term has been further decomposed into $\Delta E_{\text{Strain}(\text{Cat})}$ and $\Delta E_{\text{Strain}(\text{C3H6})}$ (**Figure 1.12C-F**). The trends for both systems are analogous: consistently with the growing-chain orientation picture, $\Delta E_{\text{Strain}(\text{Cat})}$ dominates the stereocontrol, whereas $\Delta E_{\text{Strain}(\text{C3H6})}$ (reported to the relative planar olefin in **Figure 1.12E** and **F**) slightly decreases the ΔE_{Stereo} , particularly for system **2** (**Figure 1.12F**). Additionally, a full NEDA decomposition of ΔE_{Int} for system **1** is reported in **Figure 1.12G** and **H** indicating CT component as the leading stabilization term near the TS.

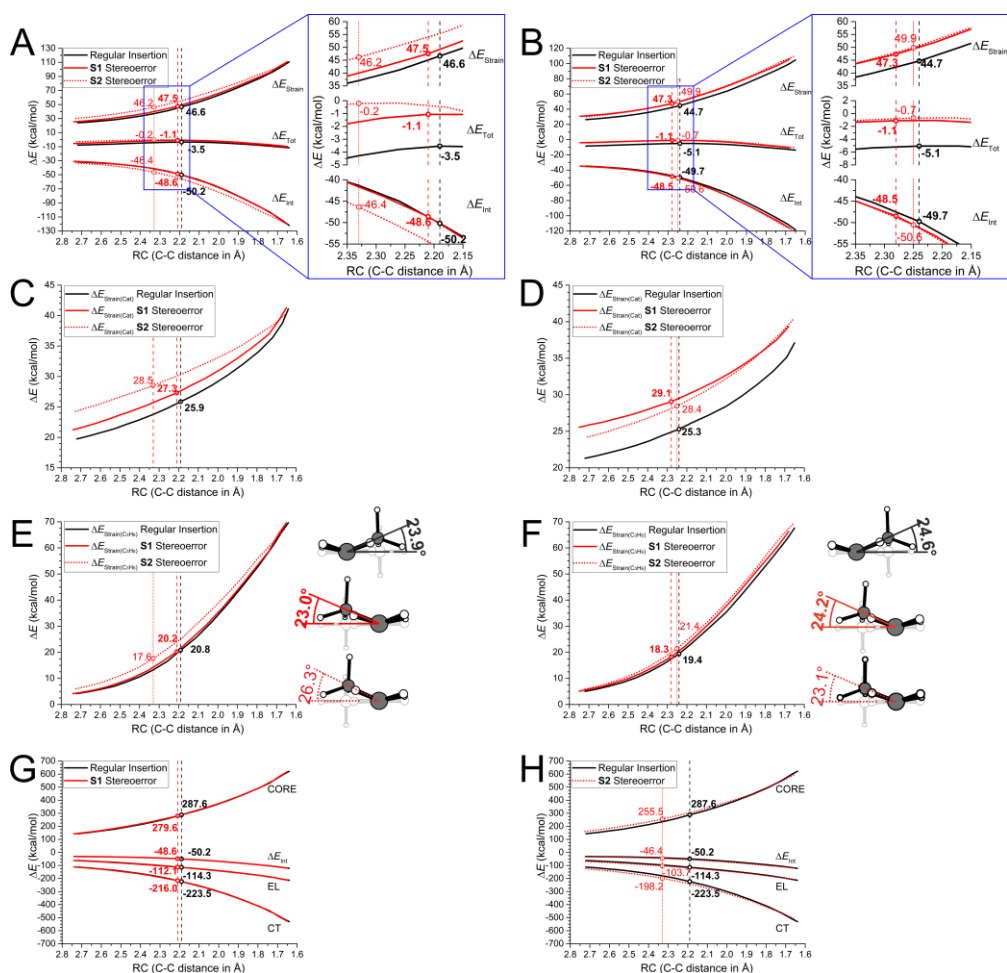


Figure 1.12. ASM-BEDA analysis of propene insertion for system 1 and 2 as a function of the reaction coordinate (C_{olefin}-C_{chain}, Å). (A,B) ΔE_{Tot} and its component ΔE_{Strain} and ΔE_{Int} , with insets on TS region. (C,D) $\Delta E_{\text{Strain(Cat)}}$ and (E,F) $\Delta E_{\text{Strain(C3H6)}}$ with propene deformation referenced to free plana propene (light grey). (G,H) NEDA decomposition of ΔE_{Int} into electrostatic (EL), CORE and charge-transfer (CT) contributions for system 1. Curves are color-coded: regular (black), S1/CMO (red), S2/MMO (red dotted). TSs are represented as circles.

To analyse the CT component from ΔE_{Int} for system 1, second-order perturbative n the TS of the regular insertion and SEs has been carried out. **Table 1.4** summarises the two main donor-acceptor interaction:

- 1) $\sigma(\text{Zr-C}\alpha)$ to $\pi^*(\text{C}=\text{C})$ interaction from metal-chain bonding orbital into the antibonding π orbital (BD^*) of the olefin.
- 2) $\pi(\text{C}=\text{C})$ to $\text{LV}(\text{Zr})$ donation from the olefin bonding orbital into an empty metal valence (“lone-vacancy, d_z^2 -like) orbital.

The corresponding $E^{(2)}$ stabilization energies are reported in **Table 1.4** are reported (larger $E^{(2)}$ indicating stronger CT stabilization) The capital letters in Table 1.4 refer to the structures visualized in **Figure 1.13**, using PNBOs (“pre-orthogonalized” NBOs). In this context, donors are shown in blue and red and the acceptors in yellow and green (rendered with Jmol program⁶⁷).

Table 1.4. Main interactions between donors and acceptors computed by NBO analysis for the propene TSs for system 1.

	Donor	Acceptor	$E^{(2)}$ (kcal/mol)
Right Insertion (A)	BD Zr-C α	BD* Olefin	71.1
S1 (B)			63.7
S2 (C)			72.5
Right Insertion (A)	BD Olefin	LV (1) Zr	49.3
S1 (B)			47.4
S2 (C)			59.6

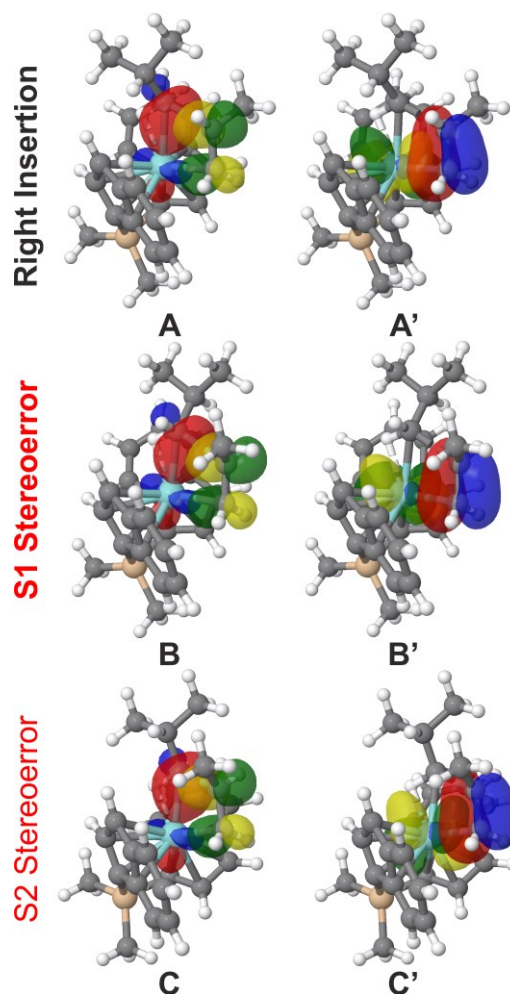


Figure 1.13. Main interactions between the electron-donors and electron-acceptors for the right (A and A'), S1 (B and B') and S2 (C and C') TSs for system 1. Uppercase letters label the couple of donor and acceptors reported in Table 1.4.

The ASM-NEDA highlights ligand-controlled strain as primary factor for stereocontrol in these systems. Tuning ligand rigidity and flexibility and the catalytic pocket geometry can induce lowering the strain of regular insertion path and raising the strain of both SE paths. Because of the different response of both SE pathways to steric and electronic changes, it is required to optimally balance the optimization

without improving one and inadvertently facilitating the other.

The ASM-NEDA has been extended to the syndiospecific octahedral system **3**. **Figure 1.14A** compares the three TSs for regular SSI (S1) and MMO (S2) along the $C_{olefin}-C_{chain}$ reaction coordinate. Notably, the two SE TSs occur at the same RC (2.20 Å), and partitioning ΔE_{Strain} into catalysts and monomer contribution (**Figure 1.14B** and **C**) shows remarkably similar deformation profiles. This indicates that the steric stress associated with a secondary growing chain and with the C_6F_5 -group, for SSI and MMO respectively, leads to comparable strain penalties for both SEs. The S1 preference over S2 ($\Delta E_{Tot} = 6.4$ kcal/mol vs. 7.6 kcal/mol) is therefore traced to a more stabilizing ΔE_{Int} . A full NEDA analysis is provided in **Figure 1.14D** and **14E**, revealing that the main contributions arise from the CORE and CT terms.

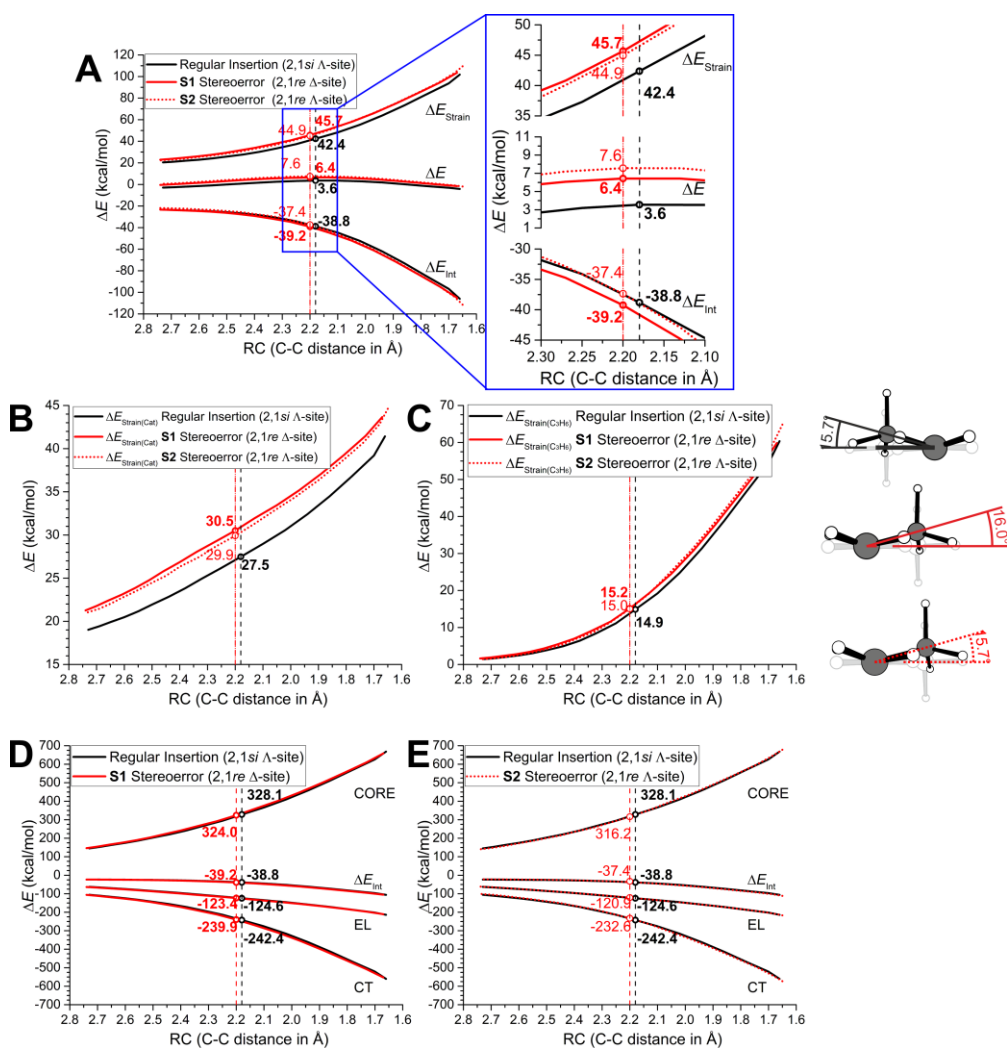


Figure 1.14. ASM-NEDA analysis of propene insertion for system 3 along the RC ($C_{\text{olefin}}-C_{\text{chain}}$, Å). (A) ΔE_{Tot} with decomposition into ΔE_{Strain} and ΔE_{Int} for regular insertion (black), S1/SSI (red) and S2/MMO (red dotted). (B) $\Delta E_{\text{Strain(Cat)}}$ and (C) $\Delta E_{\text{Strain(C3H6)}}$, monomer deformation referenced to free planar propene (light grey). (D-E) NEDA decomposition of ΔE_{Int} into EL, CORE and CT components: (D) regular insertion vs. S1/SSI and (E) regular insertion vs. S2/MMO. TSs marked by circles and all energies in kcal/mol. The colour code is black for regular insertion, red for S1/SSI and red dotted for S2/MMO.

Within the NEDA protocol, the CORE term captures purely quantum-mechanical

effect arising from occupied-occupied orbital interactions, whereas the CT term quantifies donor-acceptor electron delocalization between filled and vacant orbitals. To further characterize CORE, overlap matrix elements S_{ij} have been evaluated between highest-occupied NBOs of the two fragments: larger S_{ij} values indicate greater occupied-occupied orbital overlap and thus stronger delocalization. Differences in CT terms were investigated *via* second-order perturbation theory, focusing on $E(2)$ values, which report the stabilization associated with specific donor-acceptor pairs. Orbital visualizations were rendered with Jmol⁶⁷. CORE and CT analysis is reported in **Table 1.5** and orbital depiction is reported in **Figure 1.15**.

Table 1.5. Overlap S_{ij} between the highest occupied NBOs for catalyst+chain (H.O.NBO_{Cat}) and olefin (H.O.NBO_{C₃H₆}) fragments (CORE, panels A-C in Figure 1.15) and main donor-acceptor interactions with second-order stabilization energies $E(2)$ (CT, panels A'-C' in Figure 1.15) for system 3.

Pathway	CORE panel	H.O.NBO _{Cat}	H.O.NBO _{C₃H₆}	S_{ij}	CT panel	Donor- Acceptor	$E(2)$ (kcal/mol)
Regular insertion	A	BD σ Zr-C α	BD π olefin	0.306 3	A'	BD σ Zr-C α – π^* olefin	82.8
S1	B	BD σ Zr-C α	BD π olefin	0.298 5	B'	BD σ Zr-C α – π^* olefin	80.8
S2	C	BD σ Zr-C α	BD π olefin	0.291 3	C'	BD σ Zr-C α – π^* olefin	78.4

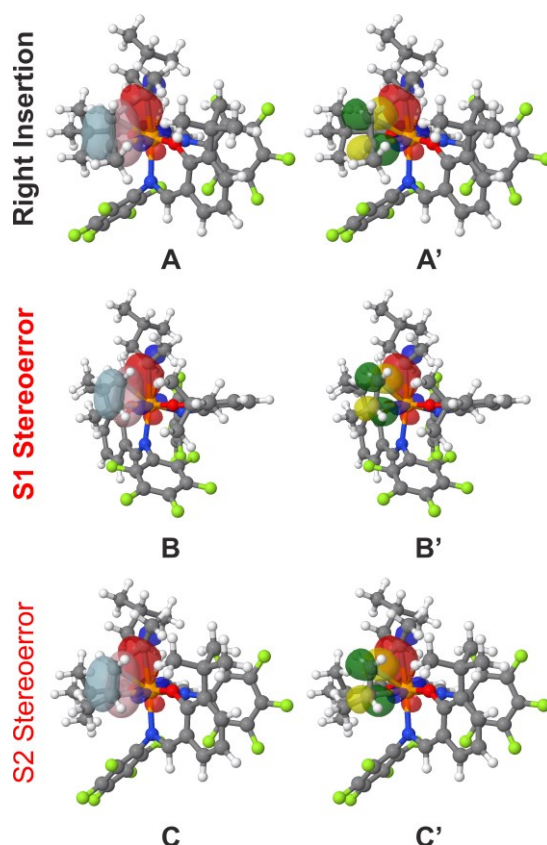


Figure 1.15. NBO visualization of the main occupied-occupied overlaps (A B and C) and dominant donor-acceptor interaction (A', B' and C') for TSs of system 3. Uppercase labels refer to the entries in Table 1.5. Filled orbitals are represented in blue/red and pink/light blue, donors in blue/red and acceptors in yellow/green.

For system **4**, stereoselectivity is dependent on the interconversion between FM and FF geometry, and both geometries put growing chain and olefin in free zones, as represented in **Figure 1.8**. ASM-NEDA approach could allow to discriminate factors governing stereoselectivity for this system. In **Figure 1.16A** is reported the ΔE_{Tot} and its decomposition terms, revealing that the FM geometry is preferred in terms of ΔE_{Strain} , which overcompensates the fact that ΔE_{Int} is more stabilizing for FF geometry.

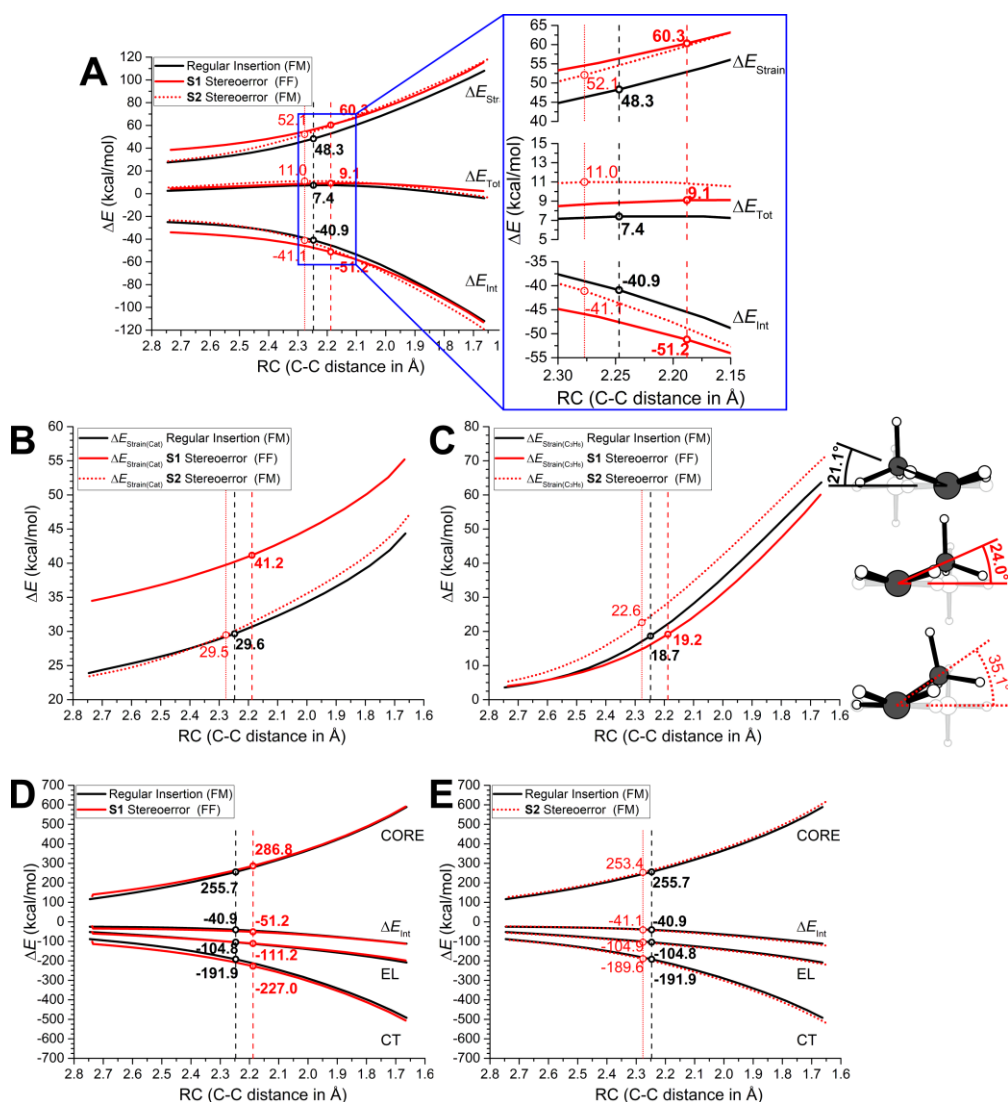


Figure 1.16. ASM-NEDA analysis of propene insertion for system 4 along the RC ($C_{\text{olefin}}-C_{\text{chain}}$, Å). (A) ΔE_{Tot} with decomposition into ΔE_{Strain} and ΔE_{Int} for regular insertion (black), FF/S1 (red) and FM/S2 (red dotted). (B) $\Delta E_{\text{Strain(Cat)}}$ and (C) $\Delta E_{\text{Strain(C3H6)}}$, monomer deformation referenced to free planar propene (light grey). (D-E) NEDA decomposition of ΔE_{Int} into EL, CORE and CT components: (D) regular insertion vs. FF/S1 and (E) regular insertion vs. FM/S2. TSs marked by circles and all energies in kcal/mol. The colour code is black for regular insertion, red for FF/S1 and red dotted for FM/S2.

Further partitioning of the strain term (**Figure 1.16B and C**) indicates that the FM advantage originates mainly from a lower deformation of the catalyst carrying the chain fragment, whereas differences in monomer deformation are small.

Since FF is favoured by interaction term, its origin has been studied (**Figure 1.16D and F**), pointing to CT term as the dominant contributor. Consistently, NBO analysis identifies a main donor-acceptor interaction between the Zr-C α bonding orbital and the olefin π^* orbital. The corresponding second-order stabilization energies, $E^{(2)}$, reported in **Table 1.6**, show the FF(S1) TS to be around 15 kcal/mol more stabilized than both the regular FM and FM(S2) insertions. From these results can be inferred that the observed stereoselectivity results from a competition between strain stabilization for FM and a stronger CT stabilization for FF, with strain dictating the overall preference for FM geometry at TS. PNBOs are reported in **Figure 1.17**, where donors are coloured blue/red and acceptors yellow/green.

Table 1.6. Main interactions between donors and acceptors computed by NBO analysis for the propene TSs for system 4.

	Regular Insertion	FF/S1	FM/S2
	(A)	(B)	(C)
Donor	BD Zr-C α		
Acceptor	BD* Olefin		
$E^{(2)}$			
(kcal/mol)	71.7	85.0	69.5

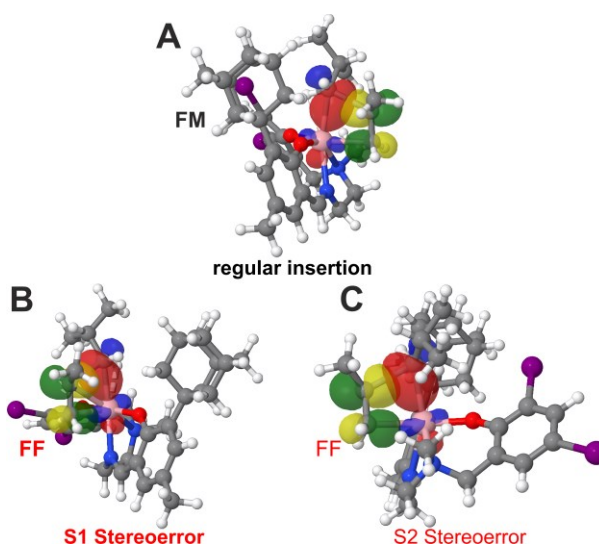


Figure 1.17. Main interactions between the electron-donors and electron-acceptors for the regular (A), FF/S1 (B) and FM/S2 (C) TSs for system 5. Uppercase letters label the couple of donor and acceptors reported in Table 1.6.

As mentioned above, system **5** is an interesting species to analyse since its stereoselectivity mechanism differs from other isoselective catalysts. Indeed, it has been said to not follow Corradini model, and it follows a CS mechanism. For this reason, ASM-NEDA analysis has been carried out at the PS sites to investigate the factors governing stereoselectivity and fully reported in **Figure 1.18**.

The activation strain plot is reported in **Figure 1.18A**, suggesting that along the full reaction coordinate, the computed stereoselectivity is dominated by strain factor, with the interaction term providing only partial compensation. ΔE_{Int} term favours the SE because its TS occurs at shorter RC distance (2.22 Å) than regular insertion TS (2.35 Å), but the additional deformation required to reach that distance overweigh the interaction gain. Decomposition of ΔE_{Strain} (**Figure 1.18B** and **C**) shows that the olefin contribution $\Delta E_{\text{Strain(C3H6)}}$ is the leading term while the $\Delta E_{\text{Strain(Cat)}}$ varies less. This pattern supports a “direct monomer selection” hypothesis by the ligand, inducing high distortion for the monomer at TS.

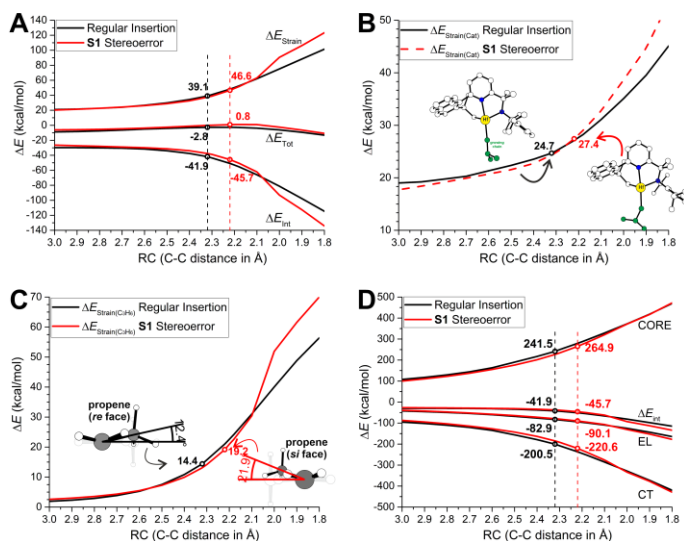


Figure 1.18. ASM-NEDA analysis of propene insertion for system 5 along the RC (C_{olefin}-C_{chain}, Å). (A) ΔE_{Tot} with decomposition into ΔE_{Strain} and ΔE_{Int} for regular insertion (black), FF/S1 (red) and FM/S2 (red dotted). (B) ΔE_{Strain(Cat)} and (C) ΔE_{Strain(C3H6)}, monomer deformation referenced to free planar propene (light grey). (D) ΔE_{Int} decomposition terms. TSs marked by circles and all energies in kcal/mol.

The last system involved in this analysis is system **6**, which is a suitable example of how modification of the *ansa*-metallocene ligand framework can induce high destabilization for both S1 (CMO) and S2 (MMO) stereoregulation. To rationalize its behaviour, its ASM-NEDA analysis has been compared to system **1** and reported in **Figure 1.19**, left panel. It reveals that stereoregulation penalties for system **6** are approximately twice those for system **1**, with energetic pattern remarkably similar. Indeed, in both cases ΔΔE_{Strain(Cat)} is the dominant factor, with interaction effects playing a secondary compensatory role. Consistently with this *scenario*, the %V_{Bur} steric maps in **Figure 1.19**, right panel, of the TS structures indicate that, relative to regular insertion (**Figure 1.19A**), the catalytic pocket expands for both SEs. Indeed, the values reported for NE and SW quadrants decrease, reflecting the pocket

enlargement, which for S1 is driven by the growing chain and monomer pushing the triptycyl moieties (NE and SW quadrants, respectively for chain and monomer). For S2 stereoerror, the SW quadrant shows lower values due to the double pushing effect of both monomer and chain, the latter in its preferred orientation. Overall, in both SEs, chain and monomer are forced into the ligand framework, raising the strain of the catalyst fragment and, consequently, the S1 and S2 TS energies relative to the regular insertion. Hence, the deformation required to accommodate the olefin is larger for system **6** than for system **1**, owing to the triptycyl substituent.

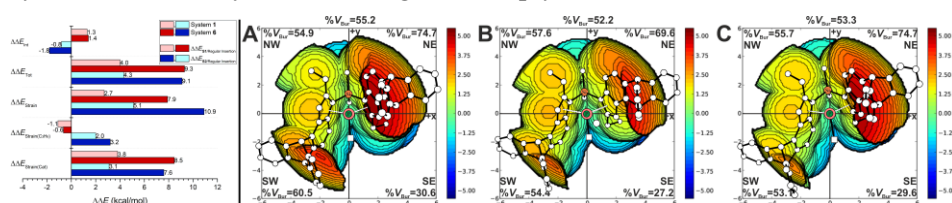
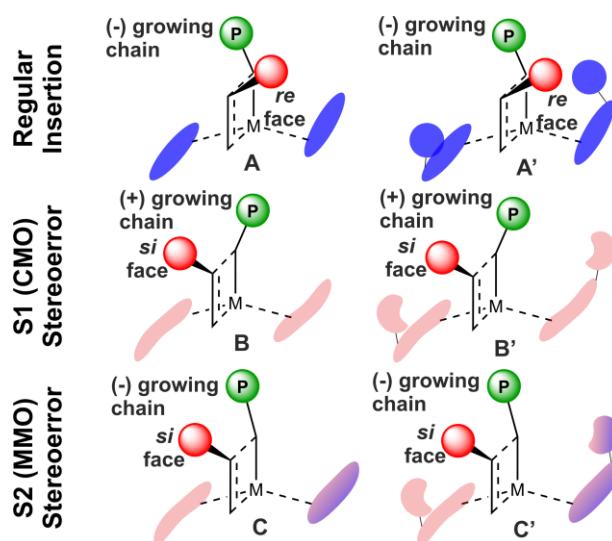


Figure 1.19. Left: Bar graph of $\Delta\Delta E_{Tot}$ and its decomposition terms for the regular insertion and S1, S2 stereoerrors for isoselective catalytic systems 1 and 6 (colour code as shown). Right: % V_{Bur} steric maps for system 6 TSs; (A) regular insertion, (B) S1 and (C) S2 stereoerrors. Total % V_{Bur} values are reported above each map; quadrant values are indicated inside. A red to blue colour scale denotes increasing of steric occupancy; white boxes marked available coordination site for the olefin or the chain.

Taken together, these observations suggest a clear strategy for the ligand design and improving isoselectivity for C_2 *ansa*-metallocene framework, based on increasing catalyst strain as depicted in **Scheme 1.10**.



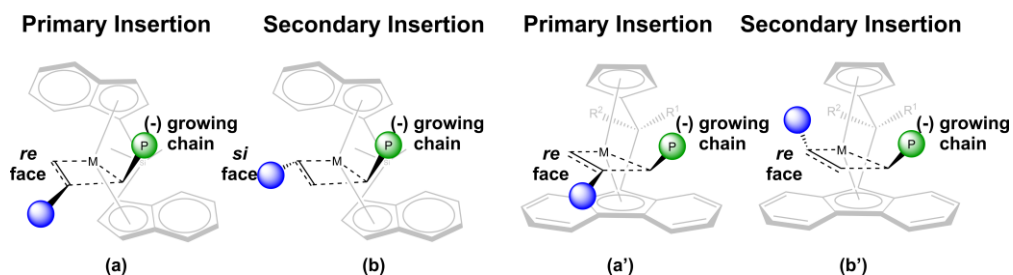
Scheme 1.10. Schematic picture of ligand and monomer enantioface driving ligand deformation in C_2 *ansa*-metallocene systems.

Finally, olefin deformation provides additional insights, especially for the MMO (S2) SE pathway. Indeed, in **Figure 1.20** olefin deformation for system **1**, **5** and **6** are compared, suggesting that the change in olefin deformation change from regular insertion to S2 stereoerror is small for the *ansa*-metallocenes but substantially larger for system **5**, supporting the picture that, depending on the ligand framework, monomer strain can support catalyst strain to suppress specific stereoerror pathways.

1.5 Regioselectivity Analysis

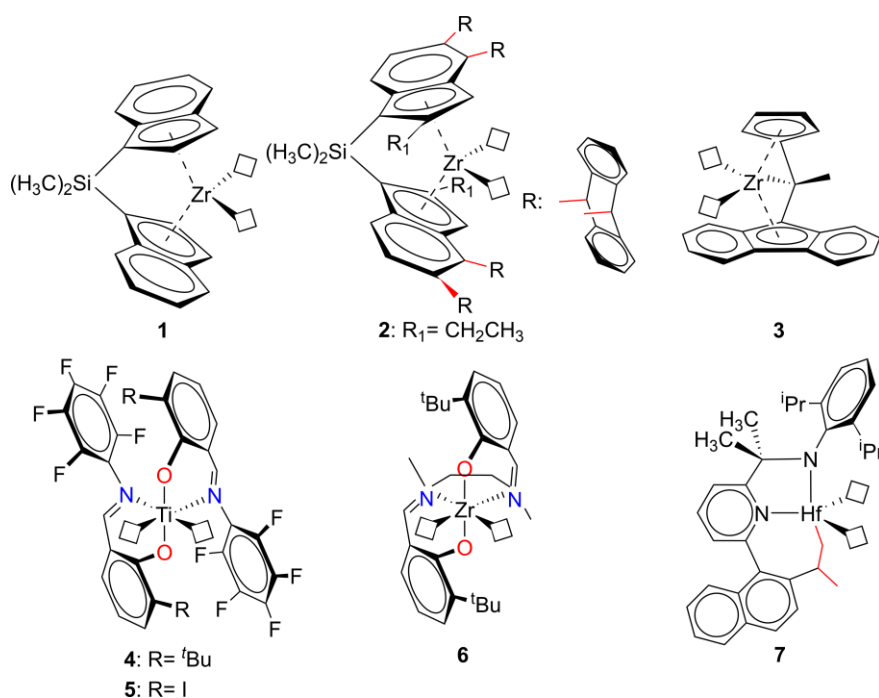
As outlined in the **Introduction**, regioselectivity in α -olefin polymerization reflects the competition between 1,2 (primary) insertion and 2,1 (secondary) insertion, with the former generally prevailing across both heterogeneous and homogeneous catalysts. Additionally, it is important to clarify that, like primary insertion, secondary insertion is enantioselective, discriminating between *re* and *si* enantioface of the incoming monomer. Combined experimental and computational studies show that C_2 -symmetric catalysts select opposite enantiofaces for primary and secondary insertion,

whereas C_S -symmetric systems tend to favour the same enantioface for both primary and secondary insertion.³ These trends have been established for metallocenes and then extended to post-metallocene systems. Pyridylamido catalysts behave analogously to C_S -symmetric systems. These aspects are summarized in **Scheme 1.11**.^{11,77,38}



Scheme 1.11. Preferred propene enantiofaces in primary and secondary insertions for C_2 *ansa*-metallocene systems (a and b) and C_S *ansa*-metallocene systems (a' and b').

On the basis of these premises, the regioselectivity analysis has been carried out on seven different catalytic systems, two C_2 -symmetry active species of *ansa*-metallocene (1, 2), a C_S -symmetric metallocene systems (3), three C_2 -symmetry active species of non-metallocene systems (4, 5, 6) and the prototype of the pyridylamido Hf system (7), represented in **Scheme 1.12**.



Scheme 1.12. Schematic representation of the active species of the systems employed for the analysis.

The DFT analysis is presented below. TSs for both primary and secondary insertion using the preferred olefin enantiofaces have been computed for all the systems. The discussion begins with system **1** and **2**, two isoselective catalysts which propagate through primary insertion. System **1** is a classical, minimal *ansa*-metallocene whereas system **2** is a recent evolution designed to overcome typical imitations of metallocene, able to produce highly stereo- and regioregular iPP even at elevated temperature (up to 150°C).⁷¹ **Figure 1.20** and **Table 1.7** reported the DFT optimized TS geometries and relative energetics.

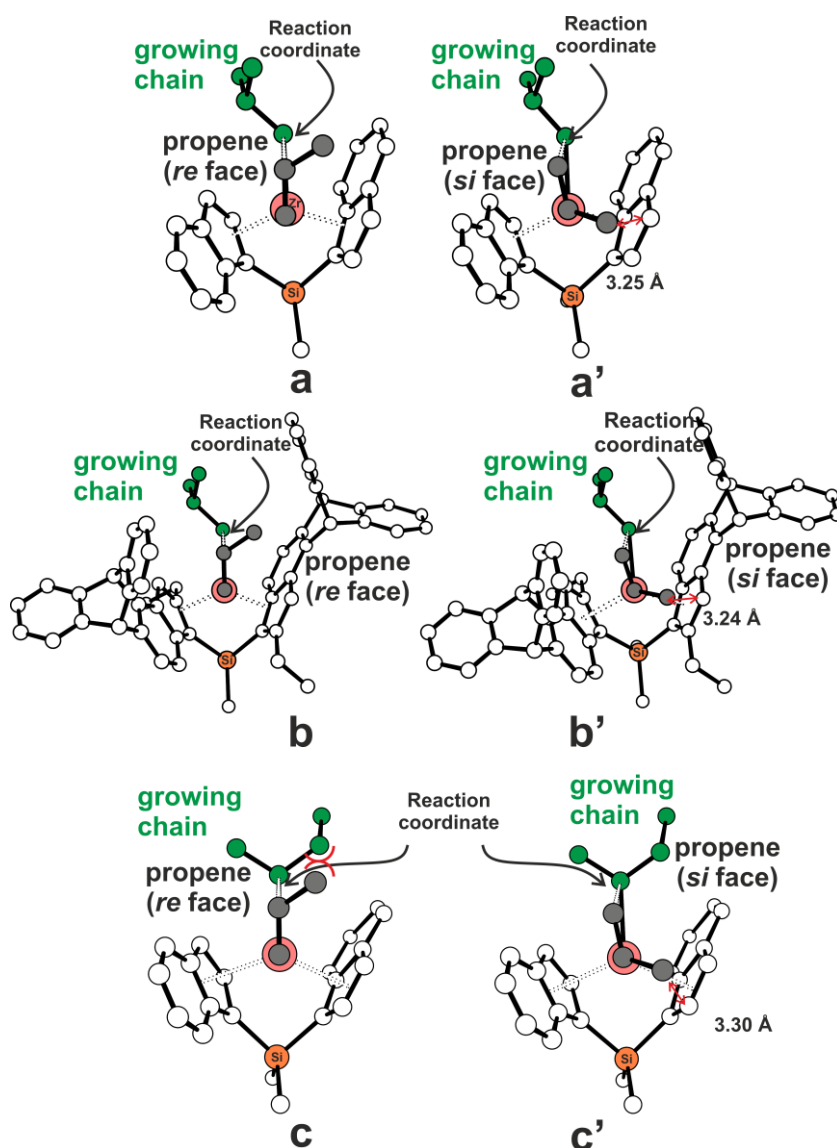


Figure 1.20. DFT optimized geometries for primary (**a**, **b** and **c**) and secondary (**a'**, **b'** and **c'**) insertion TSs for systems **1** and **2**. H atoms omitted for clarity. Distances in Å.

For both systems, the growing chain adopts its preferred chiral orientation and, energetically, primary insertion is favoured by 3.4 and 4.4 kcal/mol for system **1** and **2**, respectively (**Table 1.7**), in line with the experiment. Distances between the methyl group of the propene monomer and the ligand framework are similar for both

catalysts. However, sterics alone do not fully account for the magnitude of the preference of the primary insertion over the secondary one.

Table 1.7. DFT electronic (ΔE) and Gibbs (ΔG) energies in kcal/mol for regioselectivity, referenced to the primary insertion TS for system 1-7.

System	$\Delta E(\Delta G)_{\text{Regio}}^{[a]}$	$\Delta E(\Delta G)_{\text{Regio}}^{[b]}$
1	3.3 (3.4)	3.4 (3.6)
1 ^[c]	0.7 (0.7)	0.8 (0.8)
2	4.8 (4.4)	4.9 (4.5)
3	3.9(3.4)	3.9(3.5)
4	0.22 (-0.25)	0.26 (-0.21)
4 ^[c]	-2.2 (-3.1)	-2.1 (-2.9)
5	1.4 (1.4)	1.3 (1.3)
5 ^[c]	-2.9 (-1.8)	-2.9 (-1.8)
6	4.9 (3.2)	4.3(2.6)
7	2.1 (2.2)	1.9 (2.0)

[a] $\Delta E(\Delta G)$ including dispersion and PCM corrections; [b] $\Delta E(\Delta G)$ including dispersion correction only (no solvent); [c] values for system 1, 4 and 5 with a secondary chain.

To probe robustness, primary and secondary insertions on secondary growing chain have been analysed for system **1** (**Figure 1.3c** and **c'**). DFT predicts primary insertion is not favoured, in agreement with the experiment. Since steric arguments remain insufficient to rationalize the energetic gap, ASM-NEDA analysis has been carried out and will be discussed later.

Using the same protocol for system **1** and **2**, DFT analysis has been performed on system **3**. This C_s -symmetric metallocene is the first catalyst reported to synthesize

sPP through primary insertions.^{78,79} It presents two enantiomorphous sites, so monomer insert into M-C bond with opposite enantiofaces on alternating sites, generating syndiotactic sequence. Concerning regioselectivity, as discussed above, primary and secondary insertions proceed through the same enantioface for a given site. TSs are provided in **Figure 1.21**.

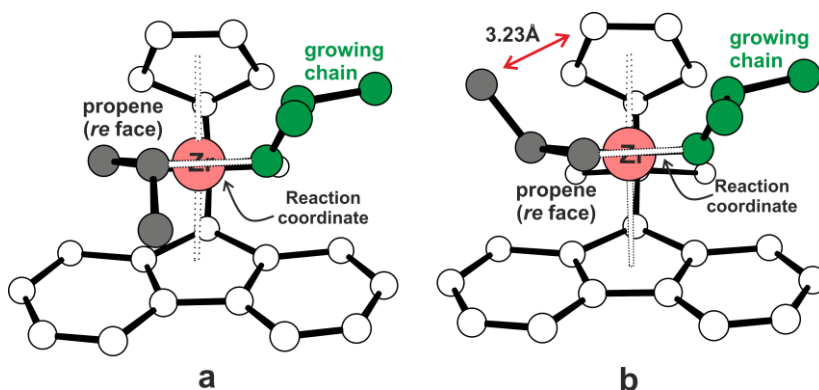


Figure 1.21. DFT optimized geometries for primary (a) and secondary (a) insertion TSs for system 3. H atoms omitted for clarity. Distance in Å.

DFT results mirror those obtained for the previous C_2 -metallocene systems. Indeed, primary insertion is preferred over secondary one (**Table 1.6**), according to the experimental data. Additionally, the distance between the methyl group of the secondary-inserted monomer and the ligand framework are very similar across the three systems (3.25 Å for system **1**, 3.24 Å for system **2** and **3**).

Transitioning to post-metallocene systems, attention moved to octahedral environment. For this analysis, three systems, **4**, **5** and **6**, were considered. These systems share a similar coordination environment around the metal centre, but with significant differences. Systems **4** and **5** lack of a bridge between the two nitrogen atoms, differing also for the R group on the phenolic ring (alkyl and halogenated, respectively). This apparently small modification leads to different polymerization behaviour. Indeed, system **4** is known to produce sPP through secondary insertions while system **5**, although was expected to synthesize sPP, leads to an iPP with a regioblock structure composed of consecutive segments arising from primary and

secondary insertions.²² System **6**, conversely, produce iPP through primary insertions. Based on this evidence, their regioselectivity has been analysed using DFT and optimized structures are reported in **Figure 1.22**, considering also insertion at secondary growing chain for systems **4** and **5**.

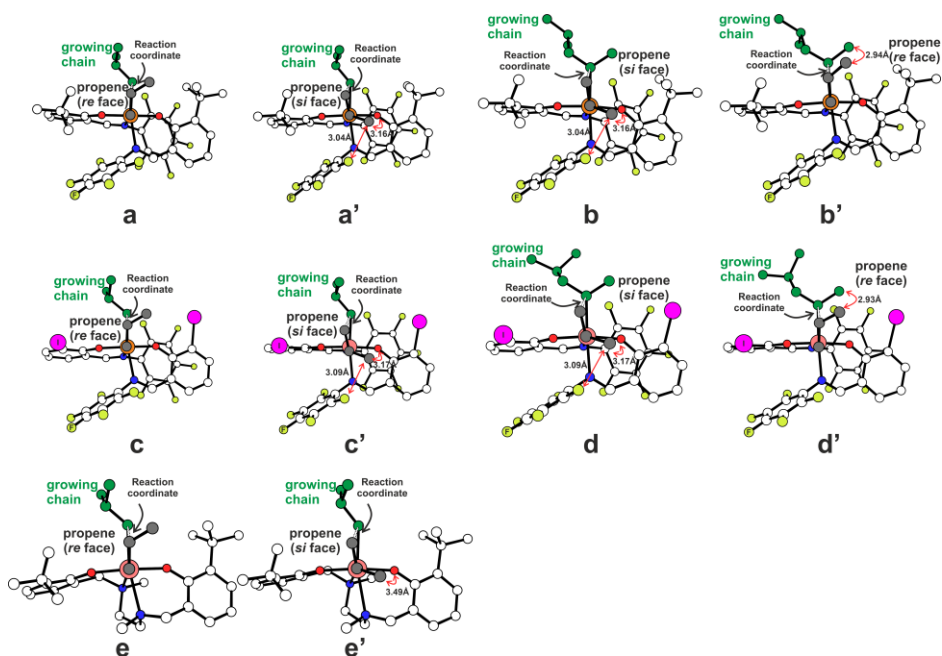


Figure 1.22. DFT optimized geometries for primary (a, c and e) and secondary (a', c' and e') insertion TSs for system **4**, **5** and **6** on primary chain. Primary (b and d) and secondary (b' and c') insertions on secondary chain for system **4** and **5**. H atoms omitted for clarity. Distances in Å.

The optimized TS structures are qualitatively similar for the three catalysts. According to **Table 1.7**, system **5** and **6** prefer primary insertion on primary chain, while for system **4** no clear preference is detected under the same conditions. The different results for system **4** and **5** require a further analysis since they only differ for the *ortho* substituent on the phenolic ring. Inspecting the TS structures, comparable steric interactions between the propene methyl group and the ligand framework in system **4** and **5** are found, while system **6** exhibits a more relaxed environment, as reported for the distances in **Figure 1.22**.

Primary and secondary insertions have been also analysed on secondary growing chain for system **4** and **5** (**Figure 1.22b/b'** and **d/d'**), which are relevant for their behaviour. Both catalysts show a net preference for secondary insertion and structural analysis on TSs points to steric interactions involving propene methyl groups with ligand framework and growing chain in secondary and primary insertion, respectively. The only steric factors, again, is not sufficient to capture the full origin for the observed stereoselectivity.

System **7**, and its family, has been proved to follow a regioselectivity mechanism similar to that showed by C_s -symmetric systems, selecting the same enantioface for both primary and secondary insertions. In **Figure 1.23** DFT TS structures are reported. The energetics in **Table 1.7** reveal preference for primary insertion. Notwithstanding the different ligand framework of this system, steric effects could induce preference for primary insertion mode.

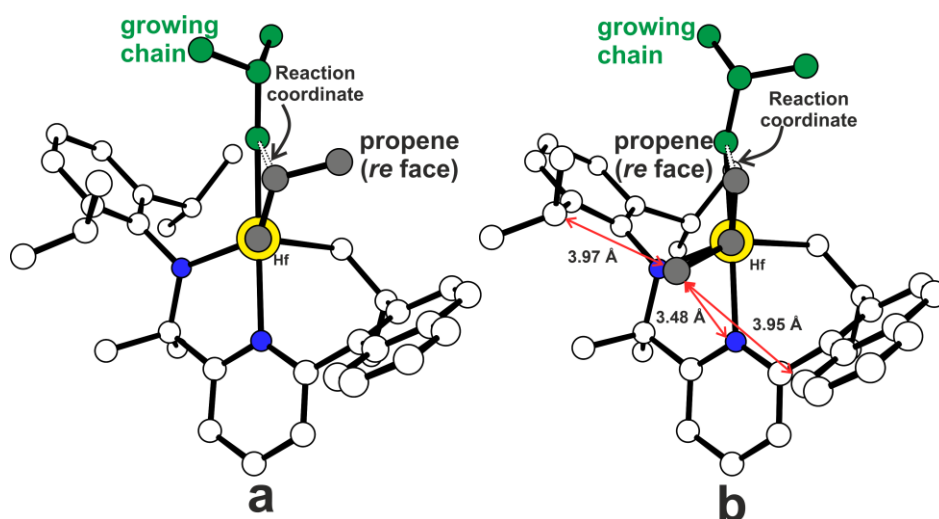


Figure 1.23. DFT optimized geometries for primary (a) and secondary (b) insertion TSs for system **7** on primary chain. H atoms are omitted for clarity and distances are reported in Å.

Buried volume analysis $\%V_{\text{Bur}}$ has been used to probe steric effects on regioselectivity.

A 5.5 Å radius and explicit hydrogen have used. The analysis is reported in **Figure 1.23** for all systems. By interpreting the analysis through the quadrant visualization, the primary and secondary propene approach often in region with medium to high % V_{Bur} values, although the colour map suggests lighter zones. This apparent inconsistency reflects a limitation of the quadrant partition, which sums contributions along both +z and -z direction, masking differences between the two hemispheres.

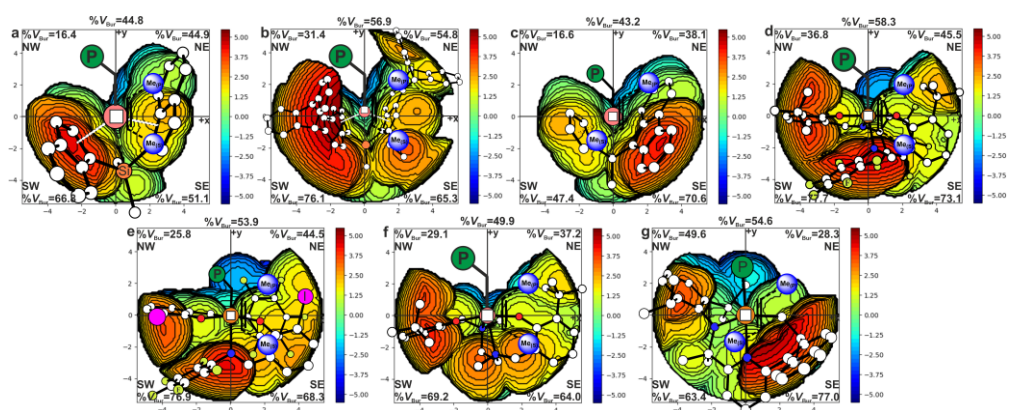


Figure 1.24. System 1-7 steric map (from a to g). Total and quadrant % V_{Bur} are reported on top and inside the maps. The available sites are represented by white boxes. Schematic representations of primary and secondary propene are reported, indicating the methyl group with a blue sphere and (P) and (S) subscripts for primary and secondary insertion.

To resolve this, octant approach, which partitions the same sphere into eight sign-defined sectors. The resulting values are reported in **Table 1.8**.

Table 1.8. Octant % V_{Bur} values for systems 1 to 7. Octant values in which primary and secondary monomers are placed in TSs are reported in bold.

Octant	System 1	System 2	System 3	System 4	System 5	System 6	System 7
% V_{Bur}	44.8	56.9	43.2	58.3	53.9	49.9	54.6
SW-z (-,-,-)	60.9	75.0	66.1	79.4	86.9	78.0	94.7
NW-z (-,+,-)	20.3	32.0	25.2	37.7	40.0	30.5	70.4
NE-z (+,+,-)	72.9	77.6	61.6	67.2	67.1	54.9	43.5
SE-z (+,-,-)	73.4	79.1	70.6	92.9	78.3	77.2	72.5

SW+z (-,-,+)	72.7	77.2	28.7	76.1	66.8	60.5	32.1
NW+z (- ,+,+)	12.5	30.8	8.0	35.9	11.6	27.8	28.7
NE+z (+,+,+)	17.0	31.9	14.5	23.7	21.8	19.5	13.1
SE+z (+,-,+)	28.8	51.4	70.6	54.1	41.7	50.2	81.5

This analysis gives a more consistent picture. For systems **1**, **2**, **4**, **5** and **6** the primary propene approaches the NE+z octant, which is less occupied than the octant in which secondary propene accommodates SE+z. For system **3** and **7**, the primary propene approaches the NE+z, while the secondary propene lies in SW+z octant, which is more crowded. The differences between the relevant octants are modest and range from about 10% to 30%, not sufficient to account for the strong experimental preference also detected computationally and are not able to rationalize the cases in which secondary insertion dominates, such as in system **3** and **4** and **5** on the secondary chain.

Steric factors have a key role in determining regioselectivity but not sufficient to fully explain the behaviour of the catalysts. ASM-NEDA results, combined with DFT and Buried Volume ($\%V_{\text{Bur}}$) analysis, could provide new insights. The discussion will follow the same order of the DFT analysis.

The AMS diagram for system **1** and the comparison between TSs for system **1** and **2** are reported in **Figure 1.25a** and **25b**.

For both catalysts, the TSs take place in a narrow coordinate window. In system **1** the right insertion occurs at 2.24 Å and the regioerror at 2.24 Å. In system **2**, the right insertion occurs at 2.25 Å and the regioerror at 2.26 Å. The regioselectivity is mainly dictated by electronic effects. Indeed, the interaction energy ΔE_{Int} stabilizes the primary insertion pathway by about 8 kcal/mol for system **1** and about 10 kcal/mol for system **2**. The strain term ΔE_{Strain} acts in the opposite direction and slightly favours the secondary insertion pathway, with a particular focus on the olefin strain, as shown in **Figure 1.25b** and **25c**.

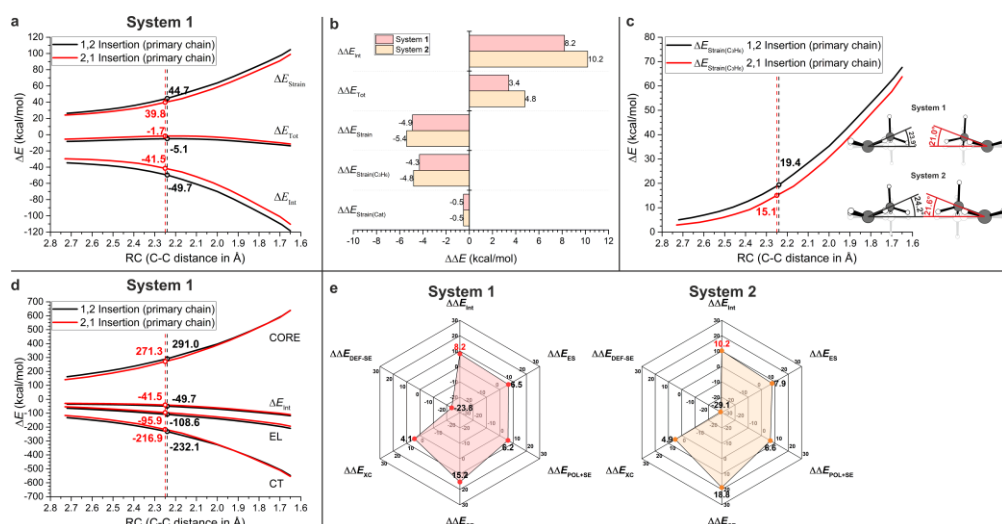


Figure 1.25. ASM-NEDA analysis for system 1 and 2. Panel a shows the ASM plot for system 1, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panel b shows a bar chart of ΔE_{Tot} and its component for right insertion and regioerror in system 1 and 2. Panel c shows $\Delta E_{\text{Strain(C3H6)}}$ profiles for system 1 and compares the olefine strain for right insertion and regioerror for both systems. Panel d shows the NEDA decomposition of ΔE_{Int} for system 1 along the reaction coordinate. Panel e summarized the relative contribution in a radar plot and reports $\Delta \Delta E$ between primary and secondary insertion for both systems.

Because ΔE_{Int} is the principal discriminator, it was decomposed in its NEDA terms.

Figure 1.25d and **25e** shows that the primary insertion gains comparable stabilization, for both systems, by CT, ES and POL(+SE) terms.

The CT terms has been analysed through second-order perturbation theory. Two donor-acceptor interactions were identified as the dominant for both systems. The first involves the methyl group bonding orbital donating into the olefin π^* . The second involves the Zr-C α bonding orbital donating into the olefin π^* . The results are summarized in **Table 1.9** and shown in **Figure 1.26**. In both cases, the $E(2)$ energies are higher for primary than for secondary insertion. This indicates stronger interaction for the primary path.

Table 1.9. Second-order NBO stabilization energies $E(2)$ for the two dominant donor-acceptor interactions at propene TSs. Values in kcal/mol. Letters refer to Figure 1.26.

Donor-Acceptor Interaction	Letters (Sys 1)	Letters (Sys 2)	$E(2)$ Sys 1 RI	$E(2)$ Sys 1 RE	$\Delta E(2)$ Sys1	$E(2)$ Sys 2 RI	$E(2)$ Sys 2 RE	$\Delta E(2)$ Sys 2
BD CH ₃ (olefin) - π^* (olefin)	a, a'	c, c'	11.6	5.5	6.1	11.9	5.4	6.5
BD Zr-C α - π^* (olefin)	b, b'	d, d'	71.1	59.9	71.4	71.4	57.7	13.7

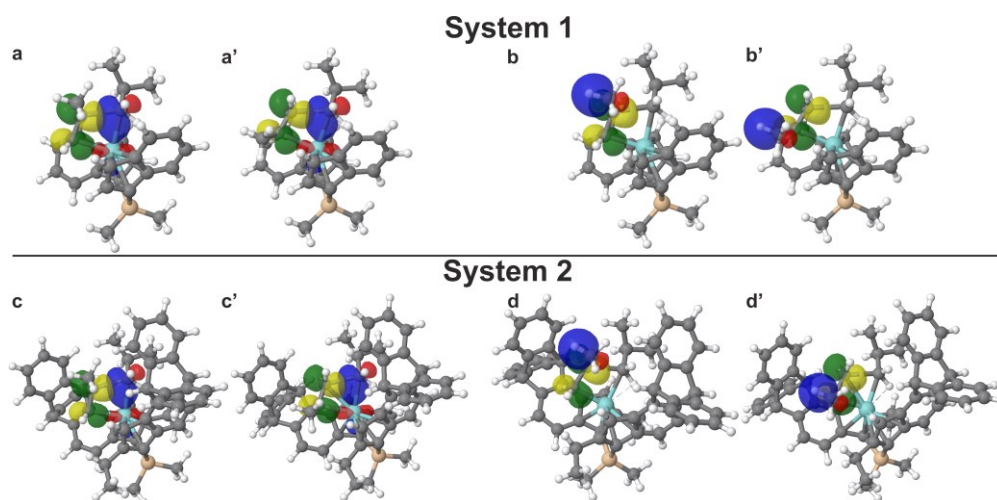


Figure 1.26. Orbital pictures of the donor-acceptors interactions used to investigate the CT term for system 1 and 2. Panels a and b refer to right insertion and panel a' and b' to regioerror for system 1. Panels c and d refer to right insertion and panel c' and d' to regioerror for system 2. Letters match Table 1.9. Donors are shown in blue and red, acceptors in yellow and green.

Taking together steric and CT factors, they appear to act in opposite directions. The secondary insertion pathway requires less olefin deformation (lower $\Delta E_{\text{Strain}(\text{C}_3\text{H}_6)}$), whereas the primary insertion pathways show stronger donor-acceptor interactions. It can be inferred that the higher olefin strain of the primary insertion is then compensated by the much stronger stabilization induced by the CT term.

ES and POL(+SE) contributions have been analysed through NBO natural charges and fragment dipoles. **Figure 1.27** reports the natural charges on the metal centre, α -carbon of the growing chain and on the olefin fragment and the dipoles of the isolated olefin in the TS geometry and the induced dipoles when the catalyst carrying the chain fragment is present for right insertion and regioerror in both systems (**Figure 1.27a** and **27b** for system **1** and **2**, respectively). The analysis of NBO natural charges and dipoles shows two different and opposite situations for primary and secondary insertions. Indeed, there is an inversion of polarity of the double bond from primary to secondary inserted olefin, revealing a situation of higher electronic stress for the olefin fragment inserting in secondary way to accommodate in the catalytic pocket. **Table 1.10** lists the relaxed, deformed and induced dipoles for the olefin fragment. In both systems, the primary insertion shows larger deformed and induced dipoles, consistent with a stronger polarization response and with a larger electrostatic stabilization.

Table 1.10. Relaxed and induced dipole moments of the olefin fragment, in Debye, for systems **1** and **2** right insertion and regioerror.

	System 1		System 2	
	Right Insertion	Regioerror	Right Insertion	Regioerror
$\mu_{\text{relaxed}}(\text{D})^{[a]}$	1.15	0.99	1.16	0.97
$\mu_{\text{deformed}}(\text{D})^{[b]}$	2.45	1.64	2.66	1.65
$\mu_{\text{induced}}(\text{D})^{[c]}$	1.34	0.76	1.56	0.80

[a] Relaxed dipole is the calculated dipole moment considering the fragment in the unrelaxed geometry, *i.e.* the geometry that adopts in the TS, in the presence of the other fragment. [b] Deformed dipole is the calculated dipole moment considering the fragment as isolated [c] Induced dipole is the shift determined by the presence of the other fragments (catalyst carrying the chain in this case).

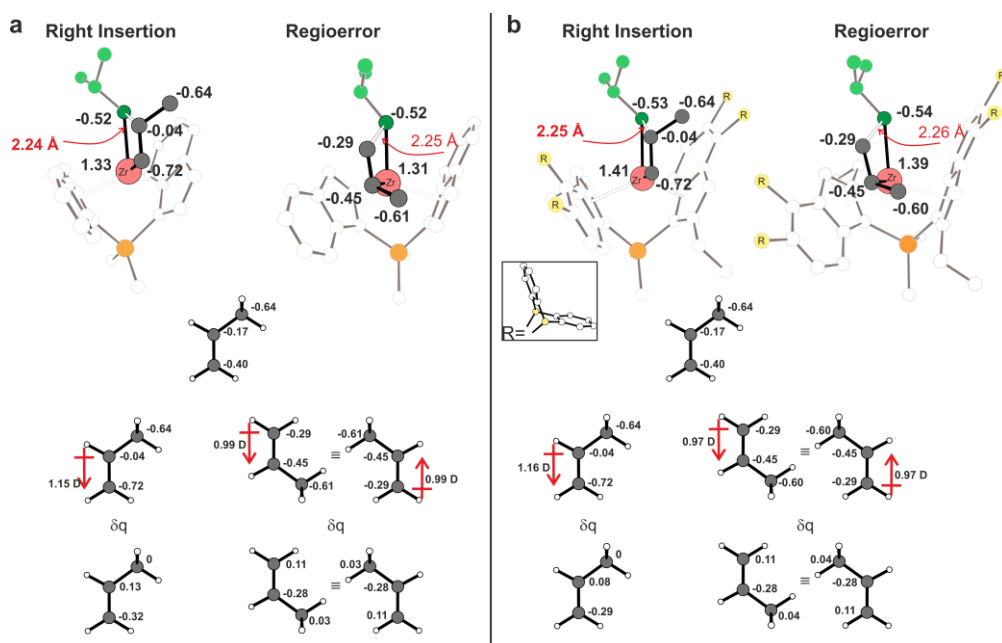


Figure 1.27. Natural charges and dipole moment for system 1 and 2 (a and b respectively).

To fully understand the results of the analysis showed above, TS geometries for primary, secondary and a deformed secondary (constrained to the primary like C-C and Zr-C distances) insertions have been analysed. The secondary insertion TS shows a longer Zr-C distance and a tilt of the torsional around the Zr-C bond. These features relieve the steric interaction between the propene methyl group and the ligand framework, reducing the olefin strain. When the secondary inserting propene is forced to the primary insertion-like distances, steric hindrance reappears and the olefin strain rises to higher values that the primary insertion. This analysis explains why the

$\Delta E_{\text{Strain}(\text{C}_3\text{H}_6)}$ is smaller for the unconstrained secondary insertion TS. The analysis is depicted in **Figure 1.28**.

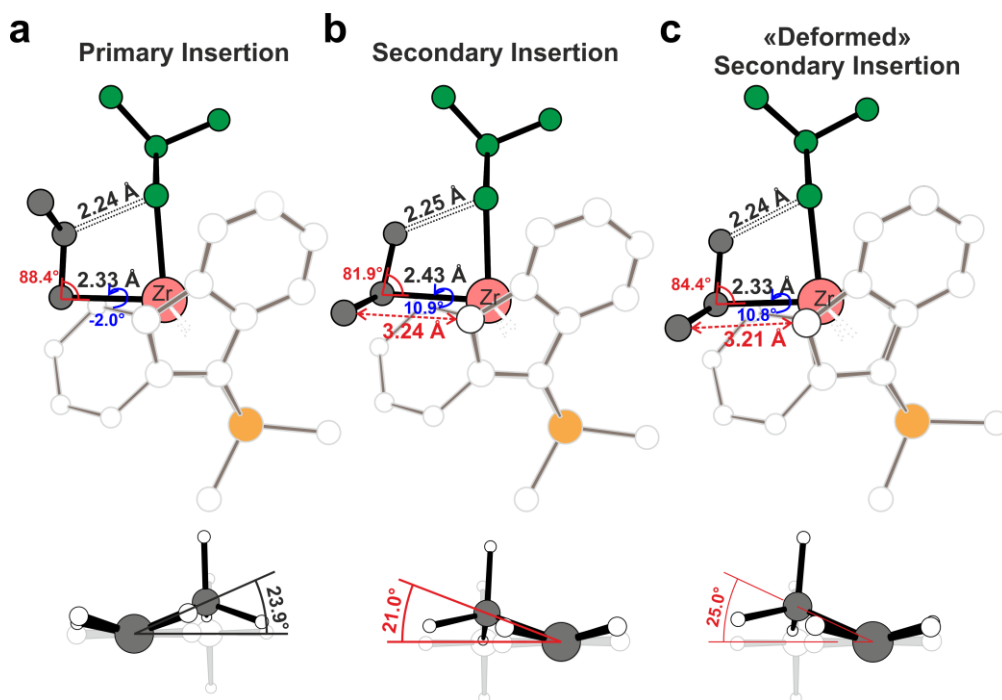


Figure 1.28. Geometric analysis of system 1 TSs. In a, primary insertion TS, in b secondary insertion TS and in c deformed secondary insertion TS, with relative olefin strain for the three geometries.

Propene insertion on a secondary chain, generated after a 2,1 event, has been analysed for system 1. In agreement with experiment, DFT indicates that the monomer insertion reverts to 1,2 insertions. ASM-NEDA analysis has been extended to this system and all the results are reported in **Figure 1.29**. In brief, the trends mirror those for the primary chain. The 1,2 insertion is preferred because ΔE_{Int} is more stabilizing than for 2,1 insertions. Strain effects are stronger at a secondary growing chain, with a notable increase in $\Delta E_{\text{Strain}(\text{Cat})}$, that could be attributed to steric interactions between 1,2-inserting monomer and the growing chain, as represented in **Figure 1.21**.

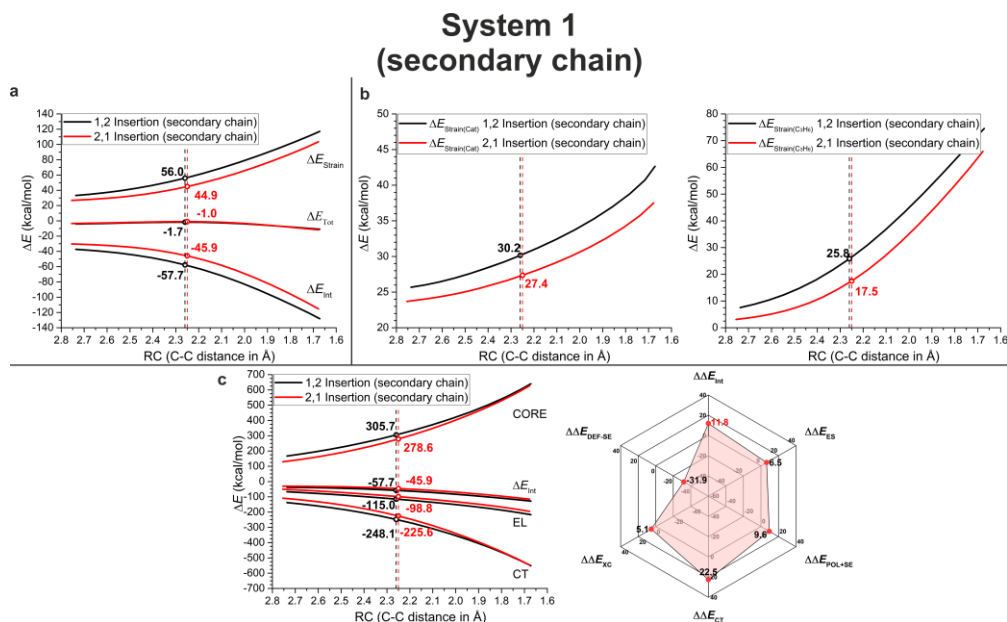


Figure 1.29. ASM-NEDA analysis for system 1 on secondary growing chain. Panel a shows the ASM plot, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panel b shows $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ profiles. Panel c shows the NEDA decomposition of ΔE_{Int} along the reaction coordinate and the relative contribution in a radar plot in which $\Delta\Delta E$ between primary and secondary insertion are reported.

System 3 differs from system 1 and 2 in the symmetry of the ligand framework (C_s vs. C_2) and in the tacticity of the polymer produced (syndiotactic vs. isotactic). A common feature is the incorporation of the monomer through primary insertion. The ASM-NEDA, indeed, is consistent with the previous cases. The preference for 1,2 insertion is governed mainly by the interaction term, while the strain term opposes it. A larger strain is found for the primary pathway, with a notable contribution from the olefin deformation. The complete results are provided in **Figure 1.30**. Considered together, these three catalytic systems, belonging to the same class yet yielding different tacticities, shows similar energetic balance for regioselectivity, with the interaction component dictating the preference for primary insertion.

System 3 (primary chain)

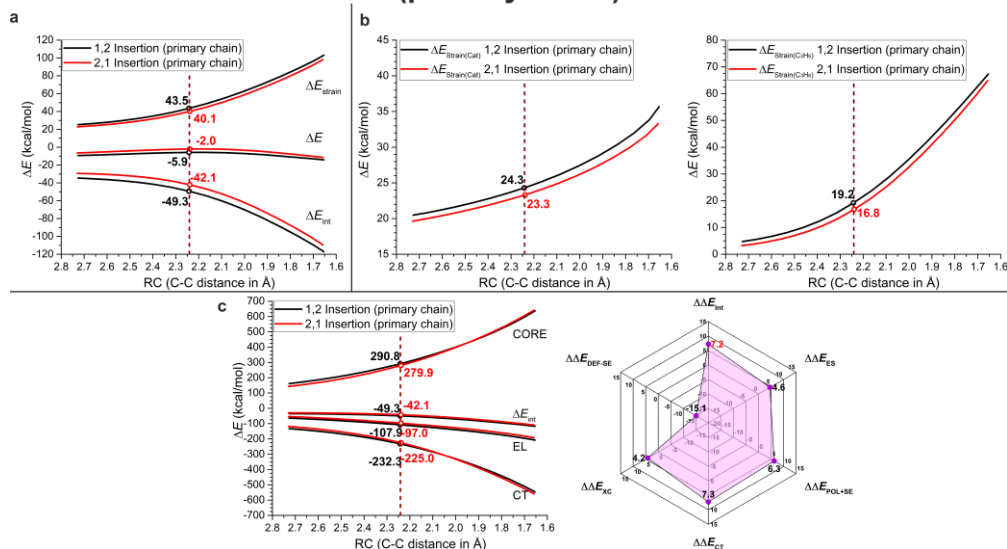


Figure 1.30. ASM-NEDA analysis for system 3 on primary growing chain. Panel a shows the ASM diagram, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panel b shows $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ profiles. Panel c shows the NEDA decomposition of ΔE_{Int} along the reaction coordinate and the relative contribution in a radar plot in which $\Delta\Delta E$ between primary and secondary insertion are reported.

With the transition to metallocene to post-metallocene catalysis, both the metal coordination geometry and the ligand environment changed, and electronic effects became central to the discussion of regioselectivity, as illustrated **Scheme 1.5**. A set of post-metallocene systems was therefore selected for analysis the ASM-NEDA. The discussion begins with system **4**, which is known to produce sPP through secondary insertion. Regioselectivity was evaluated on both a primary growing chain and secondary growing chain, as shown in **Figure 1.22**. The corresponding ASM-NEDA results are summarized in **Figure 1.31**.

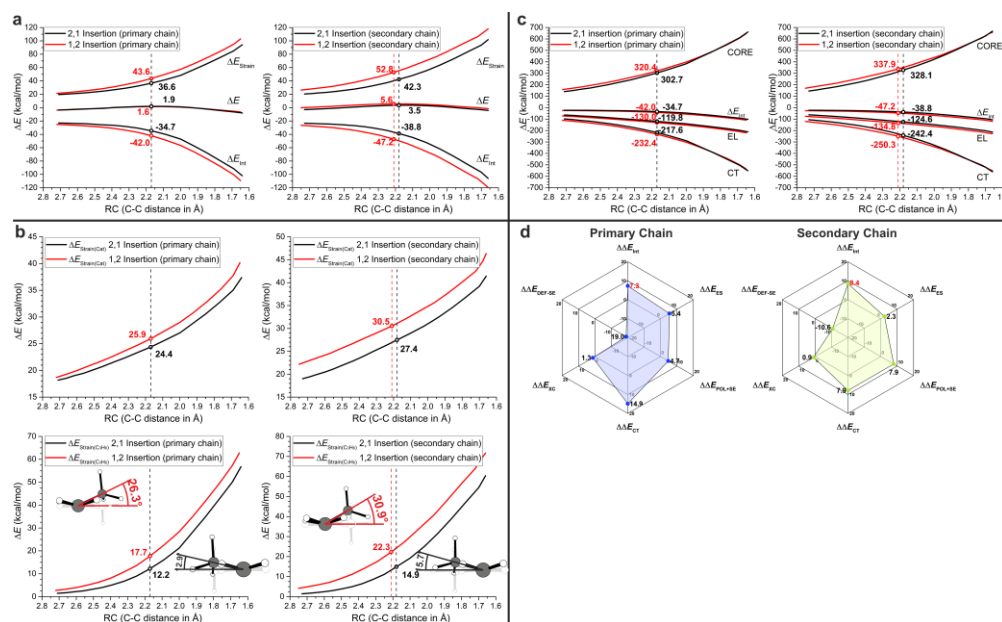


Figure 1.31. ASM-NEDA analysis for system 4 on primary and secondary growing chain. Panel a shows the ASM diagram, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panel b shows $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ profiles. Panel c shows the NEDA decomposition of ΔE_{Int} along the reaction coordinate. Panel d the relative contribution in a radar plot in which $\Delta\Delta E$ between primary and secondary insertion are reported.

Changing the ligand framework does not alter the qualitative interpretation of the energy profiles. Indeed, along the entire path in **Figure 1.31a**, primary insertion is governed by interaction effects, whereas the secondary insertion is governed by strain effects. A clear energetic preference is not found on primary chain, in agreement with DFT. In contrast, insertion on a secondary chain shows a marked preference for 2,1 insertions. As can be seen, the strain gap increases on the secondary chain and can be associated to steric interaction between the inserting monomer and the growing chain (as represented in **Figure 1.22**). The strain plot for each fragment is reported in **Figure 1.31b**, in which the increasing of the strain gap from primary to secondary chain is evident.

The ΔE_{Int} and its decomposition terms were analysed next. **Figure 1.31c** and **31d** show the NEDA contributions. Consistent with the metallocene cases, the primary insertion pathway gains stabilization from CT, ES and POL(+SE) terms, both on primary and secondary growing chain. Since system **4** propagates through secondary insertion under polymerization conditions, the secondary growing chain case has been investigated in greater detail.

The CT term was explored and three donor-acceptor interactions were considered. The first involves donation from Ti-C α bonding orbital into the olefin π^* orbital. The second involves donation from the olefin π orbital into a lone-vacancy orbital on Ti atom. The third involves donation from the methyl group bonding orbital into the olefin π^* orbital. The corresponding second-order stabilization energies are listed in **Table 1.11**.

Table 1.11. Main donor-acceptor interactions from NBO analysis on propene insertion TSs for system 4 on secondary growing chain. Second-order energies $E(2)$ are reported for right insertion (RI) and regioerror (RE). Values in kcal/mol. Letters refer to Figure 1.32.

Donor-Acceptor Interaction	Letters	$E(2)$ RI	$E(2)$ RE	$\Delta E(2)$
BD Ti-C α - π^* (olefin)	a	82.8	95.6	-12.8
π (olefin) - LV Ti	b	11.6	5.5	-11.3
BD CH ₃ (olefin) - π^* (olefin)	c	5.6	11.7	-6.1

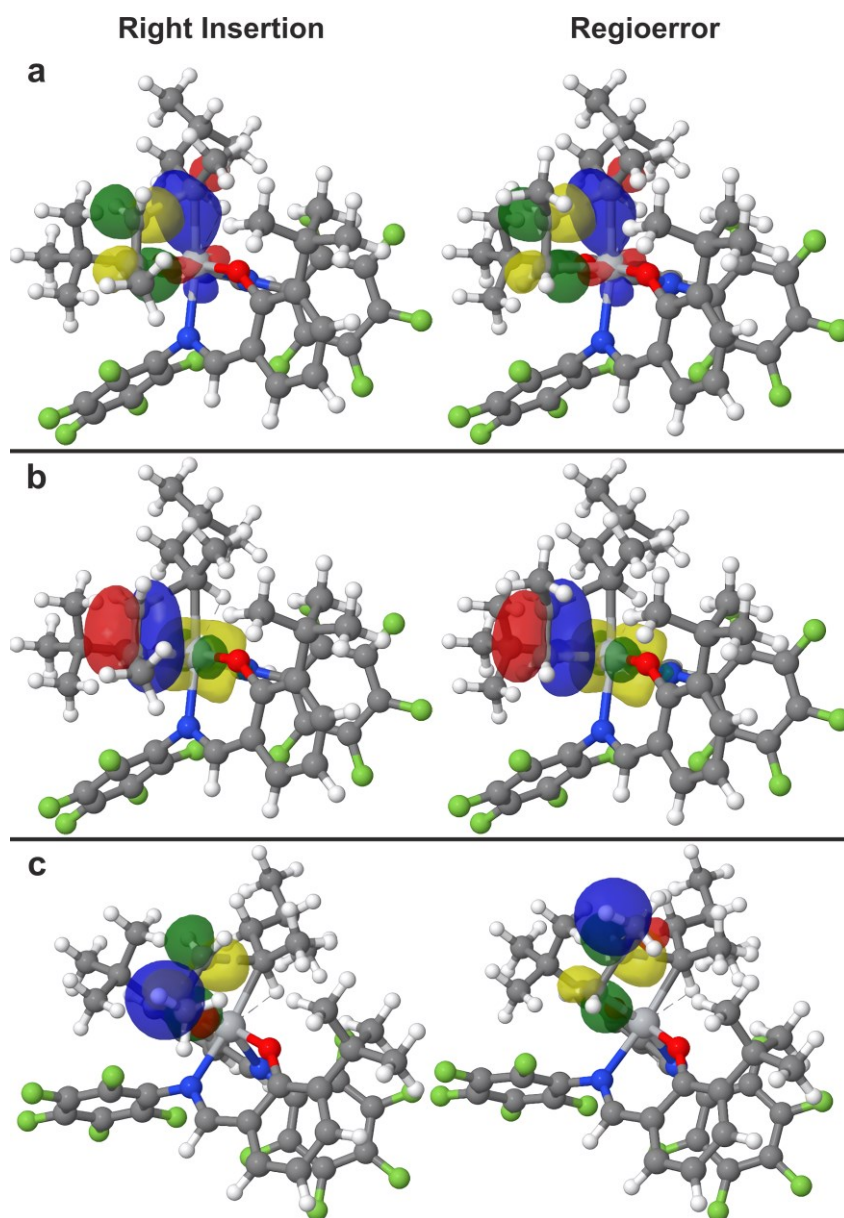


Figure 1.32. Principal donor-acceptor interactions used to analyse CT term for system 4 on secondary growing chain. Donors are shown in blue and red and acceptors in yellow and green.

Although orbital interactions stabilize the primary insertion TSs, the overall preference of system 4 remains secondary insertion. The ES and POL terms were therefore examined through NBO natural charges and fragment dipoles obtained from NEDA. **Figure 1.33** shows the charges on the metal, on the α -carbon of the chain and on the olefin fragment (**Figure 1.33a**) and the olefin dipoles (**Figure 1.33b**). The relaxed dipole of the olefin fragment in TS geometry, deformed dipole considering the fragment as isolated and induced dipole in the presence of the other fragment (catalyst carrying the chain) are reported in **Table 1.12**. The polarity of the double bond is reversed when comparing primary and secondary insertion, and the relaxed and induce dipoles shift in opposite directions, as depicted in **Figure 1.33b**.

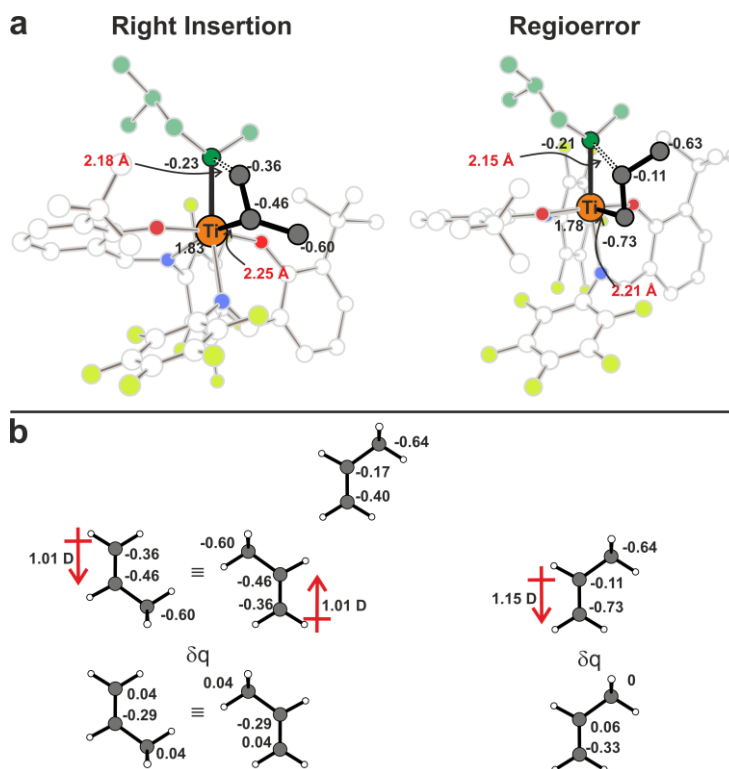


Figure 1.33. In panel a, NBO natural charges for the metal centre, the α -carbon of the growing chain and on the olefin fragment for right insertion and regioerror in system 4. In panel b, induced dipoles for olefin fragment in their unrelaxed geometry.

Table 1.12. Relaxed and induced dipole moments of the olefin fragment, in Debye, for system 4 right insertion and regioerror.

	Right Insertion	Regioerror
$\mu_{\text{relaxed}}(\text{D})^{[a]}$	1.15	0.99
$\mu_{\text{deformed}}(\text{D})^{[b]}$	2.45	1.64
$\mu_{\text{induced}}(\text{D})^{[c]}$	1.34	0.76

[a] Relaxed dipole is the calculated dipole moment considering the fragment in the unrelaxed geometry, *i.e.* the geometry that adopts in the TS, in the presence of the other fragment. [b] Deformed dipole is the calculated dipole moment considering the fragment as isolated [c] Induced dipole is the shift determined by the presence of the other fragments (catalyst carrying the chain in this case).

The CT, ES and POL analysis indicates that the secondary insertion propene is placed in a condition of less favourable electronic environment than the primary insertion. Indeed, the less secondary deformed olefin undergoes a relatively lower CT stabilization than primary olefin and it is forced to adjust its double-bond polarity within the catalytic pocket. From an interaction perspective, the primary insertion is therefore preferred. Nevertheless, this interaction stabilization is not sufficient to overcome strain penalty associated with primary insertion. Indeed, decomposition of strain term into its components suggests lower strain for both fragments in secondary insertion pathway, with a particular substantial reduction for the olefin. This steric relief is particularly relevant on the secondary growing chain than primary one.

System 5, which differs from system 4 only for the *ortho* substituent on the phenyl ring, produces regioblock iPP that propagates first in a primary mode and then in a secondary mode. Results for this system agree with those for system 4 and previous analysis for the other systems and are fully reported in **Figure 1.34**, for right insertion and regioerror on both primary and secondary growing chain.

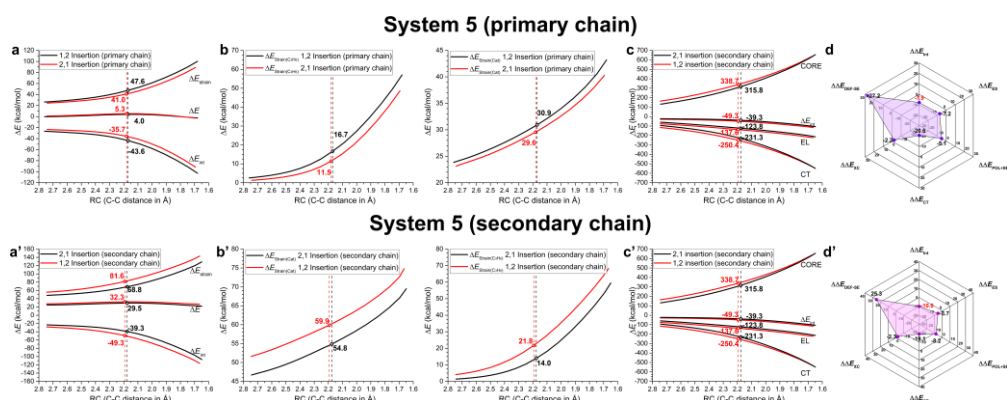


Figure 1.34. ASM-NEDA analysis for system 5, on primary and secondary growing chain in upper and lower panel, respectively. Panels a and a' show the ASM diagram, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panels b and b' show $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ profiles. Panel c and c' show the NEDA decomposition of ΔE_{Int} along the reaction coordinate. Panels d and d' show the relative contribution in a radar plot in which $\Delta\Delta E$ between primary and secondary insertion are reported.

As noted earlier, the preference for primary insertion on primary chain is more pronounced for system **5** than for system **4**, despite the single change at the *ortho* position. **Figure 1.35** reports the energy variation between the primary and secondary TSs on a primary chain for both systems. A difference of 1.0 kcal/mol is observed and arises from a delicate balance between strain and interaction. In system **4**, strain disfavors the primary insertion pathway and interaction favors the secondary insertion pathway, leading to a near balance. In system **5**, the strain difference between primary and secondary insertions decreases, while the interaction term increases in favor of primary insertions, which results in a stronger overall preference for 1,2 insertions.

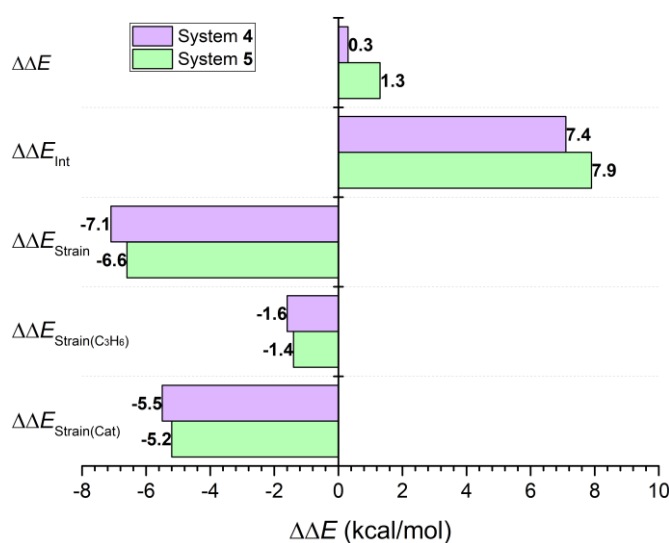


Figure 1.35. ASM-NEDA analysis for system 4 and 5 comparison of all components, on primary growing chain, reported in bar plot.

The ASM-NEDA analysis was also conducted for systems 6 and 7. In system 6, a bridge between the two nitrogen donors prevents interconversion of the ligand framework. As a result, a rigid chiral catalytic pocket is maintained along the reaction coordinate and iPP is produced through primary insertion. The obtained ASM-NEDA analysis is reported in **Figure 1.36**. The same qualitative pattern that was established for metallocenes is recovered. The primary pathway remains interaction favoured along the reaction coordinate, and the competing secondary pathway accumulates a larger strain penalty. The bridged architecture of the ligand framework constraints the catalyst fragment, limiting the catalytic pocket relaxation during the secondary insertion and, consequently, increasing the ΔE_{Strain} . This effect is consistent with the high regioselectivity exhibited by this system.

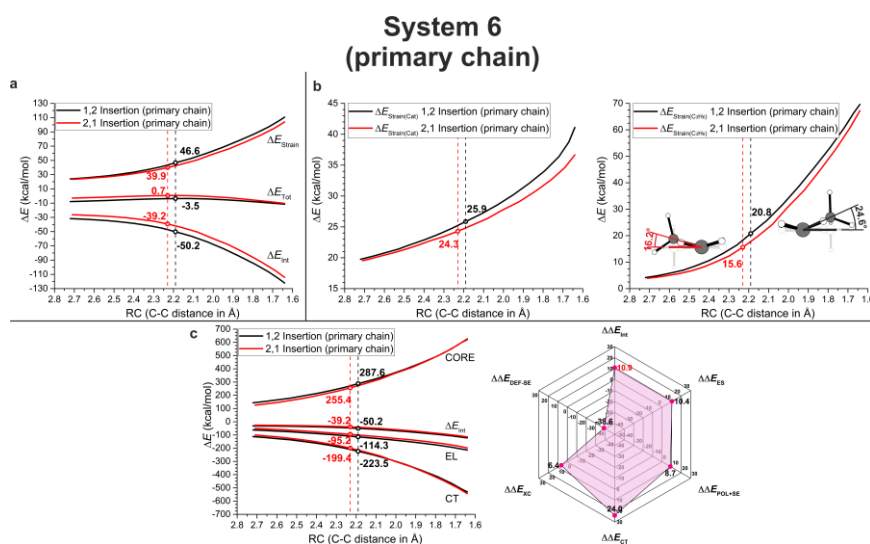


Figure 1.36. ASM-NEDA analysis for system 6 on primary growing chain. Panel a shows the ASM plot, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panel b shows $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ profiles, olefine strain comparison for right insertion and regioerror for both systems are reported as insets. Panel c shows the NEDA decomposition of ΔE_{Int} along the reaction coordinate and the relative contribution in a radar plot in which $\Delta\Delta E$ between primary and secondary insertion are reported.

A separate analysis was carried out for system 7. In **Figure 1.37**, the complete analysis is reported. The ASM-NEDA plot remains consistent with earlier cases since strain favours the regioerror and interaction favours the primary insertion pathway.

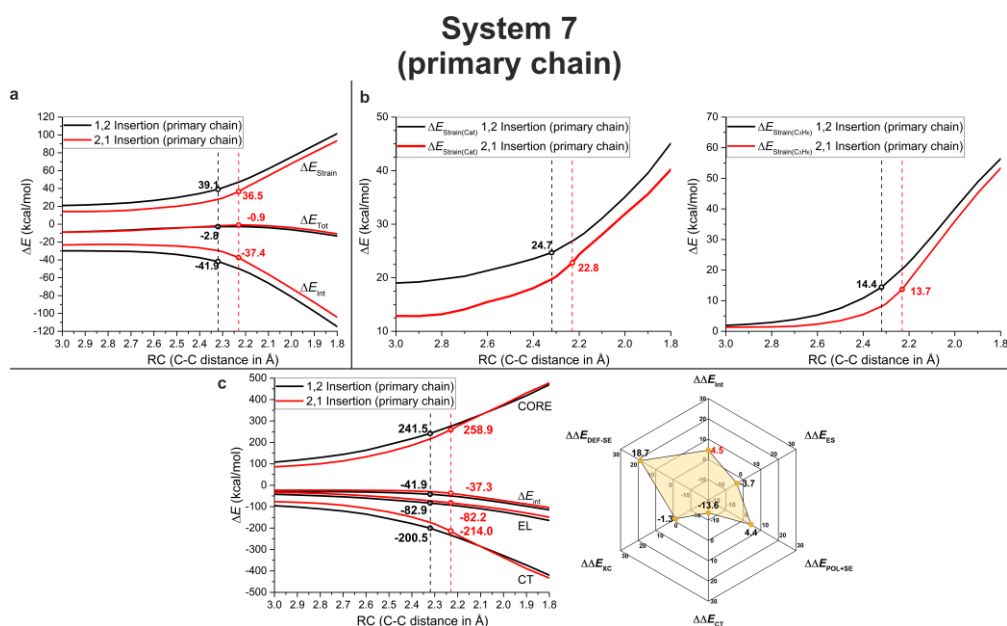


Figure 1.37. ASM-NEDA analysis for system 7 on primary growing chain. Panel a shows the ASM plot, right insertion in black and regioerror in red. TSs marked as circles and energies in kcal/mol. Panel b shows $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ profiles, olefine strain comparison for right insertion and regioerror for both systems are reported as insets. Panel c shows the NEDA decomposition of ΔE_{Int} along the reaction coordinate and the relative contribution in a radar plot in which $\Delta\Delta E$ between primary and secondary insertion are reported.

Conversely, the interaction term decomposition reveals a different internal balance of CT and ES. In this catalyst, CT and ES tend to favour secondary insertion, which sets system 7 apart from the others. The complete analysis for CT, ES and POL is reported in **Figure 1.38**. This different behaviour could be credited to the closest reaction coordinate of the secondary insertion relative to the primary insertion. Despite the difference in the magnitude and partitioning of ΔE_{Int} components, the overall interpretation is in line with the conclusion drawn above. In **Table 1.13**, CT and dipole values are reported. A system-dependent balance between strain and interaction governs the regioselectivity, and changes in ligand geometry can shift that balance toward either primary or secondary insertion.

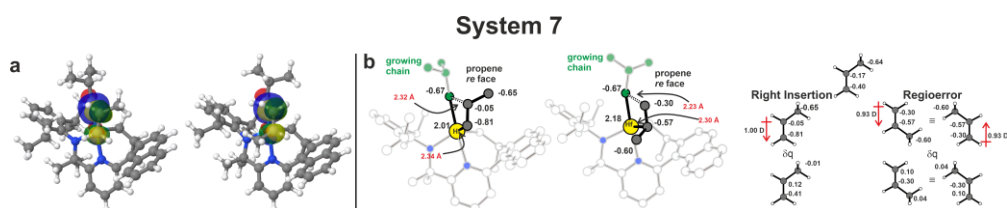


Figure 1.38. In panel a, CT analysis for primary and secondary insertion for system 7. In panel b, NBO natural charges for the metal centre, the α -carbon of the growing chain and on the olefin fragment for right insertion and regioerror in system 7 and induced dipoles for olefin fragment in their unrelaxed geometry.

Table 1.13. Main donor-acceptor interaction from NBO analysis on propene insertion TSs for system 7 on primary growing chain. Second-order energies $E(2)$ are reported for right insertion (RI) and regioerror (RE). Relaxed and induced dipole moments of the olefin fragment, in Debye, for system 4 right insertion and regioerror.

	Donor-Acceptor Interaction	BD Hf-C α - π^* (olefin)	μ_{relaxed} (D) ^[a]	μ_{deformed} (D) ^[b]	μ_{induced} (D) ^[c]
Right Insertion	$E(2)$	61.4	1.00	2.28	1.28
Regioerror	$E(2)$	70.3	0.92	1.80	1.01
	$\Delta E(2)$	-8.9			

[a] Relaxed dipole is the calculated dipole moment considering the fragment in the unrelaxed geometry, *i.e.* the geometry that adopts in the TS, in the presence of the other fragment. [b] Deformed dipole is the calculated dipole moment considering the fragment as isolated [c] Induced dipole is the shift determined by the presence of the other fragments (catalyst carrying the chain in this case).

1.6 Conclusion

This chapter showed a unified picture of α -olefin polymerization catalysts across representative metallocene and post-metallocene families, using a single workflow that combines DFT with ASM-NEDA and Buried Volume (% V_{Bur}) analysis. Treating the same reaction coordinates with the same decomposition tools allowed trends to be compared and revealing where steric and electronic effects cooperate or compete to determine mechanism, stereoselectivity and regioselectivity.

On the mechanistic side, two different propagations emerged. Classical chain migration mechanism is retained when the catalytic active pocket and its symmetry pass the chain from site to site after each insertion. In contrast, several low-symmetry systems show a possibility of a chain stationary mechanism, which origin seems to be system dependent. In bridged metallocenes, catalyst deformation dominates and is complemented by a non-negligible CT stabilization at the favoured site. In salalen octahedral systems, strain effect (here for the olefin fragment) again prevails even when a strong *trans* influence might have suggest the opposite. In pyridylamido-Hf species, the gap between PS and TBP arises mainly from monomer deformation at the disfavoured site. In all cases, steric maps rationalized the catalytic pocket anisotropy but the ASM-NEDA profiles show that sterics alone do not predict the energy gaps. For stereoselectivity, the Corradini model and stereoerror route(s) were revisited across six different systems. The combined analysis explains why iPP is retained in systems where the regular insertion minimized catalyst strain and why both stereoerror(s) remain high in energy in highly constrained metallocene framework. It also explains the distinct behaviour of C_2 phenoxy-imine system delivering sPP through secondary insertion and site inversion, and of C_1 pyridylamido-Hf species where stereocontrol is dictated by direct monomer-ligand interactions rather than a chiral chain orientation. Where ligand wrapping modes interconvert, as in salalen complexes, stereocontrol reflects a balance between lower strain in one wrapping mode and high CT stabilization in the other. These comparisons turn qualitative quadrant representations into quantitative design levers, showing which energy term must be raised or lowered to suppress a given stereoerror.

For regioselectivity, the preference for primary 1,2 insertion was confirmed for most families, with well-documented exceptions that favour 2,1 insertions. Buried volume quadrant maps sometimes suggested free space where the octant $\%V_{\text{Bur}}$ demonstrated only modest crowding differences, which explain why steric descriptors by themselves could not account for experimental results. Along the same coordinates, ASM-NEDA showed that primary insertion is often stabilized by interaction energy

while secondary insertion accumulates more strain, although selected post-metallocenes exhibit CT and EL patterns that can tilt the balance toward 2,1 insertions.

In sum, this combined approach (DFT/ASM-NEDA/Buried Volume ($\%V_{\text{Bur}}$) analysis) turns qualitative mechanistic hypothesis into quantitative, system-specific structure-reactivity rules. It explains why the occurrence of chain-stationary propagation, which steric and electronic effects set tacticity and how subtle modification of the catalytic pocket governs primary vs. secondary insertion preference.

Acknowledgement

The study presented in this **Section 1.3** is an adaptation, for text, figures and tables, of works already published:

1) **Romano, E.**; Budzelaar, P. H. M.; De Rosa, C.; Talarico, G. Unconventional Stereoerror Formation Mechanisms in Nonmetallocene Propene Polymerization Systems Revealed by DFT Calculations. *J. Phys. Chem. A* 2022, 126, 6203–6209. <https://doi.org/10.1021/acs.jpca.2c04935>. (CC by 4.0)

2) Cicoella, A.; **Romano, E.**; Barone, V.; De Rosa, C.; Talarico, G. Metallocenes and Beyond for Propene Polymerization: Energy Decomposition of Density Functional Computations Unravels the Different Interplay of Stereoelectronic Effects. *Organometallics* 2022, 41, 3872–3883. <https://doi.org/10.1021/acs.organomet.2c00534>. (CC by 4.0)

Stereoselectivity study, in **Section 1.4**, has been published and adapted from:

3) **Romano, E.**; Barone, V.; Budzelaar, P. H. M.; De Rosa, C.; Talarico, G. Revisiting Stereoselective Propene Polymerization Mechanisms: Insights through the Activation Strain Model. *Chem. – Asian J.* 2024, 19, e202400155. <https://doi.org/10.1002/asia.202400155>.

Regioselectivity study, in **Section 1.5**, is under revision for submission.

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- (1) Stürzel, M.; Mihan, S.; Mülhaupt, R. From Multisite Polymerization Catalysis to Sustainable Materials and All-Polyolefin Composites. *Chem. Rev.* **2016**, *116*, 1398–1433. <https://doi.org/10.1021/acs.chemrev.5b00310>.
- (2) Klaue, A.; Kruck, M.; Friederichs, N.; Bertola, F.; Wu, H.; Morbidelli, M. Insight into the Synthesis Process of an Industrial Ziegler–Natta Catalyst. *Ind. Eng. Chem. Res.* **2019**, *58*, 886–896. <https://doi.org/10.1021/acs.iecr.8b05296>.
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Chapter 2 - Predicting propene stereoselectivity in Transition Metal catalysts through Quantum Chemical Methods

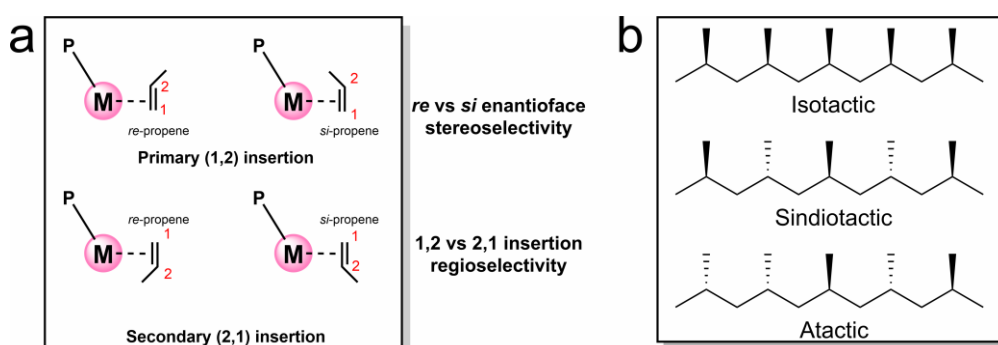
Abstract

Progresses in hardware and software has made quantum chemistry a practical tool for studying homogeneous polymerization, providing valuable insights into this field. Nevertheless, system sizes still limit the employment of high-level composite wavefunction methodologies. Rigorous benchmarks for stereocontrol in α -olefin insertion are limited. This Chapter presents a systematic comparison for propene polymerization across four representative catalysts is provided. Transition states were optimized either with or without empirical dispersion corrections, and then resulting geometries were refined through single point calculations using a broad set of functional, with D3 or D3(BJ) empirical dispersion and three different solvent models. No single protocol emerged as universally optimal to predict stereoselectivity. Instead, it appeared that the best protocol is system-dependent, in terms of dispersion and solvent model. A common-protocol screen retaining methods within a threshold were used to identify transferable protocols across the systems. On these common protocols, double hybrid functionals were tested to assess their impact on the energy and in stereoselectivity prediction. Finally, a pilot DLPNO-CCSD(T)/(T1) study is presented with preliminary results and an outlined stepwise plan to extend to protocol to test such methodologies in this field and to find the best working methodology to reproduce accurately stereoselectivity.

2.1 Introduction

The α -olefin polymerization catalysed by transition metals (TM) is governed by three aspects, namely stereoselectivity,^{1,2} regioselectivity^{3,4} and the relative rates of propagation and termination.^{5,6} Stereoselectivity refers to the preference for one enantioface of the prochiral α -olefin, *re* or *si*, at each insertion, regioselectivity

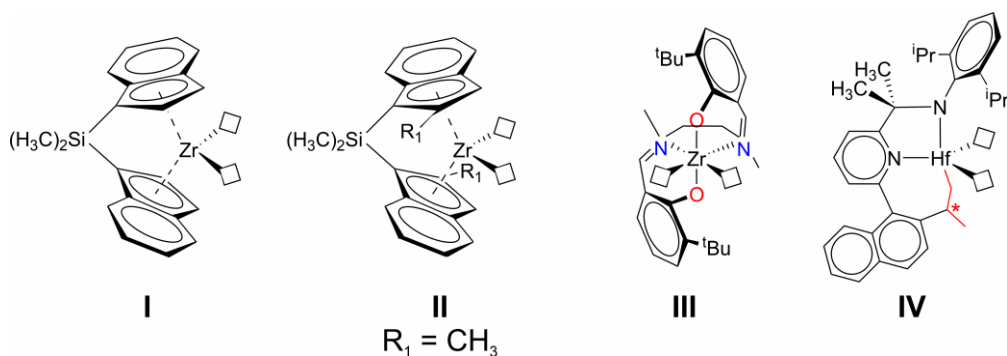
concerns the balance between 1,2 primary insertion and 2,1 secondary insertion into the growing chain, as reported in **Scheme 2.1a**. The ratio between the propagation rate and the sum of all termination events (β -hydrogen transfer to monomer, β -hydrogen elimination to metal centre and chain transfer to Al species) determines the polymer molecular mass (M_n).



Scheme 2.1. Propene insertion modes (a), microstructures for polypropylene (b).

Polypropylene (PP) provides a clear case study. Three microstructures can be accessible, as shown in **Scheme 2.1b** and the macroscopic properties depend on the degree of stereoregularity.⁷ Atactic PP is amorphous and elastomeric, while isotactic PP (*i*PP) is a semicrystalline and thermoplastic polymers. The latter is widely used in industrial applications and its performance is critically linked to stereoregularity, which is commonly expressed as the percentage of $[mmmm]$ pentads (which refers to a segment of five propylene monomer units in a PP chain with the same stereochemical orientation, *meso*) measured by ^{13}C -NMR spectroscopy.⁸ Heterogeneous Ziegler-Natta (ZN) catalysts are the current industrial main source of *i*PP production.^{9,10} The development of homogenous single site complexes has nonetheless enabled deeper insights into how ligand environment control polymer microstructure.¹ Combined experimental and theoretical efforts have clarified the

origin of stereoselectivity in propene polymerization, revealing that systems I to IV in **Scheme 2.2** favour *i*PP despite their different ligand skeleton.^{1,2}



Scheme 2.2. Schematic representation of the catalytic active species employed in the analysis.

Systems I and II are C_2 symmetric *ansa* zirconocene complexes that differ only by a methyl group at position 2 on the indenyl group, producing *i*PP with $[mmmm]$ values of 89% and 90% respectively.¹¹ System III is a stereorigid tetradentate ONNO complex with an octahedral coordination environment that resembles the active sites of traditional heterogeneous ZN catalysts. It yields *i*PP with a $[mm]$ content of 87%.^{12–14} System IV is a pyridylamido hafnium complex¹⁵ that exhibits unusual behaviour. Indeed, in the presence of monomer it undergoes *in situ* ligand modification,^{16–21} producing a C_1 symmetric active species with high isoselectivity, with $[mmmm]$ close to 91%.¹⁵

For system I to III, stereocontrol has been rationalized by the chiral orientation of the growing chain model introduced by Corradini and co-workers.^{22–24} The restricted orientational freedom of the first C-C bond of the growing chain gives rise to different activation barriers for diastereomeric pathways and thereby selects one enantioface of propene. System IV follows a different principle, in which the key factor is a direct interaction between monomer and ligand framework¹⁶ rather than the classical Corradini mechanism. More information concerning stereocontrol can be found in **Chapter 1**.

Only a limited number of systematic benchmarks have assessed how different computational approaches capture stereoselectivity in α -olefin polymerization and most available studies emphasize the insertion step.^{25–28} A comprehensive comparison was therefore undertaken that tests multiple density functionals together with dispersion corrections and solvation treatments for system I to IV in propene polymerization. Experimental stereochemical data derived from ^{13}C NMR are translated into experimental Gibbs free energies differences between the transition states (TSs) that control selection of the right versus the wrong enantioface. This translation uses the enantiomorphic site Bernoullian model^{29,30} in combination with the Boltzmann equation. All analysis adopts a Curtin-Hammet regime and the computed $\Delta\Delta G^\ddagger$ values for TSs are used to predict stereoselectivity (Figure 2.1).^{31,32}

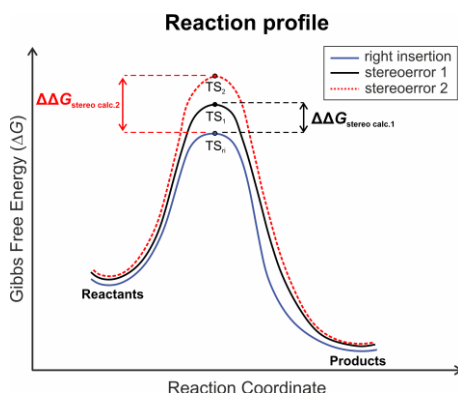


Figure 2.1. Reaction profile and transition states for diastereomeric reactions leading to enantiomeric products.

Systems I to IV were selected with three goals in mind. The set covers distinct catalyst classes that include *ansa*-metallocene for I and II and post-metallocene complexes for III and IV. The set spans different metal coordination environment, tetrahedral for I and II, octahedral for III and pseudo-octahedral for IV. The set captures diverse sources of stereocontrol: systems I to III follow the Corradini model and system IV relies on a direct monomer ligand interaction. These choices sample the principal variables that define catalytic polymerization, motivating the search for a

computational protocol that performs reliably across all cases. From now on, systems I to IV are indicated as **SI** to **SIV**.

2.2 Computational Details

All DFT calculations have been performed with Gaussian16³³ software. In all the calculations the polarized split-valence basis set (SVP)³⁴ of Ahlrichs and co-workers for H, C, N, O and Si and LANL2DZ pseudopotentials and basis sets³⁵ were employed for Zr, Hf atoms in the optimization steps. Stationary points were characterized using vibrational analyses, and these analyses were also used to calculate zero-point energies and thermal (enthalpy and entropy) corrections (298.15 K, 1 bar). Improved electronic energies were obtained from single-point calculations using the TZVP basis set for H and second-row atoms³⁶ together with the SDD basis and pseudopotentials for metals, adding a f function with exponent 0.5.³⁷ Dispersion corrections^{38–40} by Grimme (using EmpiricalDispersion=D3 or D3BJ keyword in Gaussian packages) were also added (in the optimization and/or energy refinement calculations). The Gibbs free energies issued from these improved electronic energies and SVP thermal corrections have been obtained involving bulk solvent effects by using the Polarizable Continuum Model (PCM),⁴¹ the Conductor-like Polarizable Continuum Model (CPCM)^{42,43} and the Solven Model Density (SMD)⁴⁴.

Two procedures were employed. First, geometries were optimized at B3LYP level without empirical dispersion. On these structures, energy refinement calculations were, including dispersion corrections and solvent effects, using the following functionals:

- 1) BP86, a pure generalized gradient approximation (GGA) functional combining Becke's exchange⁴⁵ and Perdew and Wang's 1991 correlation functionals^{46,47}.

- 2) B3LYP, hybrid GGA functional widely used in literature. It combines 80% Becke's and 20% Hartree-Fock (HF) exchange together with Lee, Yang, and Parr's correlation employing three parameters optimized on thermochemical data.^{45,48}

3) B3PW91, a hybrid functional closely related to B3LYP,⁴⁹ using the Perdew-Wang-91 non-local correlation^{50,51} replacing the LYP one.

4) PBE0, a parameter-free hybrid functional proposed by Adamo and Barone,^{52,53} which combines Perdew–Burke–Ernzerhof (PBE) and HF exchange together with PBE correlation. The percentage of HF exchange is fixed *a priori* to 25%.

5) M06, hybrid meta-GGA functional of Truhlar and Zhao, including 27% of HF exchange.⁵⁴

6) PW6B95(D3)⁵⁵, a six-parameter hybrid meta GGA functional based on Perdew-Wang-91 (PW91)⁵⁶ exchange and Becke-95 (B95) correlation⁴⁹. The amount, in percentage, of HF exchange is equal to 28%.

7) M062X, an hybrid meta-GGA functional of Truhlar and Zhao, including 57% of HF exchange.⁵⁴

8) M11, a range-separated-hybrid (RSH) meta-GGA functional belonging to the family of the Minnesota functionals developed by Truhlar and coworkers.⁵⁷ The percentage of HF exchange is variable and it ranges between 42.8% (at small interelectronic distance) and 100% (at large distance).

In the second procedure, each functional was employed in TS geometry optimizations (including and not including empirical dispersion correction), followed by single-point energy evaluation. All the functionals are listed below.

1) BP86, a pure generalized gradient approximation (GGA) functional combining Becke's exchange⁴⁵ and Perdew and Wang's 1991 correlation functionals^{46,47}.

2) PBE, a pure non-empirical exchange-correlation GGA functional from Perdew, Burke and Ernzerhof.^{58,59}

3) TPSS, a pure meta-GGA exchange-correlation functional from Tao, Perdew, Staroverov and Scuseria.⁶⁰

4) revTPSS, revised TPSS exchange-correlation functional of Perdew and colleagues.^{61,62}

5) M06L, a pure meta-GGA local functional of Zhao and Truhlar.⁶³

6) MN15L, a pure local global-hybrid exchange-correlation functional from Truhlar.⁶⁴

7) TPSSh, a hybrid functional combining meta-GGA (from TPSS) with a fraction of exact HF exchange (10%).^{60,65,66}

8) B3LYP, hybrid GGA functional widely used in literature. It combines 80% Becke's and 20% Hartree-Fock (HF) exchange together with Lee, Yang, and Parr's correlation employing three parameters optimized on thermochemical data.^{45,48}

9) B3PW91, a hybrid functional closely related to B3LYP,⁴⁹ using the Perdew-Wang-91 non-local correlation^{50,51} replacing the LYP one.

10) X3LYP, extended hybrid functional combined with Lee-Yang-Parr correlation functional, including 21.8% HF exchange.⁶⁷

11) APF(D), hybrid functional from Austin-Frisch-Petersson, which can include spherical atom model (SAM) for empirical dispersion correction. HF exchange percentage is around 23%.⁶⁸

12) mPW1PW91, a hybrid density functional developed by Adamo and Barone combining Perdew-Wang exchange (mPW) with Perdew-Wang 1991 correlation functional (PW91), including 25% HF exchange.⁶⁹

13) mPW1LYP, a hybrid density functional combining Perdew-Wang exchange (mPW) with Lee-Yang-Parr correlation functional (LYP), including 25% HF exchange.⁶⁹

14) mPW1PBE, a hybrid density functional combining Perdew-Wang exchange (mPW) with PBE correlation functional, including 25% HF exchange.⁶⁹

15) PBE0, a parameter-free hybrid functional proposed by Adamo and Barone,^{52,53} which combines Perdew–Burke–Ernzerhof (PBE) and HF exchange together with PBE correlation. The percentage of HF exchange is fixed *a priori* to 25%.

16) M06, hybrid meta-GGA functional of Truhlar and Zhao, including 27% of HF exchange.⁵⁴

17) PW6B95(D3)⁵⁵, a hybrid meta GGA functional containing 6 parameters and based on Perdew-Wang-91⁵⁶ exchange and Becke-95 correlation⁴⁹. The amount, in percentage, of HF exchange is equal to 28%.

18) MN15, a global-hybrid exchange-correlation functional from Truhlar, including 44% HF exchange.⁷⁰

19) mPW1K, a hybrid density functional developed by Truhlar and coworkers including 42.8% HF exchange and combining mPW91 GGA exchange and PW91 correlation.⁷¹

20) CAM-B3LYP, a range-separated hybrid function by Handy and coworkers that improves B3LYP by separating the exchange interaction into short-range (19% HF exchange) and long-range (65% HF exchange) component, using the Coulomb-attenuating method.⁷²

21) LC- ω PBE, a long-range corrected functional that uses a semi-local exchange functional for short-range interactions and pure HF exchange for long-range interactions.^{73–75}

22) LC- ω HPBE, a corrected version of the previous long-range corrected functional that uses a semi-local exchange functional for short-range interactions and pure HF exchange for long-range interactions.^{73–75}23)

23) ω B97XD, a range-separated hybrid functional incorporating D2 empirical dispersion from Grimme. It consists of 22% HF exchange at short distances and 1000% at long distances.⁷⁶

24) M11, a Range Separated Hybrid (RSH) meta-GGA functional belonging to the family of the Minnesota functionals developed by Truhlar and coworkers.⁵⁷ The percentage of HF exchange is variable and it ranges between 42.8% (at small interelectronic distance) and 100% (at large distance).

25) M06HF, a 100% global hybrid, meta-GGA functional from Truhlar and coworkers, incorporating the full amount of HF exchange.^{55,77}

The results were analysed and the best performing approaches were identified according to the selection criteria described below. These functionals were then used as the starting point for a follow-up assessment that employed double hybrid functionals (DH) functionals in single point calculations in order to gauge their impact in predicting stereoselectivity. In a DH DFT typical workflow, a Kohn-Sham (KS) DFT calculation is performed first to provide orbitals and exchange-correlation (XC) energy, then a nonlocal second-order perturbative correlation term of Møller-Plesset (MP2)⁷⁸ type is evaluated. The perturbative correction is separated into “same spin” and “opposite spin” components, with different scaling factors to mitigate double counting, which are added to the KS DFT energy with different scaling parameters to avoid double-counting correlation. Such methodology has shown strong potential to approach chemical accuracy while keeping a computational cost comparable to MP2 perturbation theory.^{79–83} The DH functionals employed are listed below.

1) B2PLYP, used D3 and D3(BJ) empirical dispersion correction and 54% HF exchange and 27% MP2 contribution.⁸⁴

2) mPW2PLYPD, dispersion corrected DH functional including 55% HF exchange and 25% MP2 contribution.⁸⁵

3) PBE0DH, 1-parameter functional with PBE0 exchange and correlation, with 50% HF exchange and 12.5% MP2 contribution.⁸⁶

4) PBEQIDH, including 69.3% HF exchange and 33% MP2 contribution.⁸⁷

5) revDSD-PBEP86-D3BJ, revised version of DSD-PBEP86, involving 69% of HF exchange and 57.9% opposite spin and 8% same spin MP2 contributions.⁸⁸

Each DH functional was used in place of the underlying function for energy refinement while keeping the same solvent model. The approaches on which DH functionals have been applied are those returning the best prediction of stereoselectivity, compared to the experimental data, within ± 0.5 kcal/mol, and replacing the previous functional in the energy refinement calculation. For the sake of completeness, these DH functionals were also applied to worst result obtained from the previous analysis.

2.3 Results and Discussion

The discussion starts from transition states (TSs) analysis for SI-SIV and reported in **Figure 2.2**. As reported above and in **Chapter 1**, two sources of stereoerrors are detected for **SI-SIII**, which are referred to as **S1** and **S2**, with **S1** coming from a “wrong” chiral orientation of the growing chain bumping into the ligand framework and **S2** generating from the “wrong” selection of the monomer enantioface with the chain in its preferred orientation, leading to a chain-monomer interaction. The preference for **S1** or **S2** is ligand framework dependent and both are needed to be calculated. For **SIV**, which stereoselectivity origin has been claimed to be different, only one stereoerror has been detected.

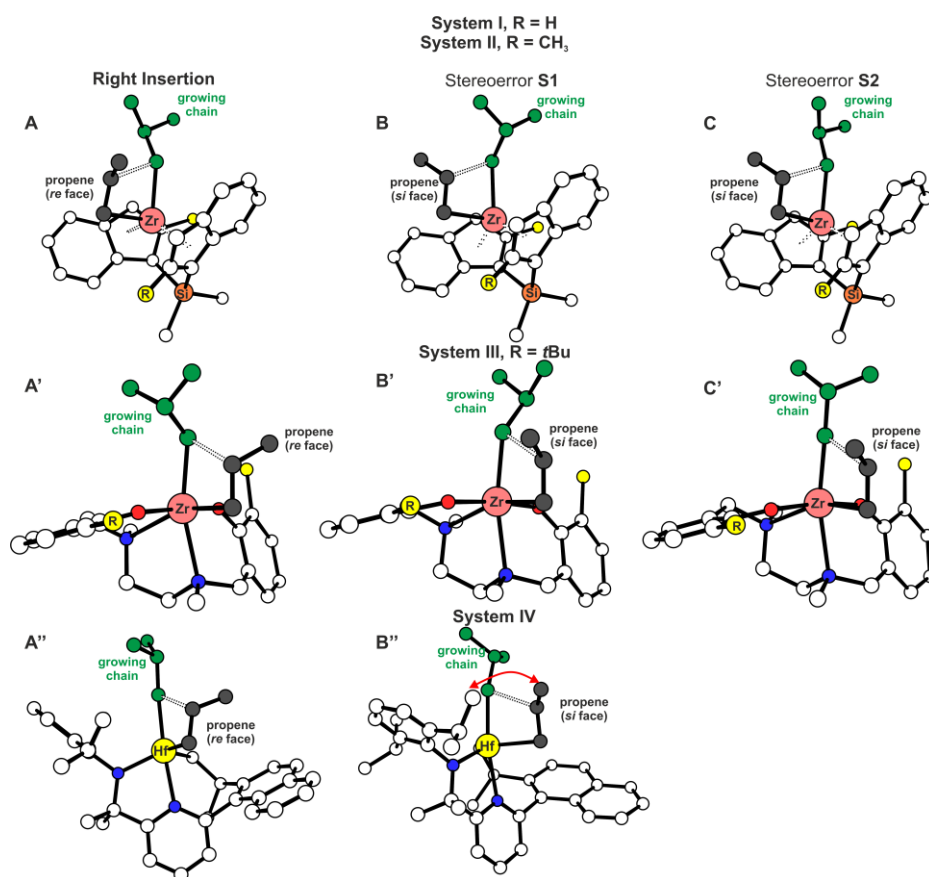


Figure 2.2. DFT Transition states of right insertions and stereoerrors for SI-IV. H atoms are omitted for clarity.

In **Table 2.1**, experimental stereoselectivity for propene polymerization are reported for SI-IV.

Table 2.1. Experimental stereoselectivity for systems I-IV calculated by ¹³C NMR data. In third column, the polymerization temperatures (*T_p*) are reported. $\Delta G_{\text{stereo}}^{\text{exp}}$ values are reported in kcal/mol.

Systems	[<i>mmmm</i>]	<i>T_p</i>	$\Delta G_{\text{stereo}}^{\text{exp}}$
I	89%	50°C	2.4

II	90%	50°C	2.5
III	87% ^{a)}	25°C	1.8
IV	91%	20°C	2.3

^{a)} This value refers to triad percentage [*mm*].

The analysis of propene stereoselectivity begins with a head-to-head comparison of different computational protocols on B3LYP TS geometries optimized without empirical dispersions. This starting point reflects frequent practice in studies of homogenous TM catalysis. The protocol for energy refinement calculations draws on the functionals reported in **Computational Details**, including D3 or D3(BJ) empirical corrections and three different solvent models. In line with the established framework, the stereoselectivity is governed by the lowest free-energy TSs, so computed values are evaluated against experimental Gibbs free energies. The results are summarized in **Figure 2.3**, as bar plots for **SI-SIV**.

For **SI**, the different functionals employed in the energy refinement calculations agree in predicting S2 as the most probable stereoerror, as shown in **Figure 2.3a**. All combinations of functional, dispersion and solvent models tend to overestimate the experimental stereoselectivity. The smallest overestimation is obtained with BP86-D3(BJ)-SMD (2.7 kcal/mol) and with BP86-D3(BJ)-PCM/CPCM (2.8 kcal/mol). The spread of $\Delta G_{\text{stereo}}^{\text{calc}}$ across methods reaches 2.1 kcal/mol, which is comparable to the overall $\Delta G_{\text{stereo}}^{\text{exp}}$ of 2.4 kcal/mol.

Agreement with experiment improves slightly for **SII**, as reported in **Figure 2.3b**. Most of the combinations of functional, dispersion and solvent favour S1 as the preferred stereoerror. Among solvent treatments, SMD reproduces the experimental trend more closely. This behaviour likely reflects the importance of non-electrostatic interactions in low-polarity media and the extensive parametrization of solvent-dependent terms in SMD. Refinement of the effective solvent radius for toluene would be expected to improve PCM and CPCM, yet a systematic optimization is deferred until a broader set of experiment-theory comparison is available. More generally, the comparison in **Figure 2.3a** and **3b** suggests caution, since a minor change in the ligand framework from R equal to H to R equal to CH₃ when moving from **SI** to **SII** leads to marked change in the computed stereoselectivity outcome, inverting the preferred stereoerror while the experimental stereoselectivity remains essentially unchanged, as reported in **Table 2.1**.

For **SIII**, most methodologies indicate S2 as the preferred stereoerror. Values of $\Delta G_{\text{stereo}}^{\text{calc}}$ obtained from the various combinations at B3LYP geometries without including dispersion correction in the optimization are reported in **Figure 2.3c**. The systematic overestimation noted for **SI** is not observed for this system. Several approaches deliver $\Delta G_{\text{stereo}}^{\text{calc}}$ values close to the experimental stereoselectivity of 1.8 kcal/mol. The best agreement is obtained BP86-D3 or D3(BJ)-PCM or CPCM, B3LYP-D3-PCM/CPMC, B3LYP-D3(BJ)-CPCM and PBE0-D3/D3(BJ)-PCM/CPM, and PW6B95 with SMD. SMD tends to give $\Delta G_{\text{stereo}}^{\text{calc}}$ values higher than PCM and CPCM for this system, while PCM and CPCM produce similar outcomes to each

other.

SIV is evaluated and the results are reported in **Figure 2.3d**. The experimental value is equal to 2.3 kcal/mol. The spread of $\Delta G_{\text{stereo}}^{\text{calc}}$ across protocols is large, reaching about 4.0 kcal/mol. Most functionals combined with SMD predict lower stereoselectivity than PCM and CPCM and tend to underestimate experimental value, whereas PCM and CPCM tend to overestimate. On B3LYP geometries, the closest agreements are obtained with BP86-D3-SMD (2.2 kcal/mol), BP86-D3(BJ)-SMD and M06-D3-SMD (both 2.1 kcal/mol). These results reinforce the observation that the solvent model exerts a strong influence for **SIV** than for the other systems and it is consistent with a stereocontrol regime different from the cases discussed above.

Additionally, to complement the $\Delta G_{\text{stereo}}^{\text{calc}}$ bar charts, signed error plots are reported in **Figure 2.4**, for all systems. It is defined as $\Delta G_{\text{stereo}}^{\text{calc}}$ minus $\Delta G_{\text{stereo}}^{\text{exp}}$, in which positive values indicate overestimation and negative values indicate underestimation.

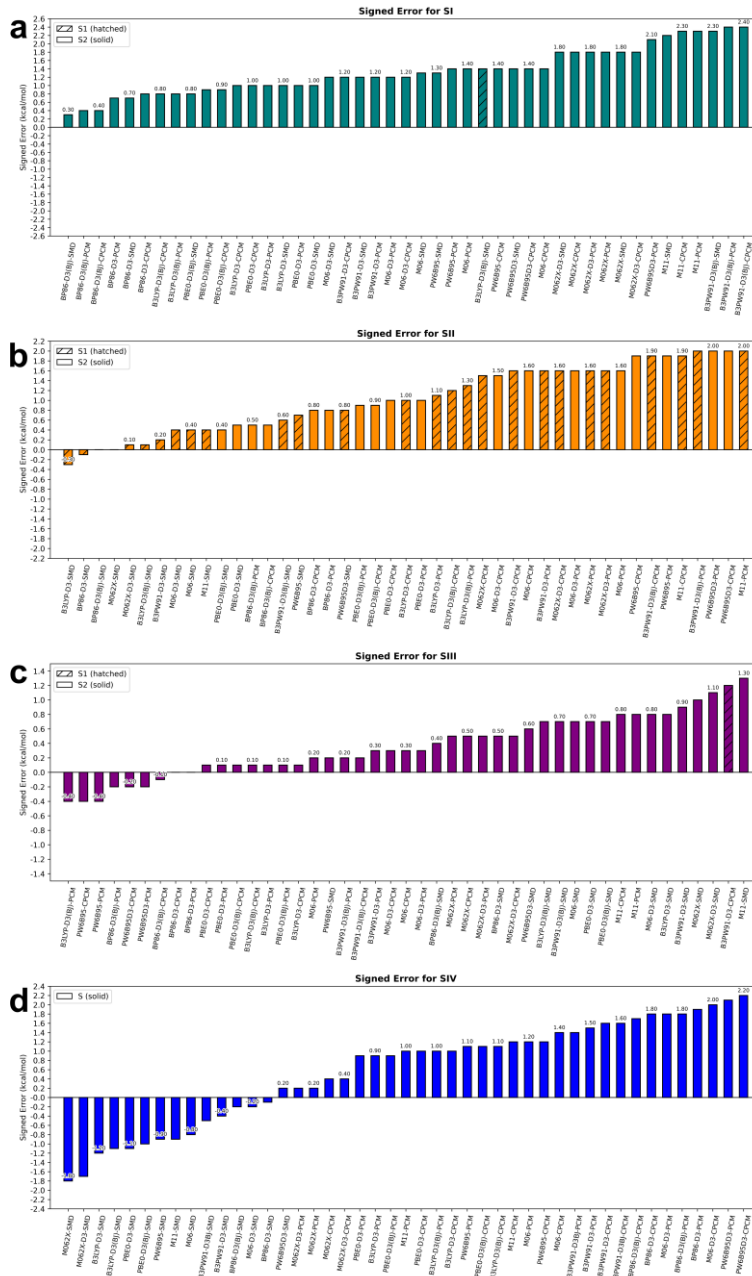


Figure 2.4. Signed error bar plots for **SI-IV** (from **a** to **d**). Positive values indicate overestimation relative to $\Delta G_{\text{stereo}}^{\text{exp}}$ and negative values indicate underestimation. S1 is hatched and S2 is solid. Axes are centred at zero with symmetric limits. Bars are ordered by signed error within each panel.

Taken together, the signed error analysis provides two practical messages. First, the direction of the systematic error can change across systems even when similar families of functionals with the same dispersion correction. Second, the solvent treatment affects the balance in a specific manner, with **SIV** notably more sensitive than other systems, as specified above. It follows that protocol selection should rely on a cross system assessment rather than on a single case, because a joint examination of signed errors reduces the risk of accidental compensations and helps in the identification of combination that are more robust for the prediction of stereoselectivity. Consistent with this view, BP86 single point refinements on B3LYP geometries deliver the lowest average deviation across **SI** to **SIV** in the present dataset and can serve as a pragmatic reference choice, although broader validation beyond these systems remains advisable.

Subsequently, all the TS geometries were re-optimized with the functionals listed in **Computational Details**, adopting the following scheme, in order the impact of the geometries using different computational approaches:

- 1) Optimizations have been carried out including or not dispersion corrections (D3 or D3(BJ));
- 2) Energy refinement calculations proceeded employing the same functional as in the optimization, adding D3 or D3(BJ) corrections and using PCM, CPCM or SMD model for implicit solvation.

All the results are reported in **Figure 2.5, 6, 7, 8** for **SI, SII, SIII** and **SIV**, respectively. In each Figure, panel **a** refers to geometry optimized without empirical dispersion corrections, whereas panels **b** and **c** report results obtained from including D3 and D3(BJ), respectively, empirical dispersion during the optimization step. On geometries optimized with D3(BJ) empirical dispersion correction, only D3(BJ) has been employed in single-point calculations.

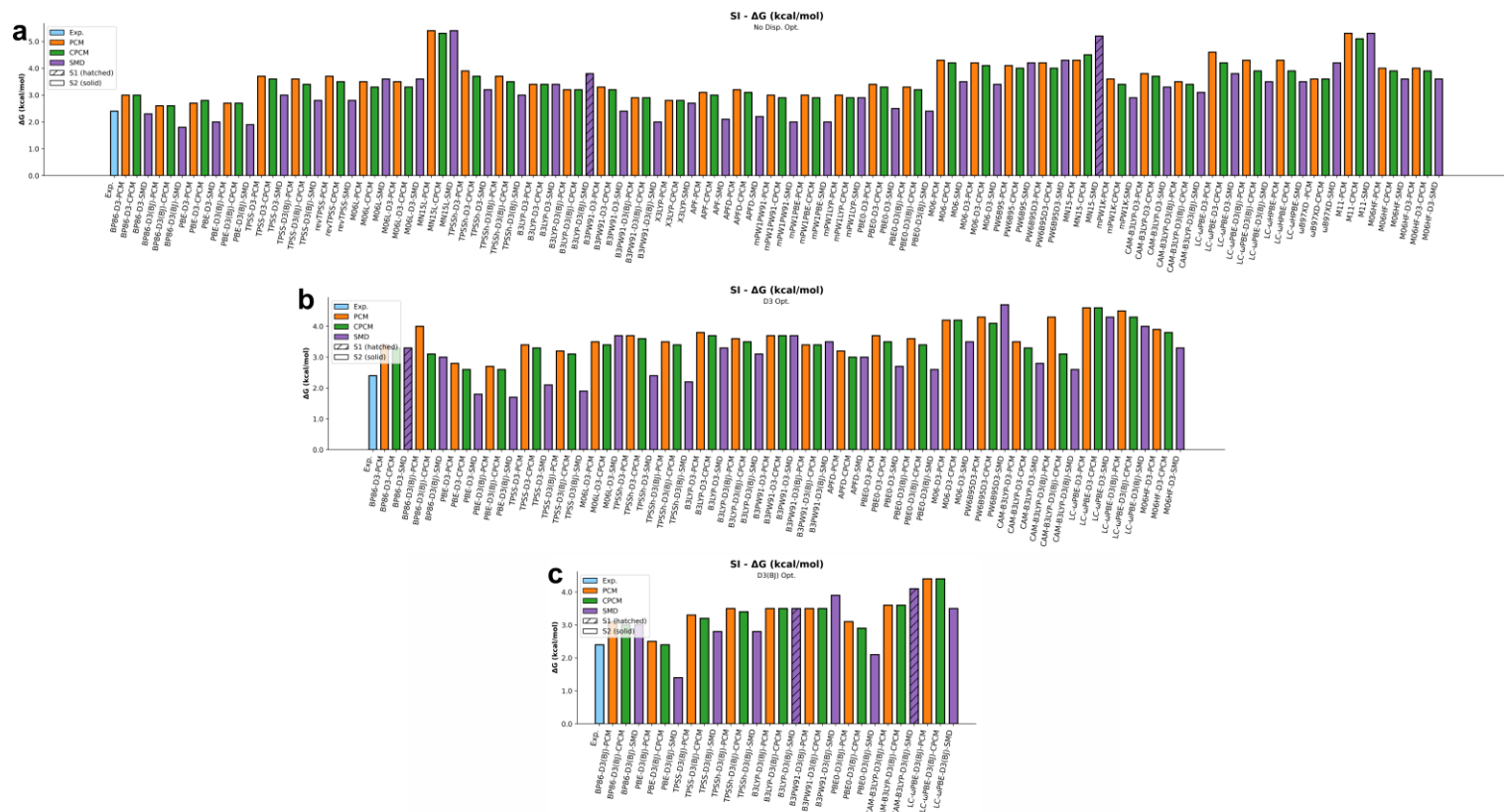


Figure 2.5. Bar plots for **SI** of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a, b and c report optimizations with no dispersion included, D3 and D3(BJ) respectively.

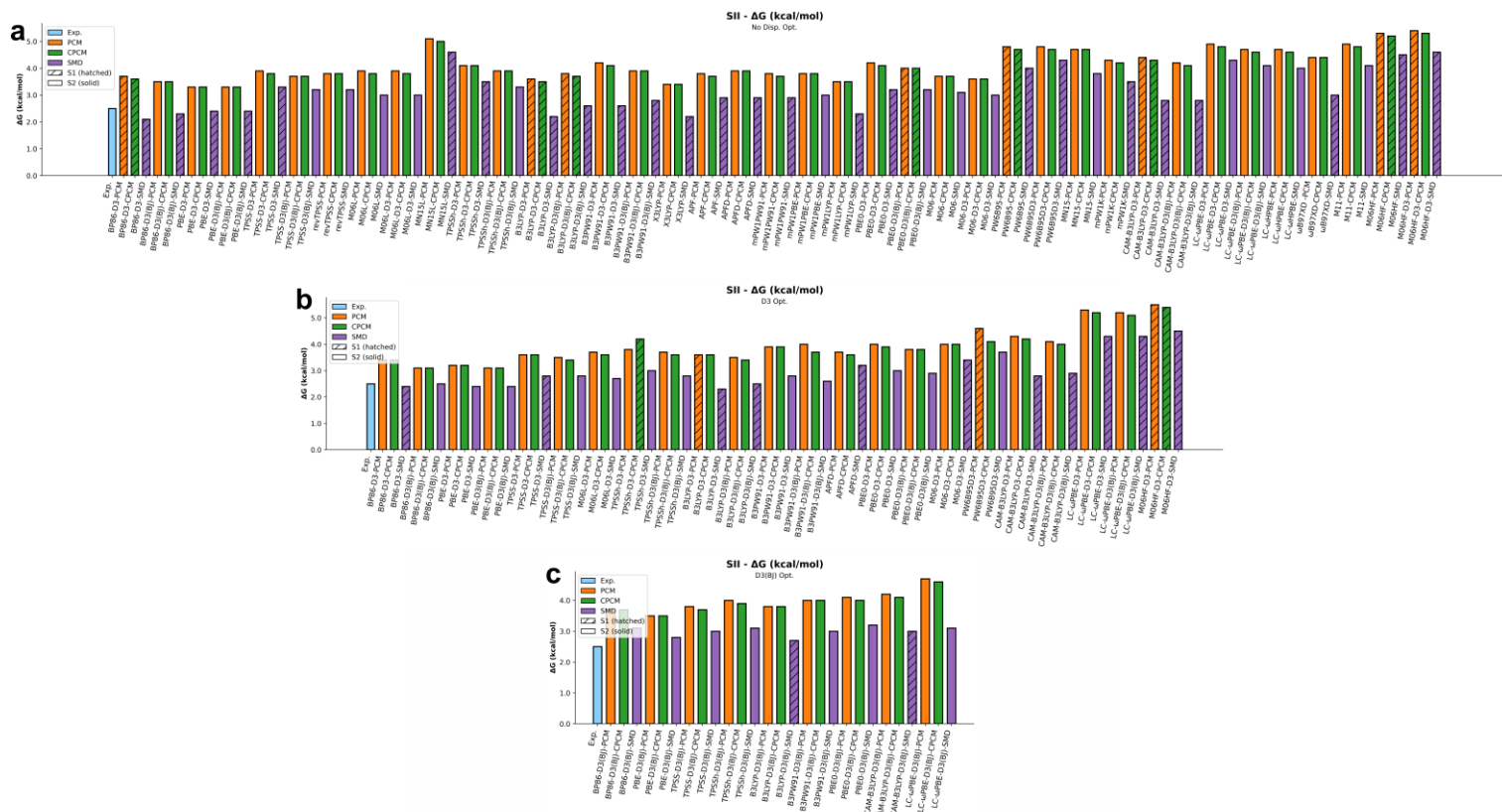


Figure 2.6. Bar plots for **SII** of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a, b and c report optimizations with no dispersion included, D3 and D3(BJ) respectively.

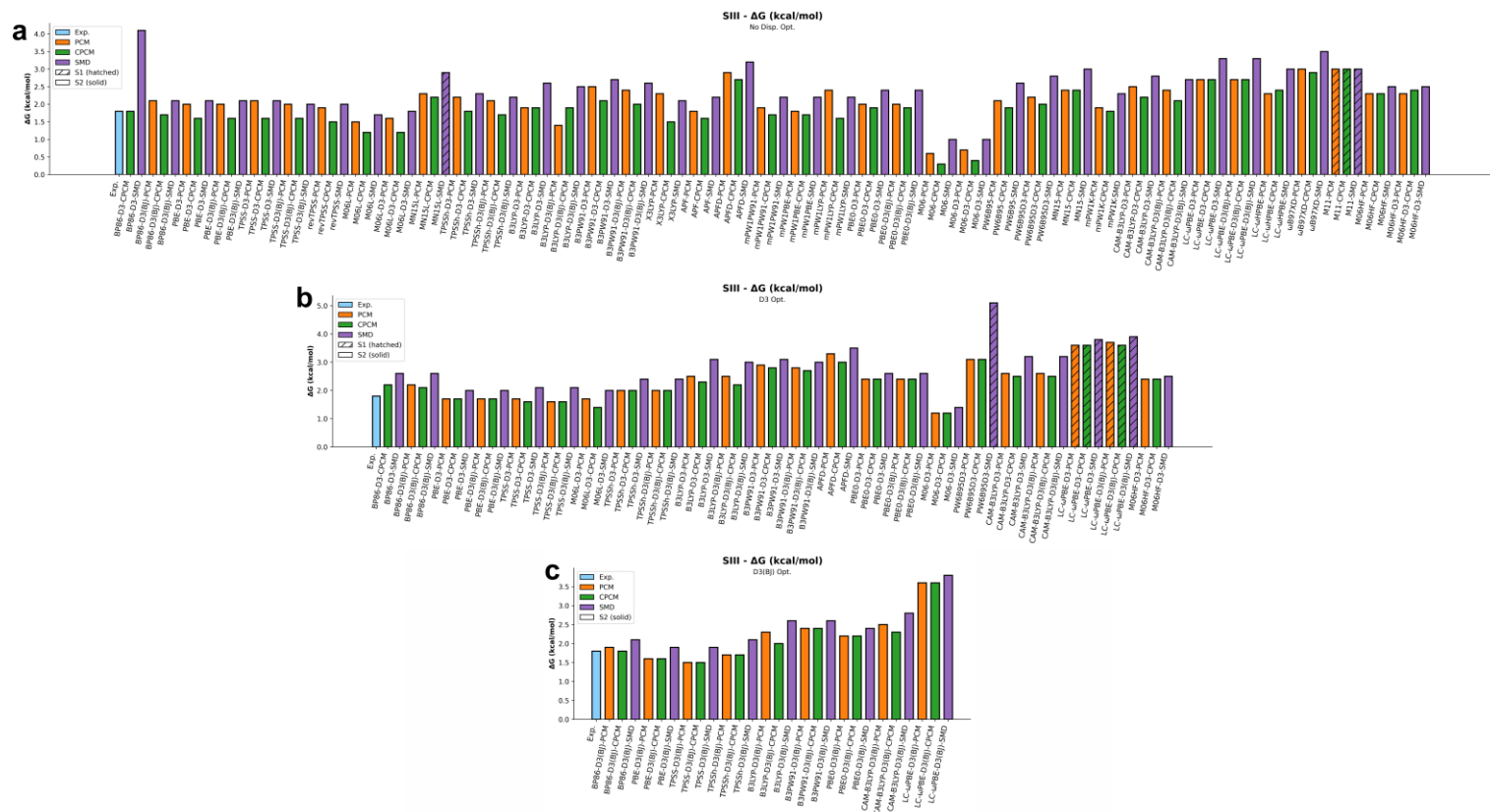


Figure 2.7. Bar plots for **III** of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a, b and c report optimizations with no dispersion included, D3 and D3(BJ) respectively.

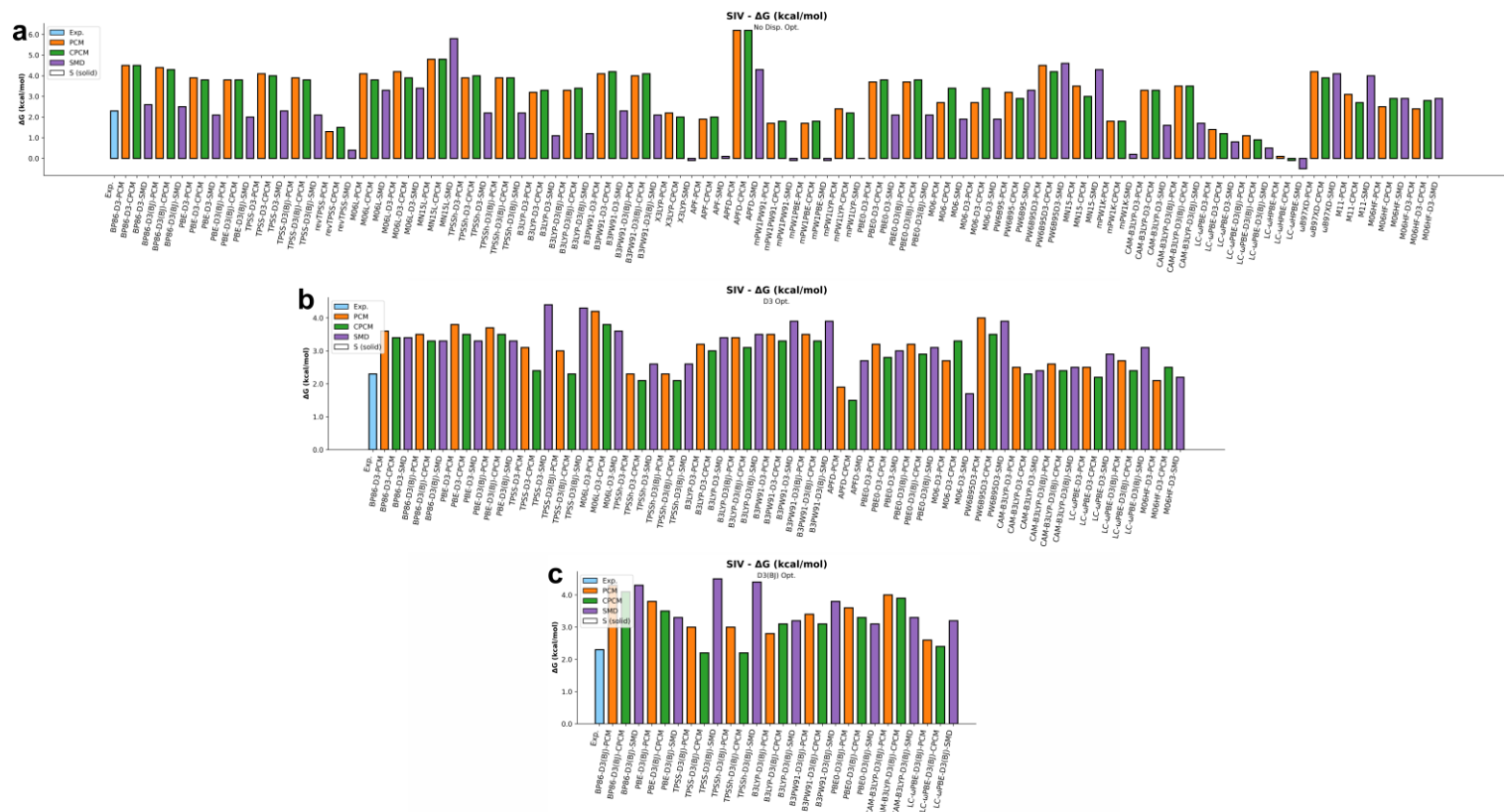


Figure 2.8. Bar plots for SIV of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a, b and c report optimizations with no dispersion included, D3 and D3(BJ) respectively.

For **SI**, the level of optimization alone does not account for the full spread across functionals, however the inclusion of dispersion during optimization generally improves the average agreement. All the results are reported in **Figure 2.5**. As in the case of B3LYP geometries, the results would tend to favour S1 over S2, regardless of the dispersion corrections and solvent model used. On geometries optimized without empirical dispersion corrections, B3PW91 and PBE0 remain consistent once D3 or D3(BJ) corrections and SMD are included in the single point calculation. Within the enlarged pool of methodologies, additional combinations are competitive, reducing the overestimation typical of PCM and CPCM. Indeed, PBE with B3(DJ) in CPCM and SMD reaches nearly zero deviations. PB86 with D3 or D3(BJ) in SMD is among the best approaches. TPSSh with D3 in SMD on D3-optimized geometries returns values in good agreement with the experimental one. Such results highlight the essentiality of dispersion corrections in single point calculations and how SMD is the safer solvent choice, independently of whether the geometry optimization includes dispersion.

Figure 2.6 shows the results concerning **SII**, for which most functionals stabilize S1 over S2 stereoerror, as occurring on B3LYP geometry optimization. The solvent effect in single point calculations is stronger than in **SI** and SMD is the most reliable choice. BP86 with D3(BJ) and SMD on D3-optimized geometries matches experiment very closely, as well as B3LYP with D3(BJ) and SMD. PBE with D3(BJ) and SMD, B3PW91 with D3 in SMD on no dispersion optimized geometries, PBE0 with D3 or D3(BJ) in SMD are among the best approaches in predicting stereoselectivity as well. These observations reinforce that for **SI** and **SII** the solvent model exerts stronger leverage than the geometry protocol once dispersion corrections are introduced in the energy refinement calculations.

The picture for **SIII** differs from the previous systems. The solvent preference is inverted, leading CPCM the most reliable for the energy refinements, while SMD tends to enlarge deviations. All the results are reported in **Figure 2.7**. Several approaches reach the experimental value when dispersion corrections are included in

the single point step. BP86 with D3 or D3(BJ) in CPCM, TPSSh with D3 in CPCM on geometries with no empirical dispersion corrections perform well. PBE0 with D3 or D3(BJ) and PCM or CPCM returns accurate results. Among the mPW family, mPW1K in CPCM on geometries that are not correct for empirical dispersion during the optimization step performs accurately. M11, on the other hand, consistently overestimates the stereoselectivity, with only minor sensitivity to solvent.

For **SIV** the stereoselectivity is more sensitive to the protocol and responds strongly to the solvent description. Including dispersion during the optimization narrows the spread across protocols and reduces the solvent dependence. Geometries optimized without the inclusion of empirical dispersion, B3PW91 with D3 and SMD solvent model reproduces experimental stereoselectivity very closely. When dispersions are introduced, CPCM and PCM become more reliable for single point calculations and pair well with those functional that balance exchange and correlation. TPSS with D3(BJ) and CPCM on D3-optimized geometries returns the best accordance, as well as TPSSh, including D3 dispersion correction and PCM solvent description on geometries optimized with D3 empirical dispersion. TPSS returns good agreement on geometries optimized with no empirical dispersion and including D3 empirical dispersion in single point calculations with SMD solvent model, confirming that the effects of solvent model and dispersion correction can be tuned coherently. Across this system, D3 correction for energy refinement calculations slightly outperforms D3(BJ) on average.

These findings suggest a coherent pattern across the four systems. The optimization step has a crucial impact, yet the best protocol is strictly system-dependent. Indeed, **SI**, **SII** and **SIV** benefit by the inclusion of dispersion correction during the optimization, while **SIH** is less sensitive and often the protocols that perform better are those in which dispersion corrections are included only at the single-point stage. The solvent model has an essential role. Indeed, if SMD is a “safer” choice for **SI** and **SII**, mitigating the overestimation and reducing the spread, CPCM works better for **SIH** and **SIV**, while SMD can return satisfactory results for **SIV** when empirical

dispersions are not included in geometry optimization. Concerning dispersion corrections, D3(BJ) is generally preferred for **SI** to **SIII**, while D3 is often the better option for **SIV**. Based on the results, several functional families can be trusted when the other two levers are set correctly. Global hybrids such as B3PW91, B3LYP and PBE0 are reliable for metallocene systems. PBE and BP86, pure GGA functionals, perform competitively when dispersion corrections and solvent are tuned, particularly PBE with SMD solvent for **SI** and **SII** and with CPCM and PCM for **SIII**. Meta GGA and meta hybrid functionals such as TPPS, TPSSh and PW6B95 perform accurately with CPCM or PCM for **SIII** and with CPCM or PCM for **SIV** after empirical dispersion inclusion in optimization step. Additionally, among range-separated hybrids CAM-B3LYP with D3 and CPCM returns results in good agreement for **SIV** after optimizations including dispersion.

Given the size of the benchmark study, a systematic selection was carried out, ranking protocols against experimental results and retaining those that reproduce stereoselectivity within 0.5 kcal/mol. This approach highlights those combinations that remain accurate across changes in geometry treatment, dispersion and solvent models. It also makes it possible to enforce similarities across systems and to identify transferable methodologies. In **Figures 2.9 to 2.12**, common protocols, with mean absolute errors (MAEs) and signed errors, are reported for SI-SII, belonging to the C_2 *ansa*-metallocene class, for SI-SII-SIII, which share C_2 symmetry, for SIII-SIV, which are both post-metallocene systems, and lastly for SI to SIV, to compare all the systems involved in the analysis.

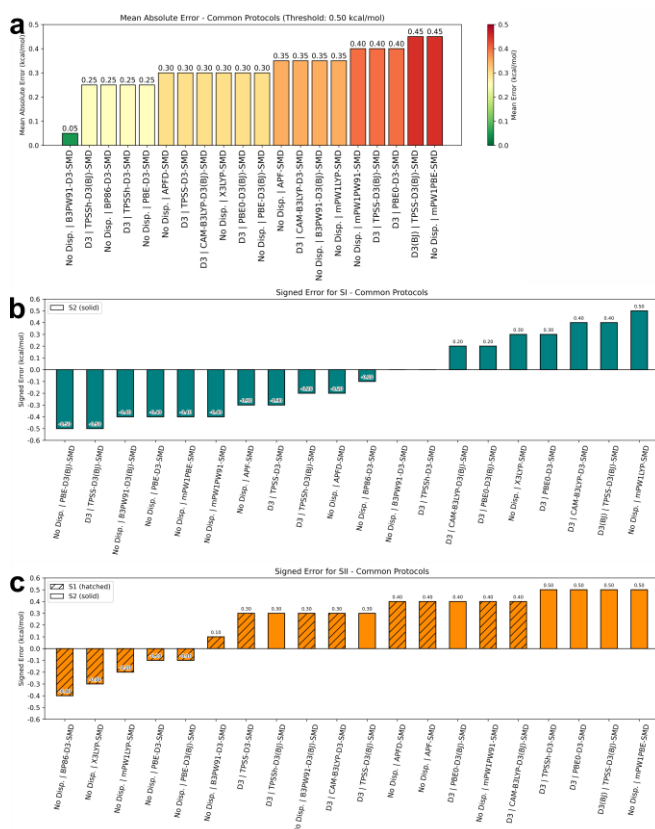


Figure 2.9. Bar plots for SI and SII of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a reports MAE for common protocols within 0.5 kcal/mol. Panels b and c report signed error for SI and SII for common protocols.

In **Figure 2.9** shows a compact cloud of MAE, approximately three tenths of kcal/mol. Because the intersection between the two systems leads to SMD solvent mode as a requirement for portability, positive deviations that show up for some PCM or CPCM variants in single-system analysis are not present. When combined with D3 and SMD, B3PW91 is the best approach to reproduce experimental stereoselectivity for both systems, followed by PBE and BP86 functionals, without including dispersion in the optimization steps and coupled with D3 empirical dispersion corrections in single point, and TPSSH, with D3 or D3(BJ) empirical dispersion in energy refinement

calculations, after D3 optimization geometries. It is noteworthy that by tracing signed-errors for **SI** and **SII**, often these values have opposite signs of small magnitude for the same protocols.

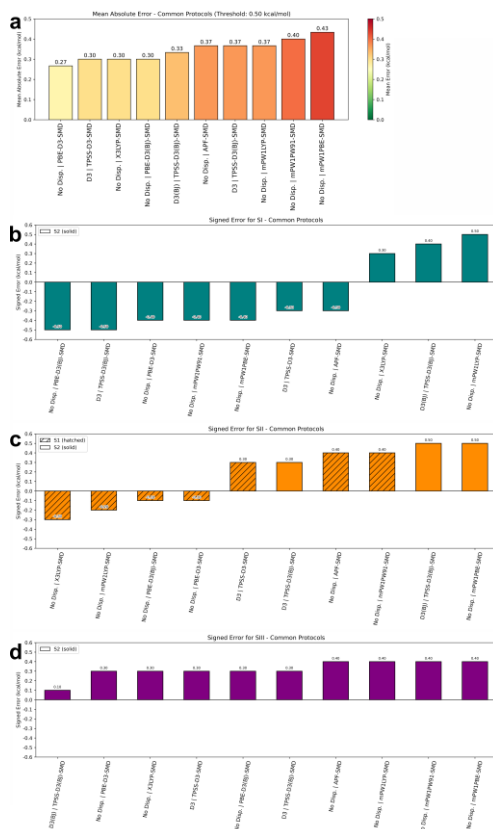


Figure 2.10. Bar plots for SI, SII and SIII of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a reports MAE for common protocols within 0.5 kcal/mol. Panels b, c and d report signed error for SI, SII and SIII for common protocols.

In **Figure 2.10** it is shown the common protocols, within 0.5 kcal/mol, for the three C_2 -symmetric systems (**SI** to **SIII**). In this case, the intersection results smaller than the previous case. The MAEs cluster around 0.3 kcal/mol. The signed-error panels show small oscillations around zero across the three systems. Again, SMD appears in every common protocol, making it crucial for better productivity. The best

performances are obtained through PBE-D3, with no dispersion corrections in the optimization step, and followed by PBE-D3(BJ), X3LYP without including dispersion in the optimization steps. The signed-error oscillated mildly around zero across three systems rather than drifting in one direction. This balanced pattern supports portability rather than tuning for a single case.

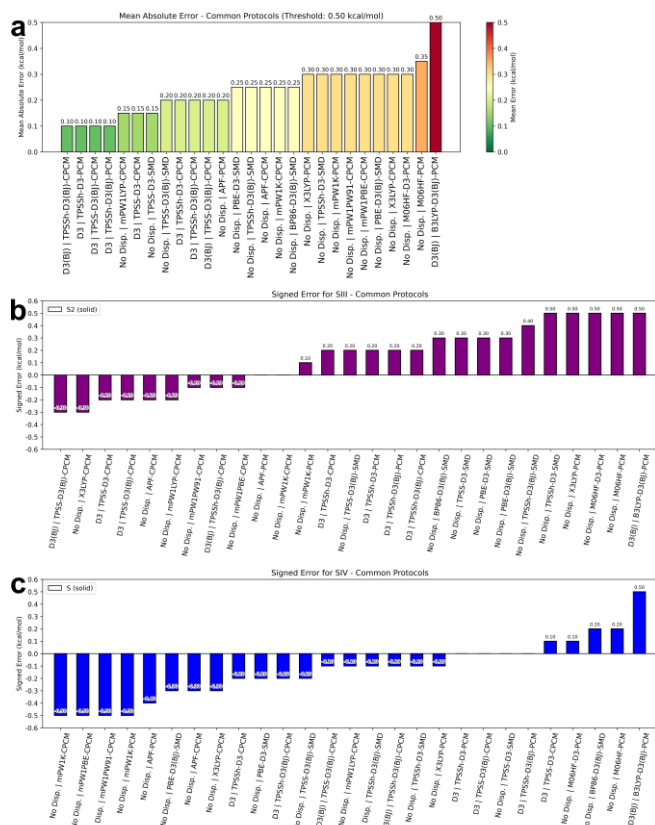


Figure 2.11. Bar plots for SIII and SIV of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panels a reports MAE for common protocols within 0.5 kcal/mol. Panels b and c report signed error for SIII and SIV for common protocols.

For the two post-metallocene systems, **SIII** and **SIV**, the common protocol set is larger and the SMD model becomes less representative. Indeed, CPCM is the most frequent and then followed by PCM. The MAE bars are tightly grouped and low, with

many entries is the order of one tenth of kcal/mol. As above, the signed-error panels show small errors and with opposite sign. Among the common protocols, TPSSH or TPSS with D3 or D3(BJ) and CPCM or PCM return the best accordance, on geometries optimized both including or not empirical dispersions. Such results consider the CPCM solvation model preference of **SI** and the highest sensitivity of **SIV**.

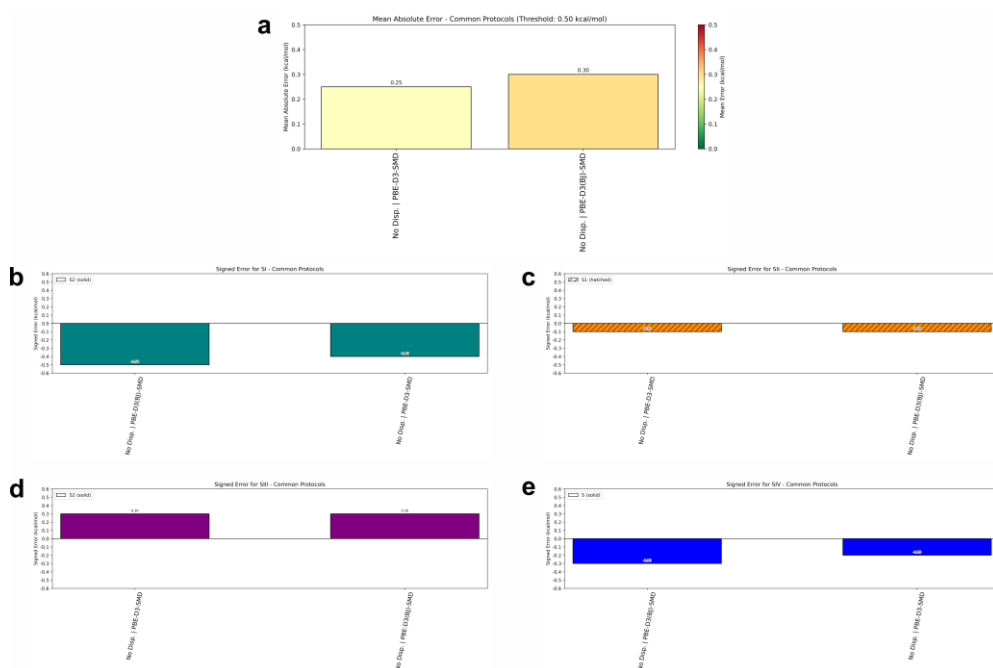


Figure 2.12. Bar plots for SI, SII, SIII and SIV of DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with different functionals, dispersion corrections and solvation models. Panel a reports MAE for common protocols within 0.5 kcal/mol. Panels b, c, d and e report signed error for SI, SII, SIII and SIV for common protocols.

Figure 2.12 shows intersection for all the systems, becoming minimal as expected when portability is enforced across four different systems. Only two protocols reproduce experimental results and share two features, which consist in the predominance of SMD solvent and geometries optimized without dispersion corrections. The MAEs oscillate between one and three tenths of kcal/mol across the

four systems. PBE-D3-SMD is the best common protocol, with PBE-D3(BJ)-SMD closely behind. On the other hand, the narrowing of the intersection after considering all systems does not contradict the single-system observation regarding dispersion-included geometry optimization. Indeed, the inclusion of dispersion in the optimization step is system-dependent, which gives specific responses, on the geometry and symmetry and nature of the ligand which reduce the overlap of methodologies across the four systems. It is worthy to note that the two common protocols are both based on a pure GGA functional.

This systematic approach based on MAEs and signed errors for common protocols provides two complementary messages. MAEs shows that several families of functional can return high accuracy once solvent and dispersion are finely tuned. The signed-error analysis confirms that common protocol does not rely on hidden compensations. With this approach, it was possible to gain insights concerning the best protocols for stereoselectivity prediction within the class of C_2 -symmetric *ansa*-metallocene (**SI** and **SII**), for C_2 -symmetric systems (**SI** to **SIII**), post-metallocene systems (**SIII** and **SIV**) and for all of them.

A complementary test was carried out by replacing the single-point functional with a set of double hybrids on the common protocols identified in the DFT screen. The aim was to study the impact of the adding non local second order correlation while keeping the same transition state geometries and the same solvent model identified in the common protocol screening, avoiding in this context the analysis of the solvent effects for DH functionals. The analysis was conducted following the same the intersection found previously, so **SI-SII**, **SI-SII-SIII**, **SIII-SIV** and **SI-SII-SIII-SIV**. Performance was evaluated by per-system MAE, system balanced average across the members of each intersection (calculated as the arithmetic mean of the per-system MAE across all systems in the intersection) and inspection of signed-error patterns.

(in case of more than one pure/hybrid DFT functionals in the same plot, the MAE of the lowest has been considered) in Figure 2.9. Panel n reports results of double hybrid functional evaluations on the worst protocol, MN15-L. Violet bars indicate SMD model for solvation, orange bars indicate PCM model for solvation.

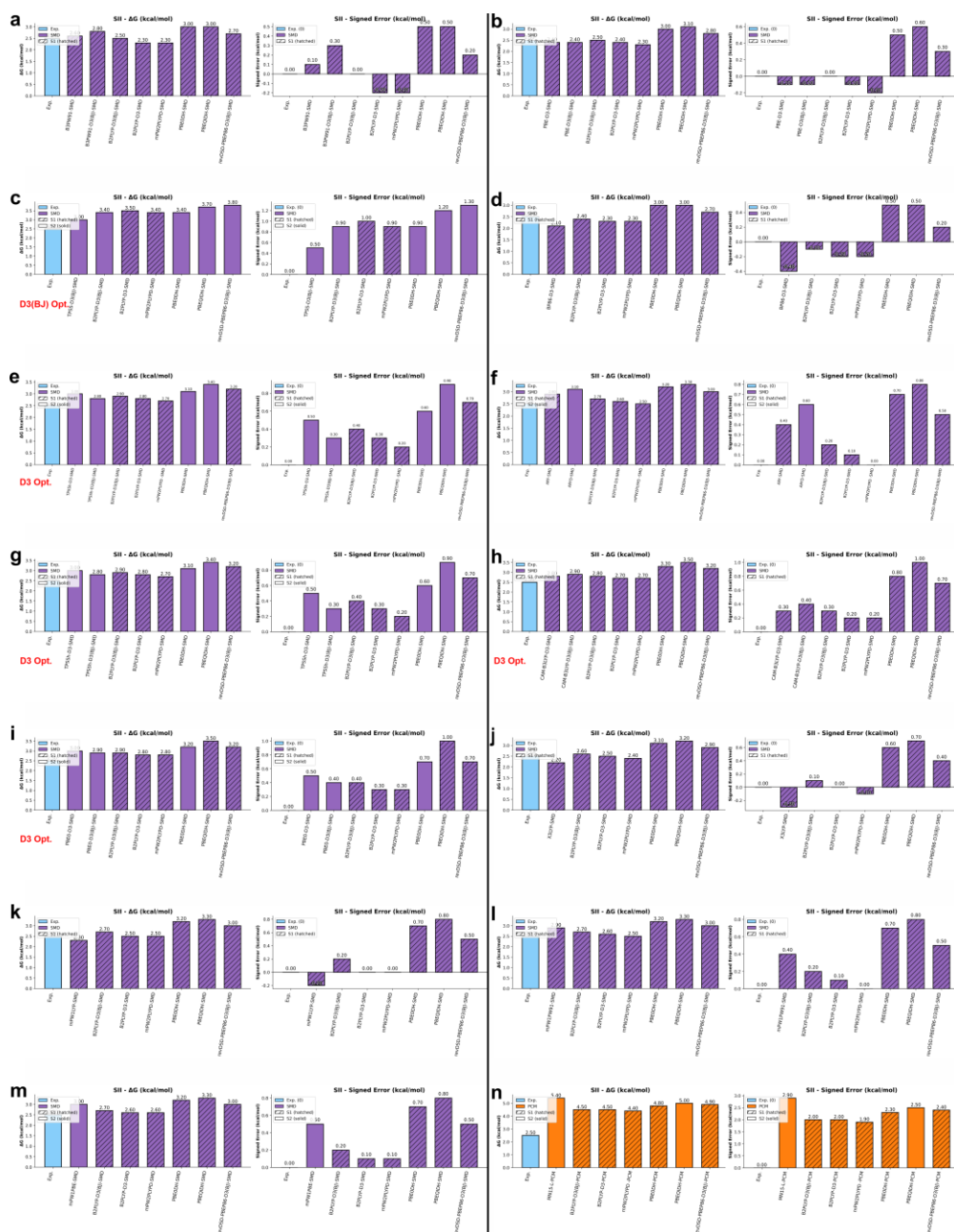


Figure 2.14. Bar plots for SII reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) and signed-error plots computed with double hybrid functionals and its pure/hybrid reference, for common protocols within 0.5 kcal/mol. All the results for common protocols between SI and SII are reported in panels from a to m, ordered by ascending MAE

(in case of more than one pure/hybrid DFT functionals in the same plot, the MAE of the lowest has been considered) in Figure 2.9. Panel n reports results of double hybrid functional evaluations on the worst protocol, MN15-L. Violet bars indicate SMD model for solvation, orange bars indicate PCM model for solvation.

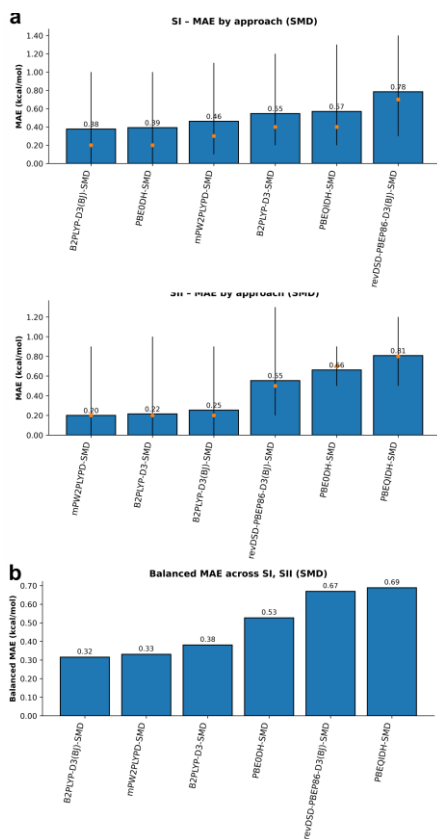


Figure 2.15. Bar plots for MAE by approach for SI and SII (a) and Balanced MAE across both systems (b).

Bar plots for DFT values and signed-error are reported in **Figures 2.13** and **2.14** and **Figure 2.15** shows bar plots for MAE by approach for **SI** and **SII** and balanced MAE across both. On **SI** the smallest MAEs are obtained with B2PLYP-D3(BJ) and PBE0DH, both delivering accurate predictions of experimental stereoselectivity. A small positive bias remains visible on average for all families of DH functionals but with a consistent prediction of S2 as the main source of stereoerror. Conversely, on

SII the gains are stronger and more uniform. mPW2PLYPD gives the lowest mean absolute error, followed by B2PLYP with D3 and then D3(BJ), providing multiple exact matches across different optimization protocols.

The two aggregate views confirm these trends. Indeed, a system balanced MAE (**Figure 2.15b**) places B2PLYP-D3(BJ) at the top across **SI** and **SII**, followed by mPW2PLYPD and B2PLYP-D3. On the other hand, revDSD-PBEP86-D3(BJ) and PBEQIDH are those returning higher values with respect to the experimental one.

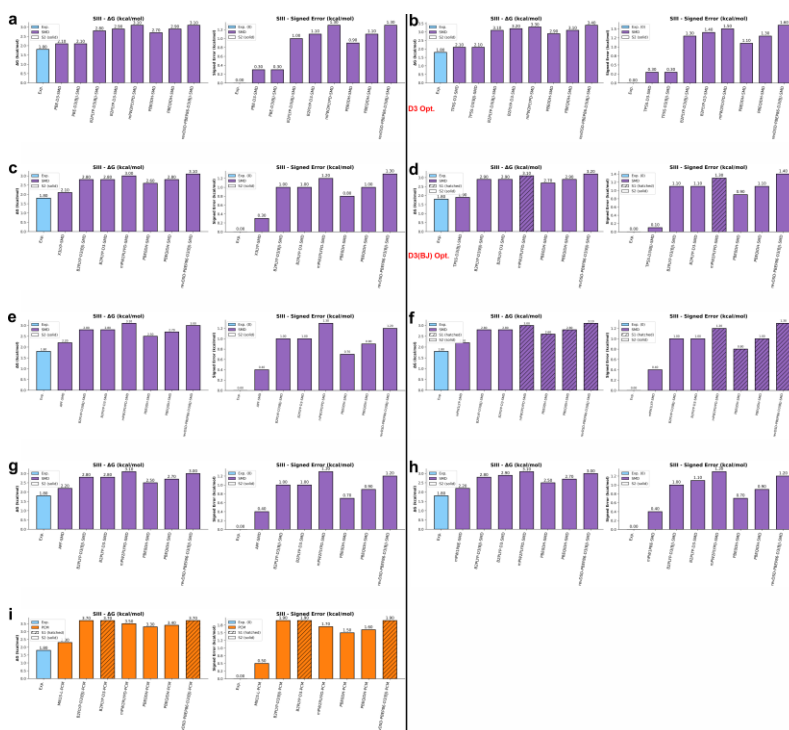


Figure 2.16. Bar plots for SIII reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) and signed-error plots computed with double hybrid functionals and its pure/hybrid reference, for common protocols within 0.5 kcal/mol. All the results for common protocols with SI and SII are reported in panels from a to h, ordered by ascending MAE (in case of more than one pure/hybrid DFT functionals in the same plot, the MAE of the lowest has been considered). Panel i reports results of double hybrid functional evaluations on

the worst protocol, MN15-L. Violet bars indicate SMD model for solvation, orange bars indicate PCM model for solvation. Common protocols to SI and SII.

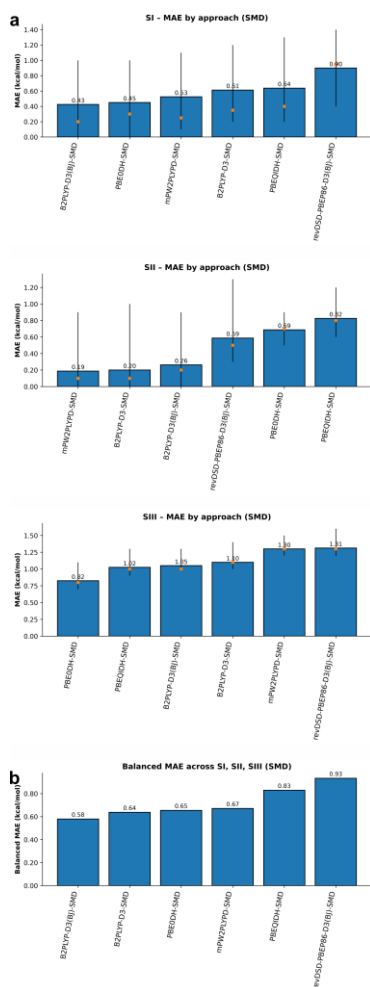


Figure 2.17. Bar plots for MAE by approach for SI, SII and SIII (a). Balanced MAE across all systems (b). Common protocols to SI and SII.

The same strategy was extended to the **SI-SII-SIII** group under the same constraints. Double hybrids preserve the favourable pattern observed for **SI-SII**. Bar plots for DFT values and signed-error are reported **Figure 2.16** for **SIII** and **Figure 2.17** shows bar plots for MAE by approach for **SI**, **SII** and **SIII** and balanced MAE across the three

systems. Indeed, B2PLYPD-D3(BJ) gives the lowest system-balance MAE, followed by B2PLYP-D3 and PBE0DH, while mPW2PLYPD, due to larger deviations on SIII, is less representative. Signed errors follows the same directions across systems, but they are not near zero once **SIII** is included. As a matter of fact, the largest positive bias is carried by **SIII**, increasing the three-system averages. On the other hand, as before the stereoassignment does not change, but the introduction of a second-order MP2 correlation does not remove the intrinsic difficulty of **SIII** in predicting stereoselectivity.

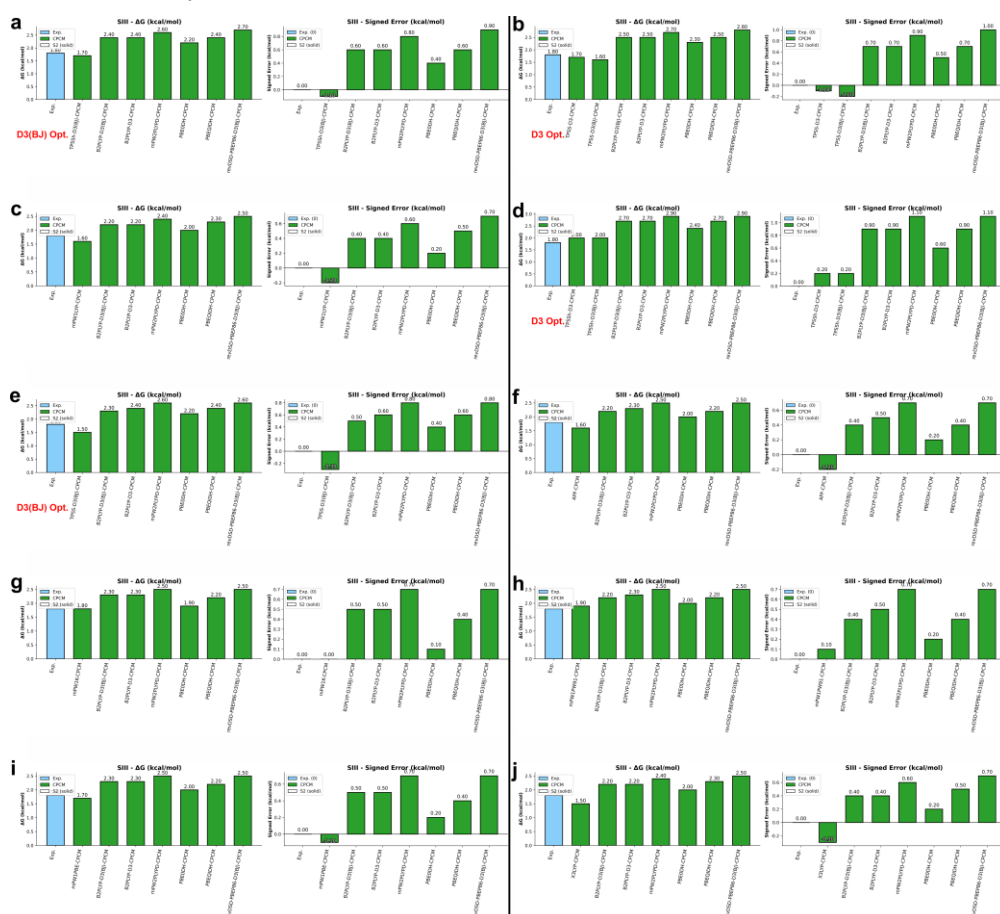


Figure 2.18. Bar plots for SIII reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with double hybrid functionals and its pure/hybrid reference, for common protocols within 0.5 kcal/mol. All the results for common protocols

between SIII and SIV are reported in panels from a to j, ordered by ascending MAE (in case of more than one pure/hybrid DFT functionals in the same plot, the MAE of the lowest has been considered) in Figure 2.11. Green bars indicate CPCM model for solvation.

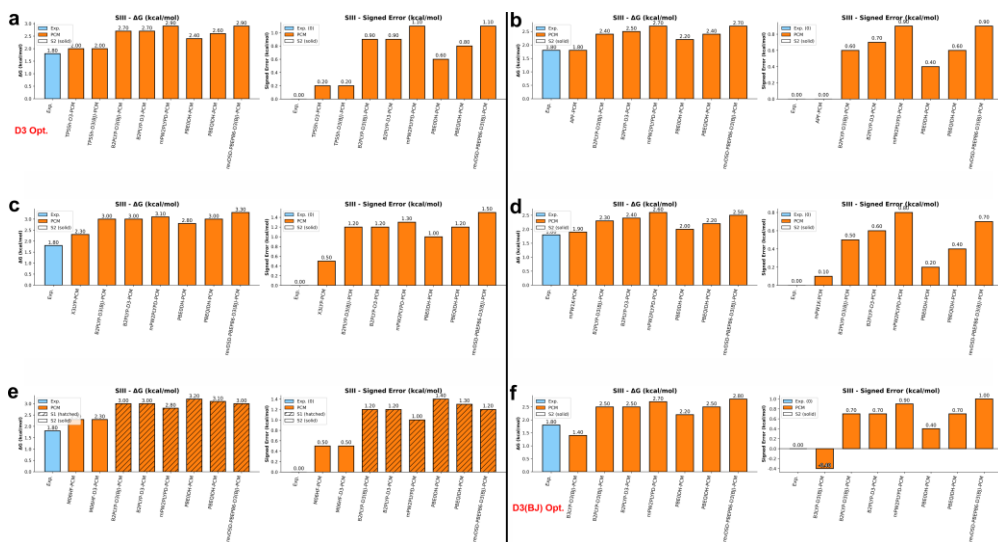


Figure 2.19. Bar plots for SIII reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with double hybrid functionals and its pure/hybrid reference, for common protocols within 0.5 kcal/mol. All the results for common protocols between SIII and SIV are reported in panels from a to f, ordered by ascending MAE (in case of more than one pure/hybrid DFT functionals in the same plot, the MAE of the lowest has been considered) in Figure 2.11. Orange bars indicate PCM model for solvation.

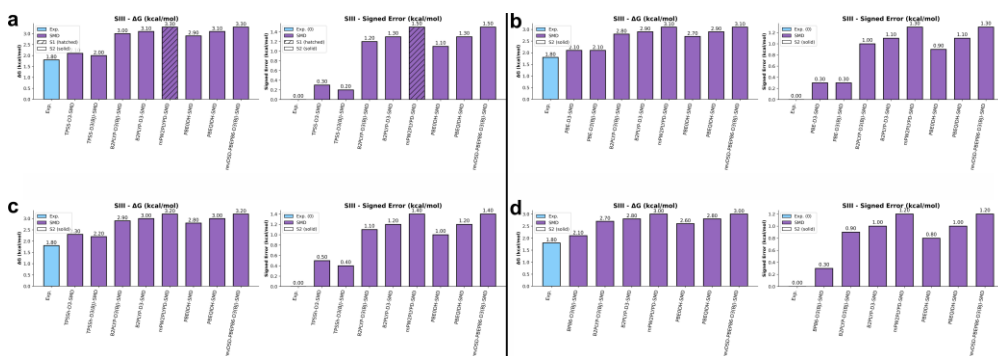


Figure 2.20. Bar plots for SIII reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with double hybrid functionals and its pure/hybrid reference, for common protocols within 0.5 kcal/mol. All the results for common protocols

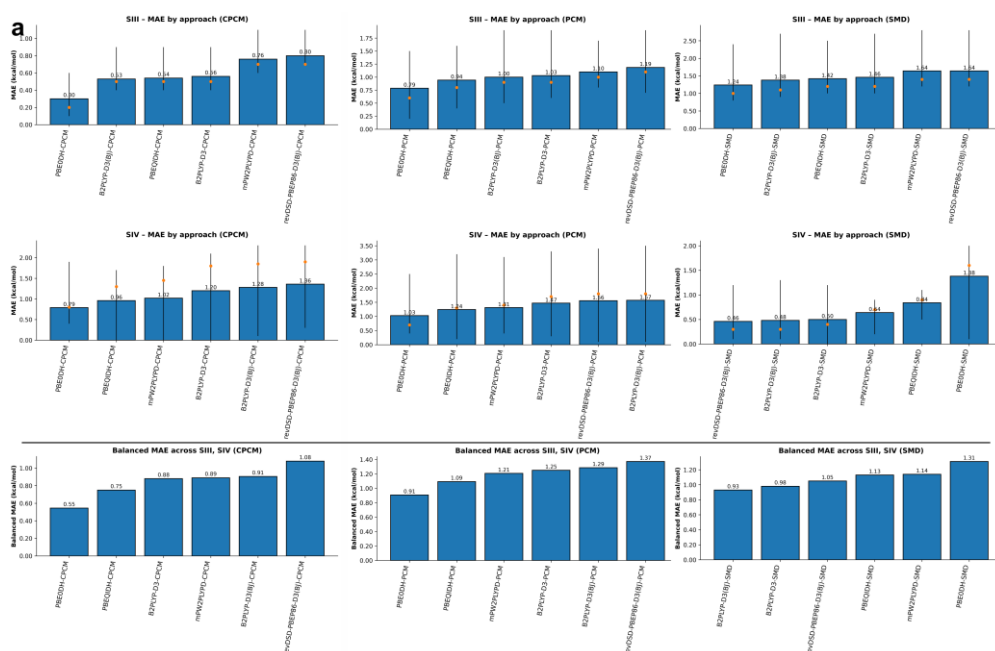


Figure 2.24. Bar plots for MAE by approach for SIII and SIV (a). Balanced MAE across all systems (b).

In **Figures 2.18** to **2.23** DFT values and signed-error plots are reported for **SIII** and **SIV** on common protocols as reported in **Figure 2.11**. CPCM is the most frequent model solvent for single point calculations, followed by PCM and SMD. In **Figure 2.24** bar plots for MAE by approach for SIII and SIV balanced MAE and are reported. In this intersection, by looking at per-approach MAE PBE0DH and PBEQIDH in CPCM are those giving the best MAE, followed by B2PLYP. In PCM the same families of functionals remain competitive. Looking at balanced MAEs, the smallest values are obtained with CPCM, followed by PCM and SMD. The apparently weaker performance of SMD in this intersection should be interpreted with caution, since SMD is less represented.



Figure 2.25. Bar plots for all systems reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) computed with double hybrid functionals and its pure/hybrid reference, for common protocols within 0.5 kcal/mol. All the results for common protocols between SIII and SIV are reported in panels from a to d, ordered by ascending MAE (in case of more than one pure/hybrid DFT functionals in the same plot, the MAE of the lowest has been considered) in Figure 2.11. Violet bars indicate SMD model for solvation (a). Bar plots for MAE by approach for all systems (b). Balanced MAE across all systems in (c). The last intersection involves all the systems analysed in this benchmark, which is the most compact. Only PBE functional, with geometries optimized with no dispersion and single point with SMD solvent model survives. In **Figure 2.24** are reported DFT values and signed-errors plot for all the systems and per-approach, balanced and paired MAEs. The balanced MAE across the four systems lies in the low-tenths range. B2PLYP-D3(BJ) and B2PLYP-D3 shows the lowest balance MAE followed by mPW2PLYPD. The paired MAE, computed on the optimization protocols common to all four systems, closely reproduces the balance MAE for each approach, which indicates that the performances are stable across the shared protocol. Signed-error plots clarify where a possible bias comes from. Indeed, **SIII** shows a positive signed-

error, about 1.0-1.3 kcal/mol for all families of double hybrid functionals, while **SIV** tends to show negative signed-errors. For example, PBE0DH tend to underpredict **SIV** of 1.4 kcal/mol and slightly overpredict **SI** and **SII**, which explained its higher balanced MAE despite acceptable per-system values in other cases. On the other hand, the stereoassignment is preserved across all entries.

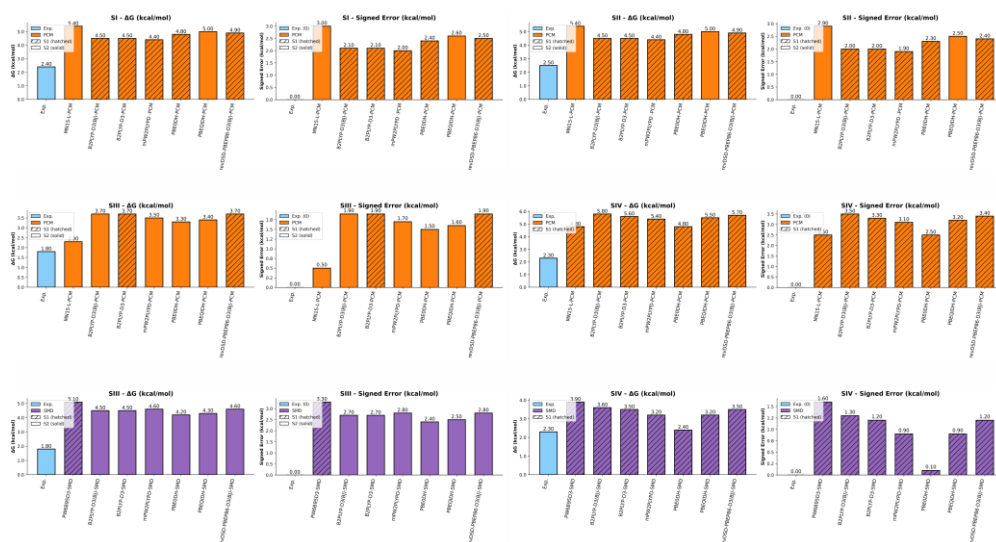


Figure 2.26. Bar plots for all systems reporting experimental values (in light blue) and DFT values for $\Delta G_{\text{stereo}}^{\text{calc}}$ (kcal/mol) and signer-error computed with double hybrid functionals and its pure/hybrid reference, for worst protocol detected for each system. Orange bars indicate PCM and violets bars indicate SMD model for solvation.

A final test has been performed on the worst protocol for each system. MN15-L for **SI** to **SIV** and PW6B95D3 for **SIII** and **SIV** have been found as those functionals reporting the largest deviations in the earlier scan. Therefore, double hybrid functionals single point calculation on those geometries were performed to probe whether the added correlation could fix an unfavourable starting point. In all cases, MN15-L and PW6B95D3 overestimate the stereoselectivity. MN15-L predictions for all systems exceed 2.5 kcal/mol and PW6B95D3 exceeds of more than 1.5 kcal/mol. Replacing these functionals with double hybrids lead to a reduction of the error by

about half to one kcal/mol but do not convert the protocol into a chemically accurate one, remaining a residual bias. This test shows that double hybrid functionals do not recover a protocol that is weak at hybrid level and that is also coupled to an unfavourable solvent choice. This leads to an accurate and critical choice of the base approach and the benefits of second order correlation are best obtained once the baselines are accurate enough.

2.4 On going studies on high-accuracy methodologies for stereoselectivity prediction

The route for obtaining results with high accuracy is a struggling process often limited by the size of the systems employed in the analysis. In this context, post-HF methodologies are indicated as computational techniques with the aim to include electron correlations, which is generally avoided in standard HF calculations, and reaching the limit of the full configuration interaction/complete basis set (FCI/CBS). In the *scenario*, coupled cluster (CC) methodologies have showed interesting results, with particular attention to CC double and perturbative triple excitation treatment (CCSD(T)).⁸⁹ Indeed, CCSD(T)⁹⁰⁻⁹² is affirmed as the “gold standard” in computational chemistry for those systems described by a single-reference wavefunction. The main concern to this type of methodology is related to the scaling of solution of CCSD equation, which scales as N^6 , with N is system size, and it increases to N^7 for perturbative triple corrections.⁹³ To overcome this limitation, which makes difficult to employ these methodologies for bigger systems, many approximations have been developed. In this context, the domain-based local pair natural coupled-cluster theory (DLPNO-CCSD(T)) has been introduction to speed up coupled-cluster calculations.⁹⁴⁻⁹⁸ The DLPNO approximation compresses electron correlation by working in pair specific natural orbital space, which is built from localized occupied orbitals. Each of occupied orbitals defines a local atomic orbital (AO) domain and the union of two single of them leads to a pair domain. Local MP2 amplitudes generate a pair density whose eigenvectors are the pair natural orbitals and those with small occupations are discarded. Electron pairs are classified by estimated

importance, for which those with significant contributions are treated at CCSD level within truncated PNO spaces while weak pairs enter the correlation energy at MP2 level or are neglected. Triples corrections are added through a noniterative correction (DLPNO-CCSD(T)) or through an iterative algorithm (DLPNO-CCSD(T1)). Many examples of applications of such methods can be found in literature, employed on proteins⁹⁹, large supramolecular complexes^{100,101}, enthalpy of formation¹⁰² and dissociation¹⁰³ and so on.

In this context, benchmark regarding stereoselective polymerization is still missing. During the sixth month stay at King Abdullah University of Science and Technology (KAUST) with Prof. Luigi Cavallo, a first attempt for the prediction of stereoselectivity using DLPNO-CCSD(T) and DLPNO-CCSD(T1) is carrying out. The starting point for the analysis takes place on B3LYP optimized geometry, not including dispersion correction as discussed above and preliminary results are showed for **SI**. Single point energies were computed with DLPNO-CCSD(T) and DLPNO-CCSD(T1) model as implemented in ORCA.^{104,105} A closed shell HF reference was used for cationic systems (charge one and single multiplicity). VeryTightSCF criteria was employed for SCF convergence. H, C and Si atoms were described with all-electron correlation consistent basis sets of the cc-pVNZ family (N = 2, D, and 3, T).^{106–108} Zr atom was described by a 28-electron small-core ECP¹⁰⁹ through cc-pVNZ-PP basis set by Peterson et al.¹¹⁰ Resolution of identity was used throughout with correlation auxiliary set for all the atoms.^{111,112} For local correlation TightPNO preset was used but explicitly declaring T_{CutPNO} as 1×10^{-7} and 1×10^{-6} in separate calculations and T_{CutMKN} as 1×10^{-4} .

Preliminary results are reported below. The employment of two adjacent cc-pVNZ level basis set was necessary to avoid the effect from the incompleteness of the basis set, using extrapolation scheme proposed by Helgaker *et al.*^{113,114}, for which E_{CBS} is expressed as following:

$$E_{CBS} = \frac{E(n_1)n_1^3 - E(n_2)n_2^3}{n_1^3 - n_2^3}$$

The results obtained through this approach are reported in **Tables 2** and **3**.

In **Table 2.4**, the results for the PNO extrapolation on CBS extrapolated energies are reported. PNO extrapolation was conducted using the following scheme¹¹⁵:

$$E = E^X + F(E^Y - E^X)$$

E^X and E^Y are energy obtained with different T_{CutPNO} threshold. F values recommended for 6/7 extrapolation is 1.5.

Table 2.2. $\Delta E_{\text{Corr_DZ}}$, $\Delta E_{\text{Corr_TZ}}$ and $\Delta E_{\text{Corr_CBS}}$ from DLPNO-CCSD(T1)/(T) calculations, $\Delta G_{\text{Stereo_CBS}}$ after correlation extrapolation and corrected from B3LYP thermal correction for SI system, for T_{CutPNO} set as 1×10^{-7} . $\Delta E_{\text{Corr_DZ}}$, $\Delta E_{\text{Corr_TZ}}$ and $\Delta E_{\text{Corr_CBS}}$ are reported in Hartree, $\Delta G_{\text{Stereo_CBS}}$ is reported in kcal/mol.

	DLPNO-CCSD(T1) PNO 1×10^{-7}				DLPNO-CCSD(T) PNO 1×10^{-7}			
	$\Delta E_{\text{Corr_DZ}}$	$\Delta E_{\text{Corr_TZ}}$	$\Delta E_{\text{Corr_CBS}}$	$\Delta G_{\text{Stereo_CBS}}$	$\Delta E_{\text{Corr_DZ}}$	$\Delta E_{\text{Corr_TZ}}$	$\Delta E_{\text{Corr_CBS}}$	$\Delta G_{\text{Stereo_CBS}}$
Right Insertion	-4.581	-5.439	-5.801	0.0	-4.568	-5.424	-5.785	0.0
S1	-4.581	-5.440	-5.801	5.274	-4.567	-5.424	-5.785	5.320
S2	-4.582	-5.440	-5.802	3.901	-4.568	-5.425	-5.786	3.932

Table 2.3. $\Delta E_{\text{Corr_DZ}}$, $\Delta E_{\text{Corr_TZ}}$ and $\Delta E_{\text{Corr_CBS}}$ from DLPNO-CCSD(T1)/(T) calculations, $\Delta G_{\text{Stereo_CBS}}$ after correlation extrapolation and corrected from B3LYP thermal correction for SI system, for T_{CutPNO} set as 1×10^{-6} . $\Delta E_{\text{Corr_DZ}}$, $\Delta E_{\text{Corr_TZ}}$ and $\Delta E_{\text{Corr_CBS}}$ are reported in Hartree, $\Delta G_{\text{Stereo_CBS}}$ is reported in kcal/mol.

	DLPNO-CCSD(T1) PNO 1×10^{-6}				DLPNO-CCSD(T) PNO 1×10^{-6}			
	$\Delta E_{\text{Corr_DZ}}$	$\Delta E_{\text{Corr_TZ}}$	$\Delta E_{\text{Corr_CBS}}$	$\Delta G_{\text{Stereo_CBS}}$	$\Delta E_{\text{Corr_DZ}}$	$\Delta E_{\text{Corr_TZ}}$	$\Delta E_{\text{Corr_CBS}}$	$\Delta G_{\text{Stereo_CBS}}$
Right Insertion	-4.570	-5.431	-5.793	0.0	-4.558	-5.416	-5.778	0.0
S1	-4.570	-5.431	-5.793	5.308	-4.558	-5.417	-5.778	5.356

S2	-4.571	-5.432	-5.794	3.938	-4.558	-5.417	-5.779	3.969
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Table 2.4. $\Delta E_{\text{Corr_DZ}}$, $\Delta E_{\text{Corr_TZ}}$ and $\Delta E_{\text{Corr_CBS}}$ from DLPNO-CCSD(T1)/(T) calculations, $\Delta G_{\text{Stereo_CBS}}$ after PNO extrapolation on CBS extrapolated correlation energies and corrected from B3LYP thermal correction for SI system, for TCutPNO set as 1×10^{-7} . $\Delta E_{\text{Corr_DZ}}$, $\Delta E_{\text{Corr_TZ}}$ and $\Delta E_{\text{Corr_CBS}}$ are reported in Hartree, $\Delta G_{\text{Stereo_CBS}}$ is reported in kcal/mol.

	DLPNO-CCSD(T1) PNO 1×10^{-6} 1×10^{-7} extrapolation				DLPNO-CCSD(T) PNO 1×10^{-6} 1×10^{-7} extrapolation			
	$\Delta E_{\text{Corr_DZ}}$	$\Delta E_{\text{Corr_TZ}}$	$\Delta E_{\text{Corr_CPS}}$	$\Delta G_{\text{Stereo_CPS}}$	$\Delta E_{\text{Corr_DZ}}$	$\Delta E_{\text{Corr_TZ}}$	$\Delta E_{\text{Corr_CPS}}$	$\Delta G_{\text{Stereo_CPS}}$
Right Insertion	-4.586	-5.444	-5.805	0.0	-4.572	-5.451	-5.821	0.0
S1	-4.586	-5.444	-5.805	5.258	-4.572	-5.451	-5.821	5.204
S2	-4.587	-5.445	-5.806	3.883	-4.573	-5.452	-5.822	3.846

The DLPNO calculations identify S2 as the preferred stereoerror for **SI**. The ΔG values derived at cc-pV(DZ/TZ) level lie about 1.5 kcal/mol per mole above experiment. The gap persists across DLPNO-CCSD(T) and DLPNO-CCSD(T1) and across the two test PNO threshold. Indeed, the difference between T and T1 and 1×10^{-6} and 1×10^{-7} as T_{CutPNO} setting is in the order a few hundredths kcal/mol.

Many elements of the present protocol plausibly account for the overestimation of the experimental stereoselectivity. First, DLPNO single points are evaluated on B3LYP optimized geometry, including no dispersion correction. It has been already stated for this methodology of optimization, through DFT single point calculations, which tends to overestimate the experimental stereoselectivity. A second point could be the extrapolation space, which limited to cc-pVDZ and cc-pVTZ, which can reduce the basis set error but without removing it, in particular for TM. Increasing the quality of the bases sets to cc-pVTZ and cc-pVTZ or the employment of augmented basis would improve the accuracy of the results. Additionally, a more accurate evaluation of the thermal corrections and the entropic terms, by using quasi-harmonic approximation, as proposed by Cramer and Truhlar¹¹⁶ or Grimme¹¹⁷.

Based on these assumptions, the study will be continued by performing DLPNO-CCSD(T/T1) single point calculations on different DFT optimized geometries, taking as a reference the one obtained above with the best accordance with the experimental results. Increasing the quality of the CBS extrapolation Scheme is another step to consider, by improving to augmented correlation consistent sets on light atoms and/or pseudopotential on metal atom.

The analysis will be also extended to the other systems (**SII**, **SIII** and **SIV**), metallocene and post-metallocene.

2.5 Conclusion

A wide matrix of density functionals, dispersion treatments and continuum models was tested for the prediction of stereoselectivity in polymerization promoted by four representative transition-metal catalysts. Transition states were optimized either without dispersion or with dispersion included, and the resulting geometries were refined by single-point calculations with D3 or D3(BJ) and with PCM, CPCM or SMD. The comparison used experimental free energies obtained from ^{13}C NMR. In the analysis, the different sources of stereoerror, revealed through DFT, were considered for a better comparison.

This analysis pointed out the importance of an accurate choice of methodology in order to reach the highest accuracy. The study highlighted the system-sensitivity to the chosen approach. Indeed, no single recipe is uniformly optimal across the systems and the main lever is determined by the solvent model in the single point calculations, followed by when and how dispersion is used. Geometry optimization level matters, playing a secondary role compared to the solvation model. The main points of the analysis are summarized below:

- Adding D3 or D3(BJ) in the energy refinement steps systematically improves agreement with experiment in all systems. Including dispersion in the optimization helps but not in all cases, as **SIII** which results the less sensitive. In terms of portability, single point with

dispersion on geometries optimized without dispersion remain the safest compromise.

- For **SI** and **SII**, SMD is the most reliable model, reducing overestimation and tightening errors. For **SIII** the preference inverts, leading CPCM and PCM reproducing better the experimental data. **SIV** shows the highest sensitivity to solvent model. Indeed, SMD often underestimates and PCM or CPCM tend to overestimate on the same geometry protocols. CPCM gives better estimation when coupled to dispersion-optimized geometries.
- Screening the common protocol with a within ± 0.5 kcal/mol identifies a limited set of robust level of theory and, hence, method-solvent combinations.

For the two *ansa*-metallocene systems **SI** and **SII**, SMD is the preferred model solvent at single point level, and dispersion correction in geometry optimization are not required. In this case, PBE-D3-SMD and B3PW91-D3-SMD provide the most accurate predictions.

When **SIII** is also considered together with **SI** and **SII**, the overlap between methods becomes narrower: SMD remains the best solvent model for the single point calculations, and PBE-D3 emerges as the best approach.

For the two post-metallocene systems, **SIII** and **SIV**, are compared, CPCM and PCM combined with TPSS and TPSSh using D3 or D3(BJ) give the best agreement with the experiment.

Across all four systems, only PBE with D3 or D3(BJ) in combination with SMD satisfies the ± 0.5 kcal/mol criterion for every case.

- On the common approaches, DH functionals deliver modest gains in accuracy and consistency. Error spreads are usually tightened in most cases keep the preferred pathway unchanged. The results remain

system dependent. The analysis on worst protocols points out the importance of an accurate selection of the parent approach to gain benefits of the MP2 correction.

- A pilot application on **SI** with DLPNO-CCSD(T)/(T1) single point on B3LYP geometries without dispersion identifies S2 as the favoured stereoerror. The results obtained are about 1.5 kcal/mol above experiment. Such results reflect the general trend found on B3LYP-optimized geometry and could be enhanced by the limited extrapolation scheme. The refinement plan includes employing the same approach used for DH functionals, larger basis set at least for light atoms.

Taken together, the present benchmark offers a solid starting point for broader work. As matter of facts, higher accuracy through double hybrid functionals could be reach also through geometries.^{118,119} Local correlation wave function methods can further refine the energetics.^{120–122} For more flexible targets, including complex monomers, the workflow could start from fast semi empirical exploration of the soft conformational landscape, guided by knowledge-based and evolutionary algorithms.¹²³ These open new routes for systematic study of more complex processes in homogenous catalysis.¹²⁴

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Chapter 3 -

From achiral aluminium to iron catalysts for ring opening polymerization of lactide and challenging monomers to achieve mechanistic insights and design rules

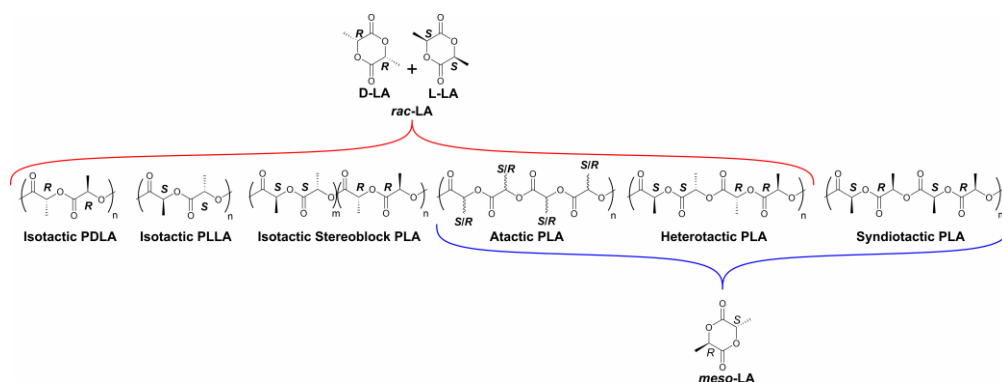
Abstract

An integrated study carried out on two different class of catalysts for sustainable ring opening polymerization. Achiral aluminium catalysts that control tacticity in rac-lactide were analysed together with pyridylamido Fe(II) systems polymerizing challenging monomers like δ -alkyl δ -lactones and ϵ -lactones. For aluminium catalyst analysis, DFT is combined with Buried Volume ($\%V_{\text{Bur}}$) analysis and ASM-NEDA to connect monomer configuration to ligand wrapping mode and analysing steric and electronic factors occurring in. Chain end control and enantiomorphic site control merge in a unique picture to explain the microstructure of obtained PLA. The iron analysis couples experimental evidence and computations. Indeed, polymerization experiments show high activity, narrow dispersities and induction periods that correlate with a light blue precipitate formation. DFT enables exploring mechanisms, proposing mononuclear, dimeric assisted and concerted pathways. The calculated barriers match the experimental rates. The combined picture provides practical design insights that links wrapping dynamics, nuclearity and monomer-chain interactions to selectivity, rate and control within an approach which is compatible with the obtainment of new materials potentially able to replace classic α -olefin based polymers.

3.1 Introduction

Plastic sustainability has become a central priority due to the environmental burden of mismanaged waste and the spread of microplastic in ecosystems and in humans.¹⁻⁵ The transition to a circular plastic economy promotes material from renewable resources with improved end of life options, including degradability, reuse

and chemical recycling to monomer (CRM).^{3,6} Aliphatic polyesters stand out in this landscape.⁷ Poly(lactic acid) (PLA) is already significant in the market thanks to biocompatibility and biodegradability, although its slow degradation in ambient environments and intrinsic brittleness motivate research on new microstructures and block architectures that enhance performance. The two stereogenic centres that characterize the LA monomer yield to the obtainment of three different diastereoisomers, *i.e.* L-LA (*S,S*), D-LA (*R,R*) and *meso*-LA (*R,S*). The mixture of the two homopolymers, PLLA from L-LA and PDLA from D-LA, brings to a stereocomplexation due to the co-crystallization of the two homopolymers, that results in a better material in terms of thermal and mechanical properties than those of the PLLA and PDLA alone.⁸ Based on these observations, the interest in polymerizing the racemic mixture, *rac*-LA (equimolar mixture of L-LA and D-LA), increased. Indeed, its employment can ensure the formation of isotactic-diblock and isotactic-multiblock PLA, exhibiting interesting performances.^{9,10} All the possible microstructure obtained from L-LA (*S,S*), D-LA (*R,R*), *rac*-LA and *meso*-LA (*R,S*) are reported in **Scheme 3.1**.



Scheme 3.1. Possible PLA microstructures affordable from L-LA (*S,S*), D-LA (*R,R*), *rac*-LA and *meso*-LA (*R,S*).

The multiple microstructures that can be achieved by LA polymerization prompted to investigate correlations between microstructure and material properties, to obtain material properties comparable to those of traditional plastics.¹¹ The variety of these

microstructures are obtainable only through stereoselective polymerization, granted by the employment of transition metal (TM) catalysts *via* ring opening polymerization (ROP) and, starting from the pioneering work of Spassky,¹² extensive efforts have been done to develop better catalysts for tailored microstructure and for higher stereoselectivity.^{13–21} Recently, interesting developments regarding the employment of organocatalysts for stereoselective ROP emerged, broadening the choice of catalysts, meeting also the requirement of green chemistry.^{22–32} Stereoselectivity in polymerization has two classical limiting pictures. In enantiomorphic site control (ESC) the chirality of the catalyst selects the enantioface of the incoming monomer, in chain-end control (CEC), the configuration of the last inserted unit determines the next enchainment. Even with achiral precursors, octahedral arrangement achieved after lactide coordinate could show a chiral environment at the active site that guide selectivity. Early achiral Al salen systems delivered modest control, with the obtainment of isotactic stereoblock [PDLA-PLLA]_n,³³ later improved by achiral Al Schiff bases³⁴ and by Al salen complexes obtained through the employment of machine learning (ML) algorithms,³⁵ which raised P_m (probability of *meso* linkage) and melting temperature of stereoblocks. Notwithstanding the increasing interest in ROP of *rac*-LA, rationalization concerning stereoselectivity are limited and are mainly focused on ESC^{36–40} and rare on CEC^{41,42} governing *rac*-LA ROP. Indeed, many studies have been conducted on stereocontrol in *rac*-LA using chiral catalysts, revealing complications arising from possible interconversion between different ligand wrapping modes.^{43–45} The knowledge acquired on Al chiral catalysts prompted to use DFT, combined with buried volume analysis^{46,47} and ASM-NEDA^{48–50}, to analyse the mechanism in stereoselective ROP of *rac*-LA. This analysis will be held in **Section 3.3**.

At the same time, the field is moving towards new monomers that favour CRM. For lactones, the equilibrium between monomer and polymers depends on ring strain, hence five and six membered rings are less prone to polymerization. The polymerization of γ -butyrolactone demonstrated that temperature management and

phase separation can enable controlled ROP with efficient recovery of monomer,⁵¹ and that fused ring monomers help by increasing effective strain.⁵² In the *scenario* of poorly polymerizable monomers, δ -alkyl δ -lactones have attracted attention due to their availability,⁵³ notwithstanding their side chain reducing ring strain and complicating kinetics.⁵⁴ Metal catalysed ROP of these substrates is scarce and often limited in molecular weight or rate, although urea cocatalysts with alkali metal alkoxides have improved control.^{55–59}

In this context, pyridylamido Fe(II) complexes offer a complementary and sustainable platform. Three coordinated precursors have shown high activity and living character in the ROP of L-LA and ϵ -caprolactone (ϵ CL).⁶⁰ In **Section 3.4**, the catalyst will be analysed for ROP of δ - and ϵ -lactones, showing high activity and control in the polymerization, which are key features to obtain polymers with tuneable mechanical properties. Exploring different scenarios through DFT approach, mechanism will be elucidated, considering different monomers and potential formation of distinct species that could be involved in the polymerization.

Behind these two research lines there is a common message, regarding the chance to provide guidance for catalysts that are both selective and practical, enabling microstructure control, high productivity and access to materials that can be chemically recycling to monomers.

3.2 Computational Details

All DFT calculations have been performed with Gaussian16⁶¹ software, using the B3LYP hybrid GGA functional^{62,63} in conjunction with the polarized split-valence basis set (SVP)⁶⁴ of Ahlrichs and co-workers for H, C, N, O and Si. For Al atom the triple- ζ basis set 6-311G(d,p)^{65,66} has been used, while LANL2DZ pseudopotentials and basis sets⁶⁷ were employed for Fe atom in the optimization steps. The choice of B3LYP is due to its wide application in the field of polymerization catalysis, as reported in the literature within the Chapter, for its good compromise between accuracy and time. Stationary points were characterized using vibrational analyses,

and these analyses were also used to calculate zero-point energies and thermal (enthalpy and entropy) corrections (298.15 K, 1 bar). Improved electronic energies were obtained from single-point calculations using the triple- ζ basis set 6-311G(d,p)^{65,66} for Al, H, C, N and O. For Fe species calculations, the TZVP basis set for H, C, N, O, Si⁶⁸ together with the SDD basis and pseudopotentials for Fe⁶⁹. Dispersion corrections^{70–72} by Grimme (using EmpiricalDispersion=D3BJ keyword in Gaussian packages) were also added. Bulk solvent effects to calculate ΔG were considered by using:

- 1) the conductor version of the polarizable continuum model (CPCM)^{73,74} and toluene as solvent for Al species;
- 2) the polarizable continuum model (PCM)⁷⁵ and dichloromethane as solvent for Fe species.

The ASM-EDA model proposed by Bickelhaupt has been used to investigate stereoselectivity in Al catalyzed-ROP.⁴⁸ It allows the decomposition of the reaction energy profile into two contributions along the reaction coordinate:

$$\Delta E_{\text{Tot}} = \Delta E_{\text{Strain}} + \Delta E_{\text{Int}}$$

ΔE_{Strain} is the energy related to the reactant deformation needed to reach the geometries required to react and ΔE_{Int} is the energy related to the strength of their mutual interactions. The former term is the sum of the strain related to each reactant: $\Delta E_{\text{Strain}} = \Delta E_{\text{Strain,frag1}} + \Delta E_{\text{Strain,frag2}}$.

In this work, the fragment 1 corresponds to the cationic active species plus the growing polymer chain ($\Delta E_{\text{Strain(Cat)}}$), whereas fragment 2 corresponds to the monomer ($\Delta E_{\text{Strain(Mon)}}$) for the insertion reactions, with each strain energy being calculated with respect to the equilibrium geometry of the pertinent fragments.

The ΔE_{Int} term has been decomposed using the NEDA (Natural Energy Decomposition Analysis),⁴⁹ which already includes the counterpoise correction for the Basis Set Superposition Error as proposed by Boys and Bernardi.⁷⁶ For this approach, no solvent correction could not be considered, hence the values reported will be

referred to the electronic energy correct only for the dispersion term. At each point along the intrinsic reaction coordinate (IRC) $\Delta E_{\text{Strain(Cat)}}$ and $\Delta E_{\text{Strain(C3H6)}}$ have been obtained from the ASM by subtracting the energy of the minimum equilibrium geometry from the energy of the respective fragment. For the same points, the NEDA has been performed using the NBO version 7 software linked to Gaussian16 (in conjunction with the parameters used for energy refinement).⁵⁰ This permits to obtain ΔE_{Int} and all its components, namely electrostatic, polarization, charge transfer, exchange and deformation components: $\Delta E_{\text{Int}} = \text{ES} + \text{POL} + \text{CT} + \text{XC} + \text{DEF}$ where ES = classical electrostatic interaction; POL = polarization interaction; CT = charge transfer based on interaction between filled and empty orbitals; XC = exchange-correlation interaction; DEF = the energy cost to distort a fragment wavefunctions in the field of all other fragments of the complex. Dispersion contributions have been also estimated by the D3(BJ) model of Grimme.

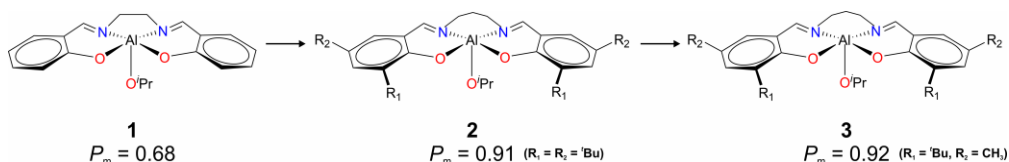
Buried volume analysis ($\%V_{\text{Bur}}$) has been carried out to quantify the steric impact of the ligand environment around the metal centre.⁴⁷ This approach evaluates the percentage of buried volume, defined as the fraction of a spherical volume centred on the metal that is occupied by the ligand atoms within a given radius. The analysis provides a quantitative measure of the steric hindrance exerted by ligands in the coordination sphere. It has been performed using the SambVca 2.1 tool⁴⁶, on DFT optimized geometry, with the aim to rationalize the results obtained with different catalytic systems and correlated with DFT and ASM-NEDA.

Non-covalent interactions (NCIs) analysis has been conducted through NCIPLOT⁷⁷ software and visualized by VMD⁷⁸.

3.3 Stereoselectivity analysis for achiral Al-Salen complexes catalysing ROP of *rac*-LA

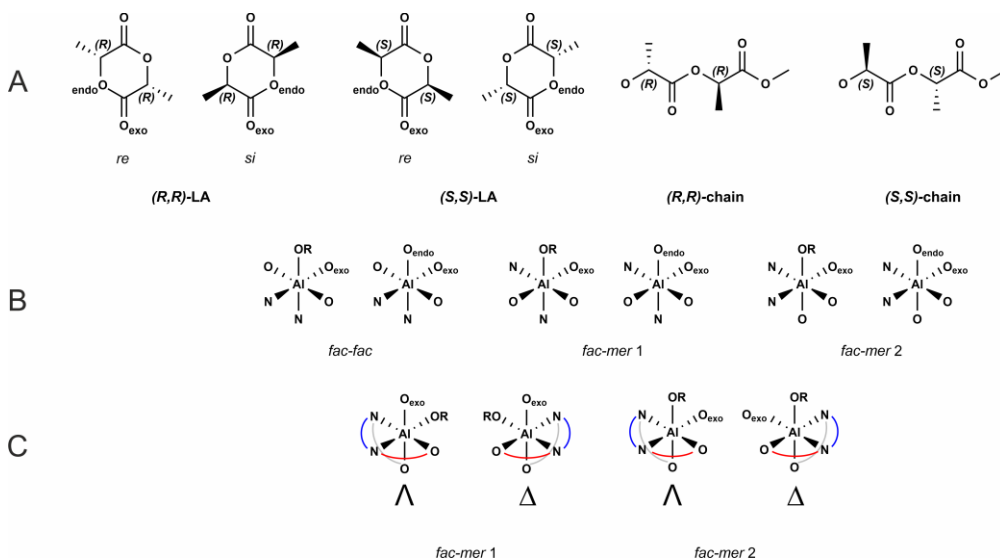
As mentioned above in the **Introduction**, the evolution of achiral catalysts lead to increased stereocontrol and obtainment of isotactic stereoblock PLA with improved thermal properties.^{33–35} **Scheme 3.2** shows the catalysts involved in this evolutive process and, intrigued by the remarkable stereocontrol achieved by system **3**, obtained

through the employment of ML technique, it has been chosen to pursue DFT analysis gain information regarding CEC and its chemical features.³⁵



Scheme 3.2. Achiral Al systems for stereoselective *rac*-LA ROP by CEC.

Computational analysis starts taking in consideration, as mentioned, all the elements of chirality for ROP of *rac*-LA, which are reported in **Scheme 3.3**. Indeed, as anticipated, *rac*-LA is an equimolar mixture of two diastereoisomers, *R,R*-LA and *S,S*-LA, each with their own enantioface. Once polymerized and the growing chain is formed, it has its own chirality, dictated by the stereogenic centre. The chirality of the metal centre is to be considered, in terms of different wrapping modes, *i.e.* *fac-fac* (*ff*), *fac-mer* 1 (*fm1*) and *fac-mer* 2 (*fm2*). Additionally, *ff* and *fm* isomerism could present Λ and Δ enantiomers.



Scheme 3.3. Elements of chirality. Monomer chirality and enantiofaces, chain chirality (A); octahedral configurations for Al complexes (B) and Λ and Δ configurations for *fac-mer*1 and *fac-mer*2 wrapping modes (C).

Chiral Al-salan systems exhibit no energetic preference for *ff* or *fm* wrapping mode,⁴³ conversely for system **3**, a 5.5 kcal/mol preference for *fm* was found, by using bidentate acetylacetonate (*acac*⁻) to saturate the coordination, the structures are reported in **Figure 3.1**. Indeed, inspecting the DFT optimized geometries for *acac*⁻ coordination at system **3** in *ff* and *fm* mode, structural differences emerged: the three-carbon enforces a near linear O-Al-O angle compressing the active-site pocket, disfavouring the *ff* wrapping mode and omitting it from the mechanistic analysis.

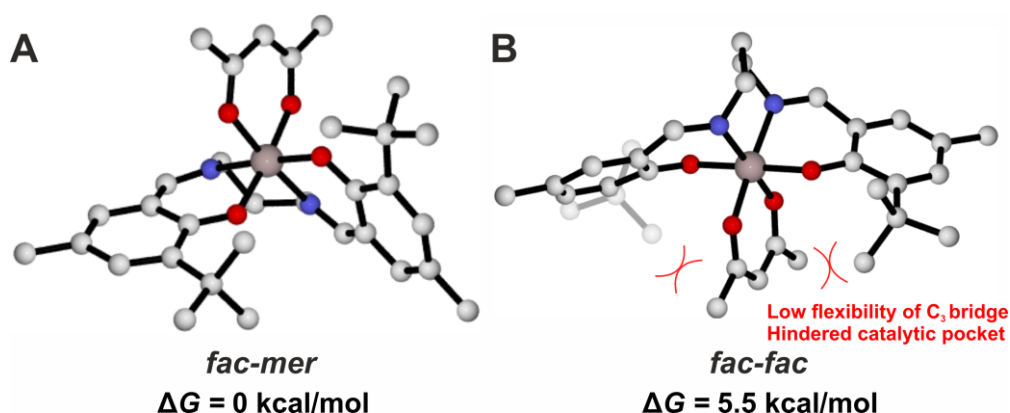


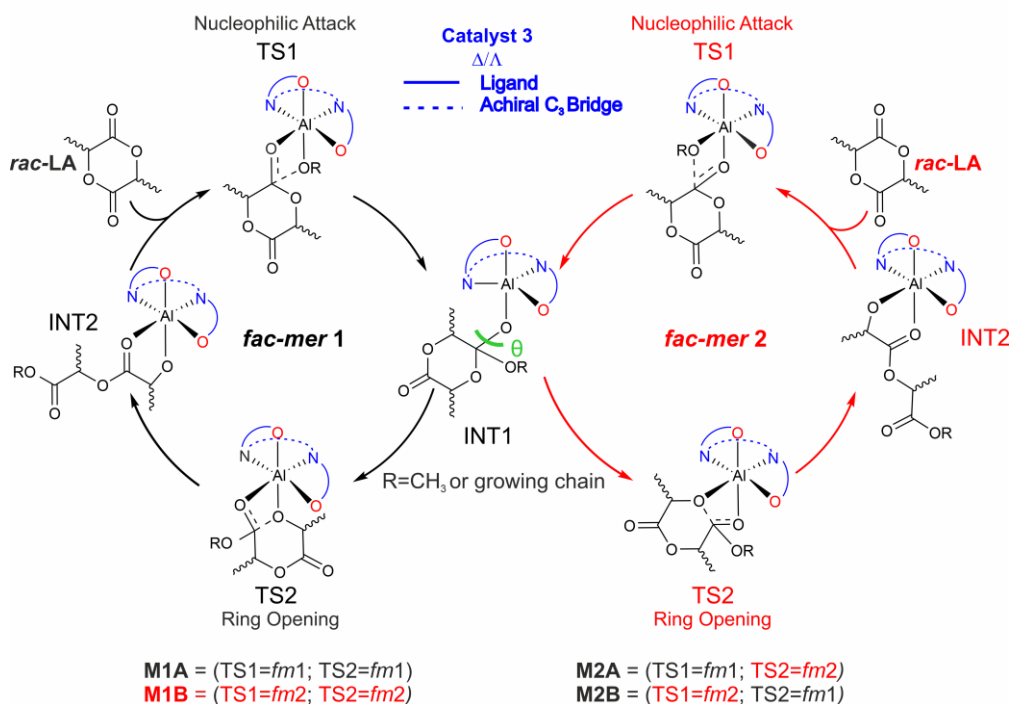
Figure 3.1. DFT optimized geometries for the coordination of *acac*⁻ to system **3**, considering *fm* (A) and *ff* (B) wrapping modes.

Replacement of the symmetric bidentate *acac*⁻ ligand with the LA monomer and growing chain splits the *fm* isomer into two configurations, *fm1* and *fm2*. These arrangements differ in the relative position of the methoxide or growing chain and of the monomer at the metal centre, as shown in **Scheme 3.3**. This emerging asymmetry requires careful treatment in ROP studies. A coordination-insertion mechanism built around two catalytic cycles is therefore adopted, as presented in **Scheme 3.4**. The first elementary step, denoted as TS1, is defined as the nucleophilic attack of the methoxide group to the carbonyl group of the monomer leading to the first intermediate, INT1. The second transition state, TS2, involves the opening of the cyclic monomer ring and affords the second intermediate INT2. The catalytic cycle then repeats, with the

growing chain as nucleophile.

The two non-equivalent coordination sites generated by the monomer and the growing chain leads to the onset of two mechanistic pathway. Mechanism M1A and B are intended to proceed with the same wrapping mode, either *fm1* or *fm2* for both TSs. In mechanisms M2A and B, TS1 and TS2 proceed in different wrapping modes, with TS1 in *fm1* followed by TS2 in *fm2*, or TS1 in *fm2* followed by TS2 in *fm1*, respectively M2A and B.

Catalytic Cycles



Scheme 3.4. Catalytic cycles for coordination-insertion mechanisms for ROP of *rac*-LA, catalysed by achiral-Al system considering two possible wrapping modes.

Based on these premises, LA first insertion into the Al-OCH₃ on has been modelled, taking into account all the elements of symmetry and the mechanisms proposed above. To sake of completeness, only catalyst in Δ configuration has been considered since the same results for Λ configuration are obtained by simply inverting the chirality of

the whole system (including monomer and growing chain). The results are reported in **Table 3.1**. The minimum energy paths (MEP) for *R,R*-LA on the right and *S,S*-LA on the left are reported in **Figure 3.2**.

Table 3.1. TS Gibbs energies ΔG in kcal/mol for system 3, in toluene, considering *R,R*-LA and *S,S*-LA and their enantiofaces, for both mechanism M1 and M2 (A and B variants). In bold, low-lying paths.

Mechanism	Variant	<i>R,R</i> <i>re</i>	<i>R,R</i> <i>re</i>	<i>R,R</i> <i>si</i>	<i>R,R</i> <i>si</i>	<i>S,S</i> <i>re</i>	<i>S,S</i> <i>re</i>	<i>S,S</i> <i>si</i>	<i>S,S</i> <i>si</i>
		TS1	TS2	TS1	TS2	TS1	TS2	TS1	TS2
M1	A	8.6	3.5	6.5	6.0	9.4	7.8	7.4	4.3
M1	B	10.8	8.1	7.5	10.0	6.6	16.1	7.5	4.6
M2	A	8.6	8.1	6.5	10.0	9.4	16.1	7.4	4.6
M2	B	10.8	3.5	7.5	6.0	6.6	7.8	7.5	4.3

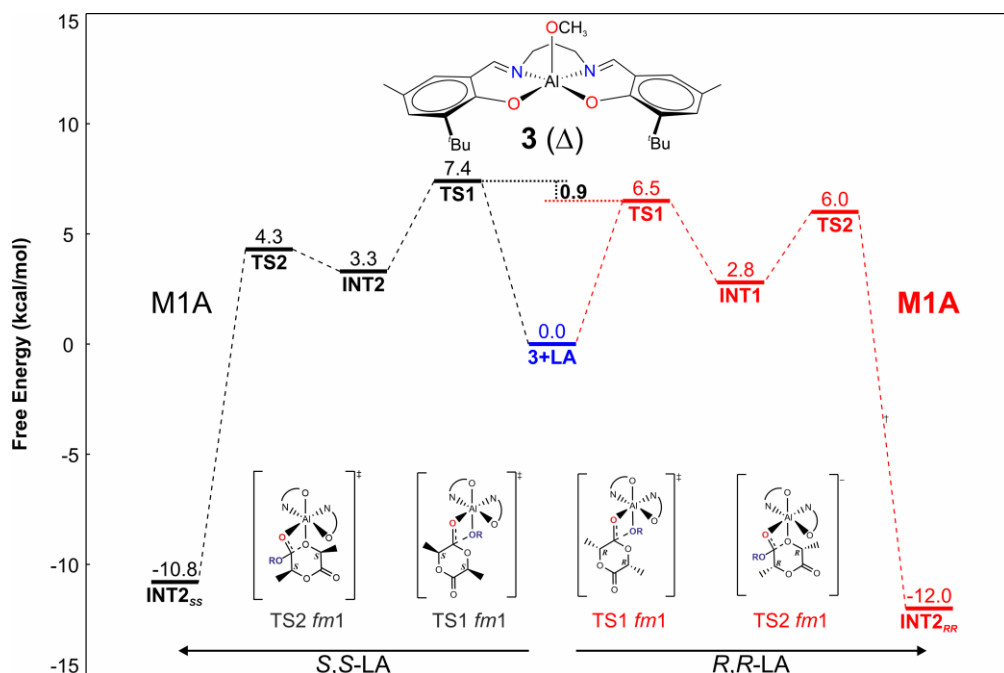


Figure 3.2. MEP of *R,R*-LA and *S,S*-LA insertion into the Al-OCH₃ bond for system 3, Δ configuration. In bold red, low-lying mechanism.

As can be inferred from the data showed, a modest stereoselectivity, of 0.9 kcal/mol for *R,R*-LA insertion on *fm1* wrapping mode under M1A mechanism has been detected. On the other hand, because the model lacks a chiral growing chain, these data cannot be directly compared with the experiment. Hence, the ROP was modelled using chiral growing chain obtained from previous insertions of *R,R*-LA and *S,S*-LA, considering only isotactic enchainment. The results are listed in **Table 3.2** and the MEP are reported in **Figure 3.3**.

Table 3.2. TS Gibbs energies ΔG in kcal/mol for system 3, in toluene, considering *R,R*-LA and *S,S*-LA and their enantiofaces, inserting on *R,R*- and *S,S*-chain for both mechanism M1 and M2 (A and B variants). In bold red and red low-lying paths.

Mechanism	Variant	<i>R,R</i>	<i>R,R</i>	<i>R,R</i>	<i>R,R</i>	<i>S,S</i>	<i>S,S</i>	<i>S,S</i>	<i>S,S</i>
		chain	chain	chain	chain	chain	chain	chain	chain
		<i>R,R</i>	<i>R,R</i>	<i>R,R</i>	<i>R,R</i>	<i>S,S</i>	<i>S,S</i>	<i>S,S</i>	<i>S,S</i>
		mon.	mon.	mon.	mon.	mon.	mon.	mon.	mon.
		<i>re</i>	<i>re</i>	<i>si</i>	<i>si</i>	<i>re</i>	<i>re</i>	<i>si</i>	<i>si</i>
		TS1'	TS2'	TS1'	TS2'	TS1'	TS2'	TS1'	TS2'
M1	A	15.5	11.6	17.0	12.6	17.1	14.0	19.8	23.6
M1	B	18.1	16.6	23.6	17.1	14.0	12.3	12.3	22.5
M2	A	15.5	16.6	17.0	17.1	17.1	12.3	19.8	22.5
M2	B	18.1	11.6	23.6	12.6	14.0	14.0	12.3	23.6

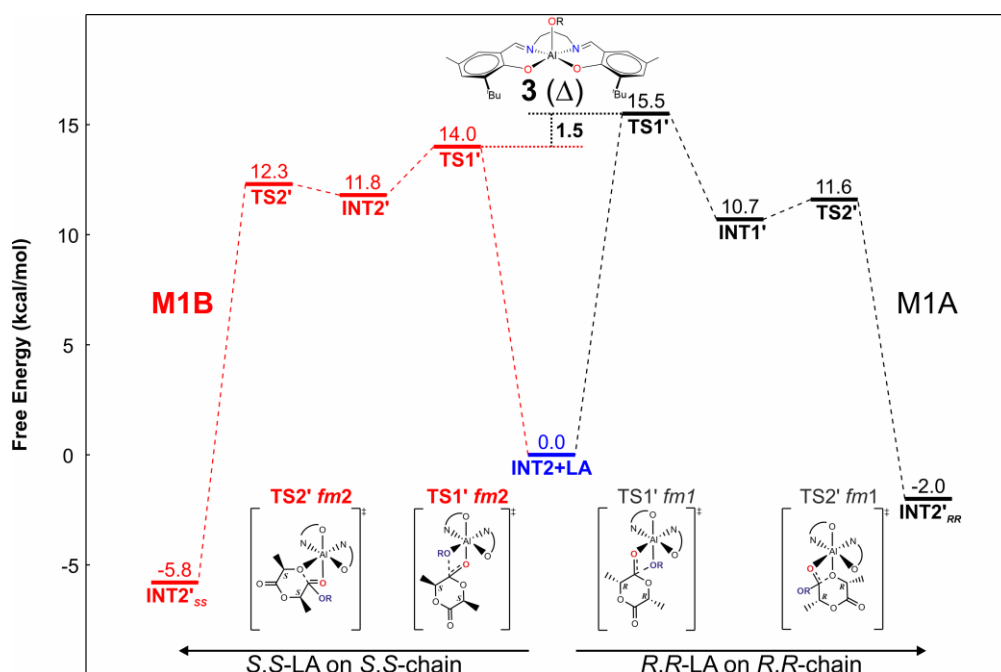


Figure 3.3. MEP of *R,R*-LA and *S,S*-LA propagation on system 3, Δ configuration. In bold red, low-lying mechanism.

Notably, computational analysis and the profiles indicate two different mechanisms for the propagation. Indeed, *S,S*-LA propagation occurs through M1B mechanism, whereas *R,R*-LA propagation takes place *via* M1A, designating a preference for *fm2* and *fm1* wrapping mode, respectively. The rate limiting step (RLS) is TS1' in both cases, obtaining a stereoselectivity of 1.5 kcal/mol, consistent with the experimental trend.³⁵

The origin of the preference for *S,S*-LA propagation appears to involve steric factors at the RLS. The buried volume analysis (% V_{Bur}) on RLS, in **Figure 3.4**, shows that *S,S*-chain at *fm2* occupies less hindered sector of the SE quadrant, along the negative *y* axis, while *R,R*-chain in *fm1* points toward the positive *z* axis into a more crowded sector of the same quadrant where the ^tBu substituents are located.

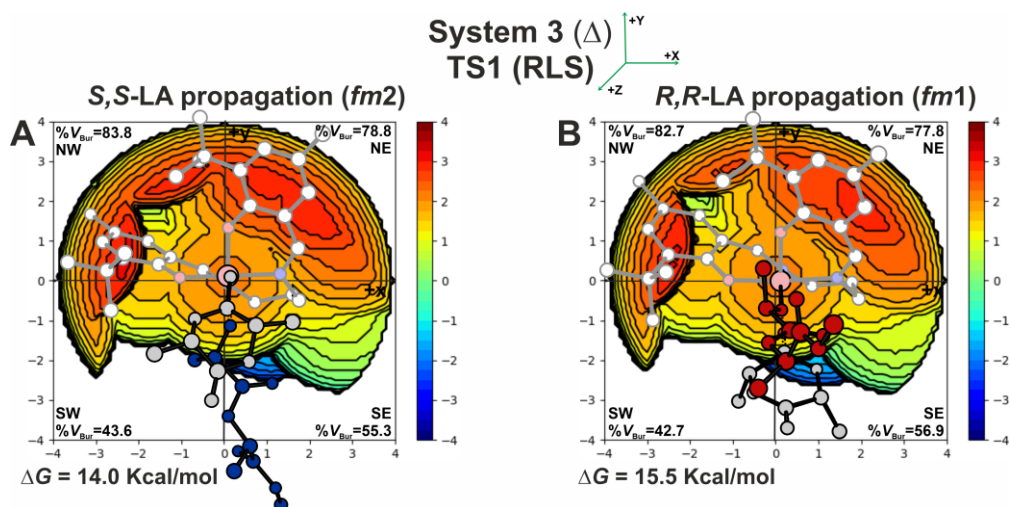


Figure 3.4. $\%V_{\text{Bur}}$ steric maps of RLSs for *S,S*-LA (A) and *R,R*-LA (B) propagation on system 3, Δ configuration.

Optimized DFT geometries for the two RLSs are shown in **Figure 3.5**, in which it emerged that the two monomers exhibit different conformation, with methyl groups in equatorial position for *S,S*-LA and in axial position for *R,R*-LA.

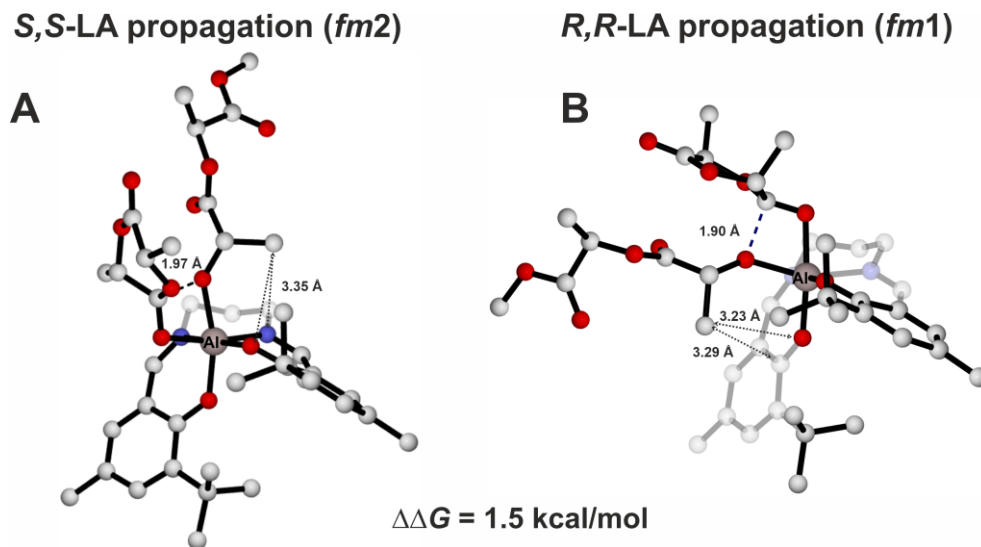


Figure 3.5. DFT optimized geometries for the two RLS of *S,S*-LA (A) and *R,R*-LA (B) propagation on system 3, Δ configuration. H atoms are omitted for clarity and distances are reported in Å.

A more complete picture of the origin of stereoselectivity and of the energetic changes associated with the wrapping modes was obtained with the ASM-NEDA analysis. The results are list in **Table 3.3**. In this framework, the variation of the electronic energy between different assemblies. Reported as $\Delta\Delta E_{\text{Tot}}$, is partitioned into a strain term and interaction term. The former is further decomposed into the deformation of the catalyst fragment including catalyst and growing chain and into the deformation of the incoming monomer.

Table 3.3. ASM-NEDA analysis for isotactic enchainment in ROP of *rac*-LA promoted by system 3. Values in kcal/mol and reference to the corresponding low-lying TSs.

Entry	Assembly mode	Wrapping mode	$\Delta\Delta G$	$\Delta\Delta E_{\text{Tot}}$	$\Delta\Delta E_{\text{Strain}}$	$\Delta\Delta E_{\text{Int}}$	$\Delta\Delta E_{\text{Strain(Cat)}}$	$\Delta\Delta E_{\text{Strain(Mon)}}$
1	(<i>S,S</i>)-LA on <i>S,S</i> -chain	<i>fm2</i>	1.5	1.3	11.8	-10.5	6.8	5.0
	(<i>R,R</i>)-LA on <i>R,R</i> -chain	<i>fm1</i>						
2	(<i>R,R</i>)-LA on <i>R,R</i> -chain	<i>fm1</i>	2.6	4.6	11.1	-6.5	4.5	6.6
	(<i>R,R</i>)-LA on <i>R,R</i> -chain	<i>fm2</i>						
3	(<i>S,S</i>)-LA on <i>S,S</i> -chain	<i>fm2</i>	3.1	1.3	23.6	-22.3	10.7	12.9
	(<i>S,S</i>)-LA on <i>S,S</i> -chain	<i>fm1</i>						

Entry 1 compares the RLS TS of the two isotactic propagations. The positive $\Delta\Delta G$ indicates a preference for the *S,S*-LA insertion on *S,S*-chain in the *fm2* geometry. The

strain analysis clarifies the origin of this preference. The catalyst fragment is less deformed for the *S,S*-chain in *fm2* than for the *R,R*-chain in *fm1*. The monomer deformation follows the same direction, reinforcing the preference. This outcome aligns with the Buried Volume ($\%V_{\text{Bur}}$) steric maps in **Figure 3.4** where the *R,R*-chain in *fm1* points into the crowded SE quadrant near the ^tBu groups while the *S,S*-chain in *fm2* occupies a less hindered sector.

Entries 2 and 3 probe the sensitivity to the wrapping mode within each isotactic series. For *R,R*-LA propagation the *fm1* arrangement is favoured over the *fm2*, *viceversa* for *S,S*-LA propagation. The deformation of the catalyst fragment and the deformation of the monomer contribute with comparable magnitude, indicating a cooperative steric origin involving both the ligand framework and the conformational response of the lactide. Indeed, the monomer strain term is consistent with the DFT optimized geometry showed in **Figure 3.5**, where the methyl groups adopt an equatorial orientation for *S,S*-LA and an axial orientation for *R,R*-LA. The interaction term partially compensates the strain penalty but does not reverse the situation for the analysed cases.

A more complete assessment of the role of the chiral growing chain was obtained by exploring multiple assembly modes that pair each monomer diastereoisomer with each chain end. Indeed, insertion of *S,S*-LA and *R,R*-LA were therefore examined on system **3** bearing *S,S*- and *R,R*-chain. Key energetics are reported in **Table 3.4** and the optimized structures of the RLS TSs are shown in **Figure 3.6**. Complete analysis is reported in **Table 3.2** and **Table 3.5**. The analysis indicates that *S,S*-LA insertion is favoured over *R,R*-LA on *S,S*-chain, which is reversed when the last inserted unit is *R,R*, giving an *R,R*-chain, in line with the CEC and with trend discussed above.

Table 3.4. Gibbs activation energies $\Delta G^\ddagger$ for the RLS and $\Delta\Delta G$ values relative to the lowest minim-energy pathways for *R,R*-LA and *S,S*-LA insertions as a function of the assembly mode. Values in kcal/mol.

Assembly mode	$\Delta G^\ddagger_{\text{RLS}}$ (kcal/mol)	$\Delta\Delta G$ (kcal/mol)
(<i>S,S</i>)-LA on <i>S,S</i> chain	14.0 (TS1)	0.0
(<i>R,R</i>)-LA on <i>S,S</i> chain	15.3 (TS2)	1.3
(<i>R,R</i>)-LA on <i>R,R</i> chain	15.5 (TS1)	1.5
(<i>S,S</i>)-LA on <i>R,R</i> chain	15.9 (TS1)	1.9

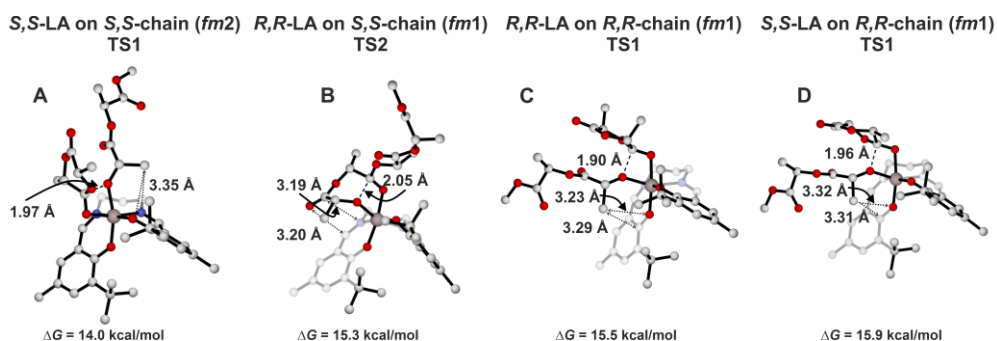


Figure 3.6. DFT optimized geometries for the RLS on *S,S*-chain of *S,S*- and *R,R*-LA (A and B) and on *R,R*-chain of *R,R*- and *S,S*-LA (C and D) on system 3, Δ configuration. H atoms are omitted for clarity and distances are reported in Å.

Table 3.5. TS Gibbs energies ΔG in kcal/mol for system 3, in toluene, considering *R,R*-LA and *S,S*-LA and their enantiofaces, inserting on *S,S*- and *R,R*-chain, respectively, for both mechanism M1 and M2 (A and B variants). In red the low-lying paths.

Mechanism	Variant	<i>R,R</i> chain	<i>R,R</i> chain	<i>R,R</i> chain	<i>R,R</i> chain	<i>S,S</i> chain	<i>S,S</i> chain	<i>S,S</i> chain	<i>S,S</i> chain
		<i>S,S</i> mon.	<i>S,S</i> mon.	<i>S,S</i> mon.	<i>S,S</i> mon.	<i>R,R</i> mon.	<i>R,R</i> mon.	<i>R,R</i> mon.	<i>R,R</i> mon.
		<i>re</i>	<i>re</i>	<i>si</i>	<i>si</i>	<i>re</i>	<i>re</i>	<i>si</i>	<i>si</i>
		TS1'	TS2'	TS1'	TS2'	TS1'	TS2'	TS1'	TS2'
		15.9	11.0	15.4	23.5	16.9	15.3	15.8	11.6

M1	B	18.0	12.1	18.9	24.0	14.7	21.0	17.5	15.5
M2	A	15.9	12.1	15.4	24.0	16.9	21.0	15.8	15.5
M2	B	18.0	11.9	18.9	23.5	14.7	15.3	17.5	11.6

In these profiles, the RLS depends on the assembly mode. Indeed, TS1 is RLS in three cases, whereas *R,R*-LA insertion on *S,S*-chain proceeds with TS2 as RDS. The computed activation energy differences in **Table 3.4** range from 1.3 to 1.9 kcal/mol. At this point, it is useful to revisit the kinetic experiments reported by Nomura on related achiral Al-salen catalyst, where polymerization rate constant for enantiopure *S,S*-LA is higher than that measured for *rac*-LA.³⁴ The activation energies in **Table 3.4** are consistent with this trend and the experimental data in **Figure 3.7**. Within system 3, the Δ configuration shows a clear preference for *S,S*-LA, while Λ configuration prefers *R,R*-LA. Subsequent insertion of *R,R*-LA, producing *R,R*-chain, introduces a mismatch at the active site⁷⁹ and increases the activation energy, as marked by the computed barriers in **Table 3.4**.

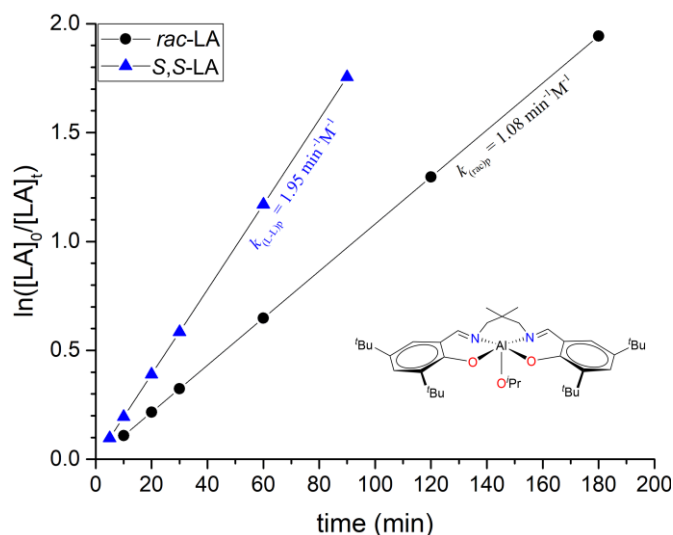
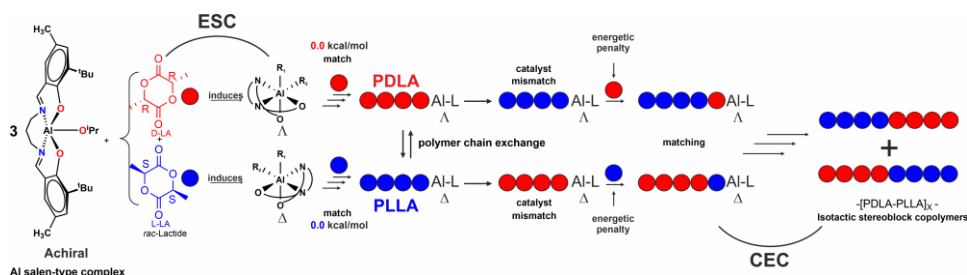


Figure 3.7. Kinetic studies on *rac*-LA (black) and *S,S*-LA (blue) polymerization on complex 8 reported by Nomura³⁴ with the following conditions: toluene as solvent, T = 90°C, $[S,S\text{-LA}]_0 = [rac\text{-LA}]_0 = 1.0 \text{ M}$; $[LA]_0/[Al]_0 = 100$.

These features point to a mechanism that merges ESC, which is expressed through the chiral rearrangement associated with the *fm* wrapping mode, and CEC, expressed through the inversion of preference between *R,R*- and *S,S*-LA as the chain-end switches. This dual control provides a rationale for the formation of isotactic stereoblock microstructures, as depicted in **Scheme 3.5**. Such pictures account for the formation of highly isotactic stereoblock through the polymer exchange mechanism proposed by Coates.⁸⁰ Indeed, the two preferred Δ/Λ configuration could exchange *R,R*- and *S,S*-ending chains after a suitable number of insertions.



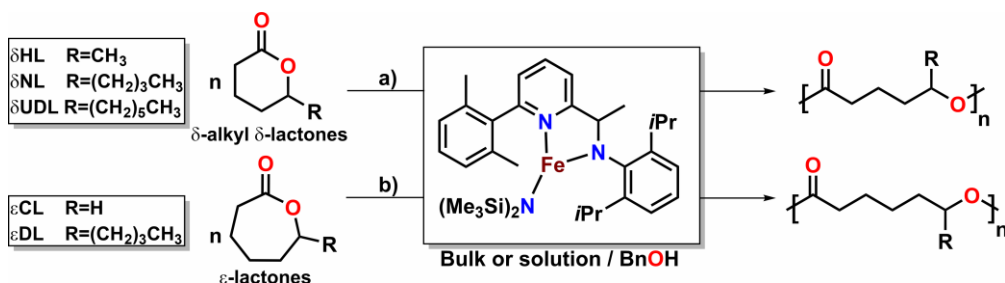
Scheme 3.5. Mechanism proposed for the formation of isotactic stereoblock copolymers of PLA by coupling ESC and CEC.

Such approach, combining DFT, Buried Volume ($\%V_{\text{Bur}}$) analysis and ASM-NEDA, allowed the rationalization of the obtainment of that specific microstructure of PLA by linking monomer configuration to preferred wrapping modes on achiral Al salen systems. Hence, the stereocontrol is delivered through CEC driven by monomer directed wrapping dynamics.

3.4 Iron catalysts for low-strain lactone ROP

Progress toward chemically recyclable polyesters requires for catalysts able to polymerize low-strain lactones while maintaining microstructure control. Iron systems are attractive because they are earth abundant and have already shown high activity and good control in the ROP of L-LA and ϵ CL.⁶⁰ In this Section, the focus shifts to δ -alkyl δ -lactones and to ϵ -lactones where side chain substitution and ring

size make to propagation slower.^{53–59} In **Scheme 3.6**, the heteroleptic Fe(II) pyridylamido catalyst and the set of examined monomers are shown.



Scheme 3.6. ROP of δ -alkyl δ -lactones (a) and ϵ -lactones (b) catalysed by Fe(II) catalyst.

The Fe(II) pyridylamido catalyst promotes the ROP of δ -alkyl δ -lactones and ϵ -lactones through a coordination and insertion pathway. These substrates are challenging because of their low ring strain and propagation generates secondary alcohols. Bulk experiments at 30°C, the δ -lactones shows a turnover frequencies (TOF) values in the range of about 60 to 300 h^{-1} for δHL and in the tens of h^{-1} for δNL and δUDL , delivering well controlled polymers with narrow dispersities, while high monomer/catalyst ratios or long reaction times can reduce control. The increasing of the temperature leads to obtain higher values of TOF for all the monomers. The kinetic analysis is reported in **Figure 3.8** and summarises the main trends. Indeed, ϵCL reacts fastest and shows no induction period. Among the δ lactone, δ -hexalactone (δHL) is more reaction than δ -nonalactone (δNL) and δ -undecalactone (δUDL), which show similar rates. Additionally, ϵ -decalactone (ϵDL) is the slowest under the same conditions. Induction times are observed for all of them. Interestingly, in all polymerizations there is the occurrence of a light blue precipitate, which dissolves as the reaction proceeds. This is consistent with initial aggregation and subsequent solubilization of these species.⁸¹

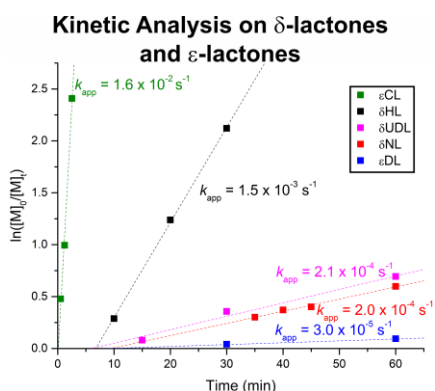


Figure 3.8. Kinetic studies on ϵ CL (green, $R^2=0.98$), δ HL (black, $R^2=0.99$), δ UDL (pink, $R^2=0.99$), δ NL (red, $R^2=0.99$) and ϵ DL (blue, $R^2=0.98$). Experimental conditions: $[M]/\text{Fe}/\text{BnOH} = 100:1:1$, $T=30^\circ\text{C}$.

These observations motivate a focused computational study on ϵ CL, δ HL and δ NL homopolymerization, with the aims to rationalise the presence or absence of an induction period, to identify RLSs for each monomer and to quantify how ring size and side chain influence the barrier. Particular attention is given to the nature of the iron alkoxide species generated *in situ* in the presence of alcohol and to the possible role of multinuclear aggregates at early times.⁸¹ For the computational analysis, the methyl substituent at bridge between the pyridyl and amido moieties has been replaced by an hydrogen atom, in order to reduce the complexity associated with ligand chirality. Despite this simplification, the ligand remains asymmetric and presents two diastereotopic coordination sites at the metal centre, labelled S1 and S2 for clarity. Buried Volume ($\%V_{\text{Bur}}$) analysis, in **Figure 3.9**, on the neutral precursor reveals a more congested situation on the western sector at S2 and a more accessible sector at S1, suggesting that both the incoming monomer during initiation and the growing chain during propagation preferentially occupy the less hindered site

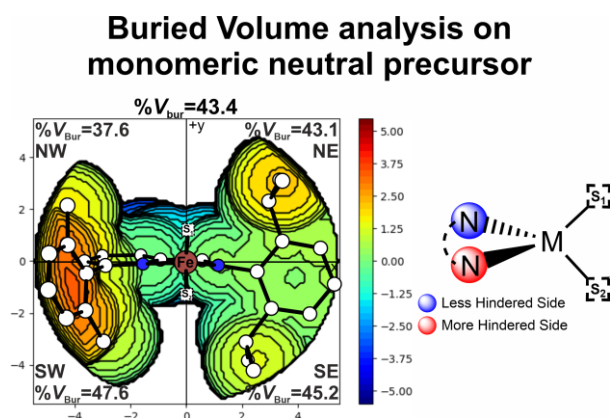
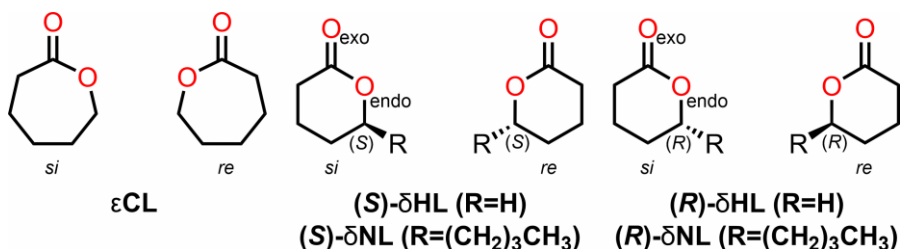


Figure 3.9. Steric map of the neutral precursor with the two available diastereoisotopic sites. Computational details: a sphere of 5.5 Å centred on the metal centre, with a mesh of 0.1 Å and excluding the hydrogen atoms in the computation

It is worth to note that to analyse the ROP mechanism the stereochemistry of the monomers needs to be considered. Indeed, each monomer can insert with two different enantiofaces, *re* and *si*, and δ HL and δ NL are available as *R* and *S*. All the results will be reported considering the *S* enantiomers of those monomers. All the chirality elements are reported in **Scheme 3.7**.



Scheme 3.7. Elements of chirality associated to the analysed monomers.

Additionally, spin-state accessibility is a defining feature of Fe(II) chemistry. Low-spin singlet and triplet states and the high-spin quintet state were examined, requiring geometry optimizations for all the accessible spin-state. Electronic and Free energy comparisons identify the quintet as the most stable state for neutral precursors, as reported in **Table 3.6**. Based on the computational methodology described in **Section**

3.2, robustness of the approach was assessed by re-evaluating relative spin-state stabilities on B3LYP geometries with a broad set of functionals. The test set covered meta-GGA M06L⁸², with and without D3⁷¹ dispersion, hybrid GGAs B3LYP^{62,63}, PBE0⁸³ and PBE0-D3BJ⁷², hybrid meta-GGA M06-2X⁸² and M06⁸² with and without D3⁷¹ dispersion, TPSSh⁸⁴-D3BJ⁷² and the range-separated ω B97X-D⁸⁵.

Table 3.6. Functional, type of functional, percentage of HF exchange, electronic and free energies (in kcal/mol) reported for iron(II) neutral precursor for singlet (S), triplet (T) and quintet (Q) states with respect to quintet spin state. Spin contamination values ($\Delta\langle S^2 \rangle$) for Triplet and Quintet and the average for each functional have been reported.

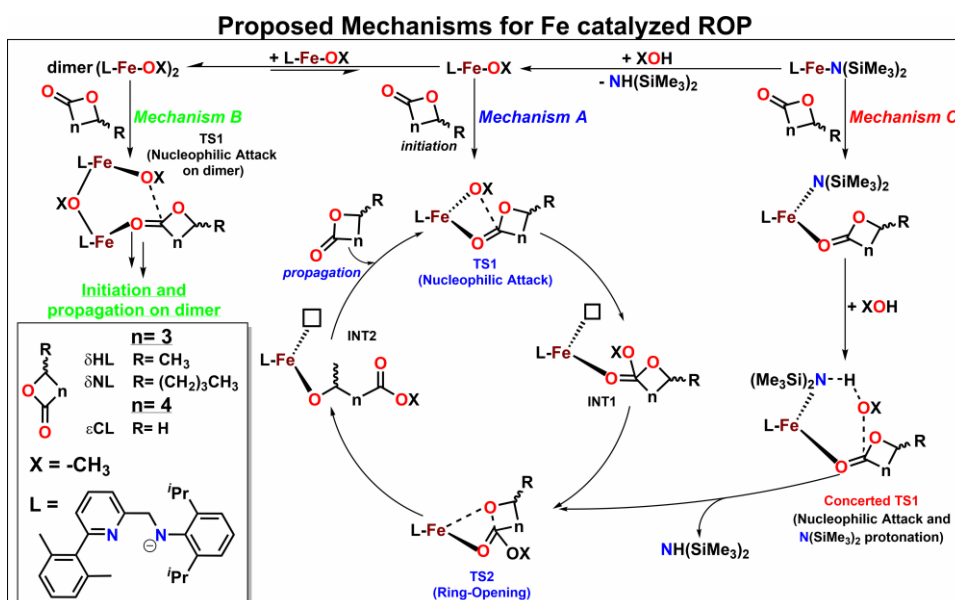
Functional	Type	Exc. HF%	ΔE S/Q	ΔE T/Q	ΔG S/Q	ΔG T/Q	$\Delta\langle S^2 \rangle$ T	$\Delta\langle S^2 \rangle$ Q	Avg. $\Delta\langle S^2 \rangle$
M06L-D3	Meta-GGA	0	42.2	18.3	45.7	19.3	0.0062	0.0002	0.0032
M06L	Meta-GGA	0	42.4	18.5	45.9	19.6	0.0062	0.0002	0.0032
TPSSh-D3BJ	Hybrid Meta-GGA	10	45.4	17.6	48.9	18.6	0.0066	0.0001	0.0034
B3LYP-D3BJ	Hybrid GGA	20	42.8	18.6	46.3	19.6	0.0029	0.0001	0.0015
ωB97X-D	Hybrid Range-sep.	22-100	48.5	22.9	52.0	23.9	0.0028	0.0000	0.0014
PBE0-D3BJ	Hybrid GGA	25	56.1	24.5	59.5	25.6	0.0081	0.0001	0.0041
PBE0	Hybrid GGA	25	59.6	26.5	63.1	27.6	0.0081	0.0001	0.0041
M06-D3	Hybrid Meta-GGA	27	61.9	32.3	65.4	33.4	0.0078	0.0002	0.0040
M06	Hybrid Meta-GGA	27	62.8	33.0	66.3	34.0	0.0078	0.0002	0.0040
M062X	Hybrid Meta-GGA	54	79.9	42.3	83.4	43.4	0.0059	0.0001	0.0030

The functionals differs in exact exchange content, which spans about 20% to 54%, and in the case of ω B97X-D varies from roughly 20% at short range to full exchange

at long range. They also differ in whether empirical dispersion is included. Despite the differences, the qualitative ordering of spin states remained consistent. The quintet emerges as the lowest state in both electronic and Gibbs energies.

Among the tested functionals, TPSSh-D3BJ and M06L, with or without D3 dispersion, reproduced the B3LYP-D3BJ spin gaps closely and maintained balanced separation between states. The trends indicate that spin energetics in Fe(II) complexes are sensitive to the fraction of exact exchange. Indeed, low to moderate HF exchange ($\leq 20\%$) gives balanced gaps. Increasing the percentage beyond about 27% tends to over-stabilize the high-spin state. Spin contamination was monitored as $\Delta\langle S^2 \rangle$, defined as the difference between the annihilated $\langle S^2 \rangle$ value and $S(S+1)$, and was evaluated only on energy refinement calculations. Contamination is minimal for quintet states and slightly higher for the triplet, which point to B3LYP and ω B97X-D as reliable choices when spin purity is a priority. These results highlight the need to carefully choose functionals when multiple spin states are accessible. The outcome supports the choice of a quintet spin state for the analysis of ROP mechanisms.

The computational analysis of ROP of ϵ CL, δ HL and δ NL started on three mechanistic hypotheses, which are showed in **Scheme 3.8**.



Scheme 3.8. Mechanisms for ROP of ϵ CL, δ HL and δ NL. Mechanism A coordination and insertion on mononuclear species. Mechanism B initiation from dimeric iron species. Mechanism C concerted nucleophilic attack with amido departure.

Mechanism A corresponds to a classical mononuclear coordination and insertion process. The neutral precursor reacts with one equivalent of alcohol to form an iron alkoxide. The alkoxide attacks the monomer at TS1 and ring opening follows at TS2 forming a growing chain with an alkoxide terminus. After that, propagation takes place (TS1' and TS2'). The MEPs for ϵ CL and δ HL are reported in **Figure 3.10** with a blue path for the mononuclear pathway for both initiation and propagation, reporting the RDSs, and in **Table 3.7** for δ NL.

DFT analysis of MEPs

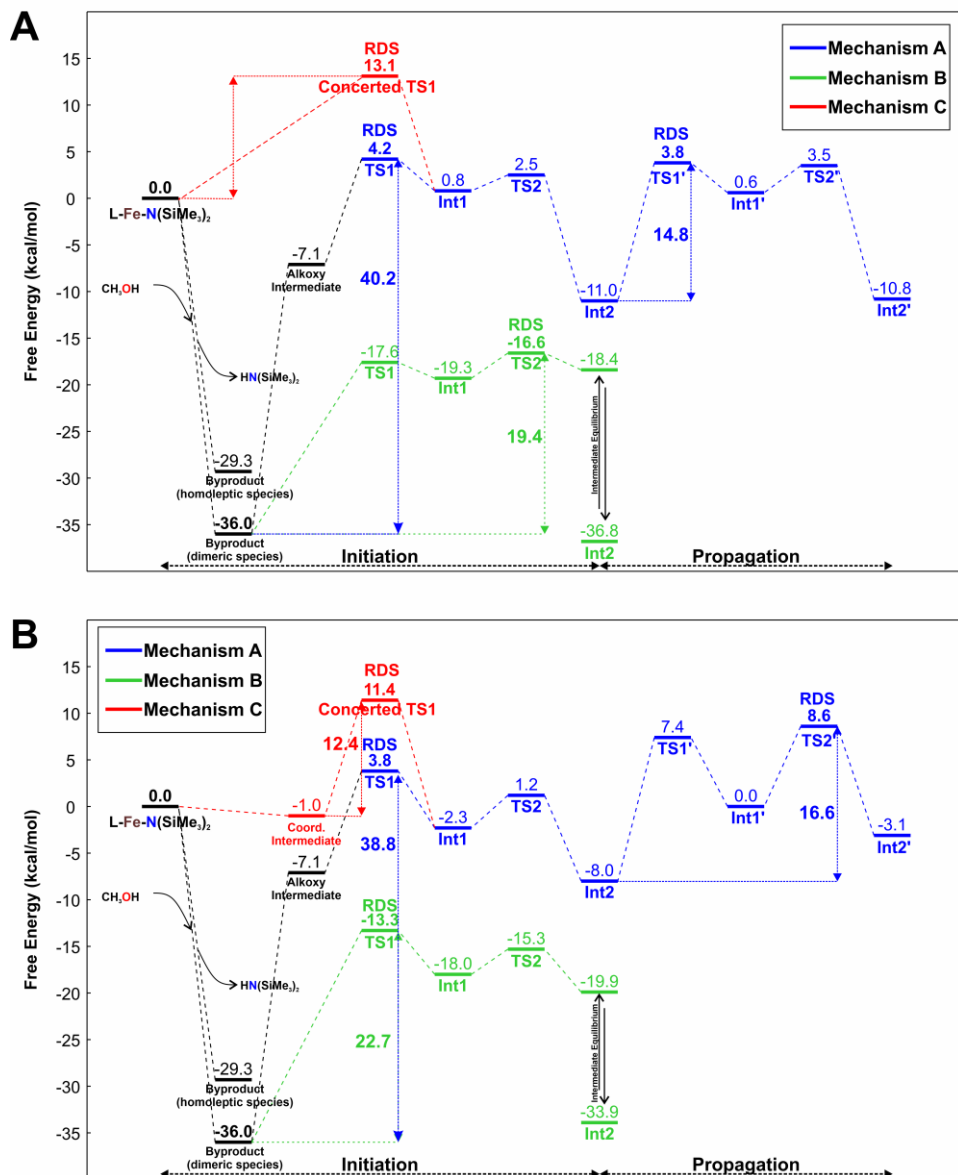


Figure 3.10. MEPs for ROP of ϵ CL (A) and δ HL (B), for initiation and propagation.

Table 3.7. Free energies ΔG in kcal/mol for δ NL for critical points. All the values are reported with respect to the neutral precursor.

	Concerted TS1	Int2	TS1'	TS2'	TS1 on Dimer	TS2 on Dimer
ΔG (kcal/mol)	11.7	-8.5	8.1	10.1	-14.3	-16.4

Experimental evidence indicates the formation of a light blue precipitate at early times that dissolves as polymerization proceeds. This behaviour and the known tendency of iron alkoxides to aggregate suggest that polynuclear species form during activation in the presence of the alcohol (for the simulation, methanol has been used). The stability of such aggregates was tested in *Mechanism B* (Scheme 3.8), assuming that metal alkoxide can lead to polynuclear adducts of (MOX)_n type. In Figure 3.10, the formation of (MOX)₂ (X= CH₃) is thermodynamically favourite, creating a kinetic bottleneck (-36.0 kcal/mol). The energetic stability has been computed following the reaction scheme RS1 below and the structure is reported in Figure 3.11.

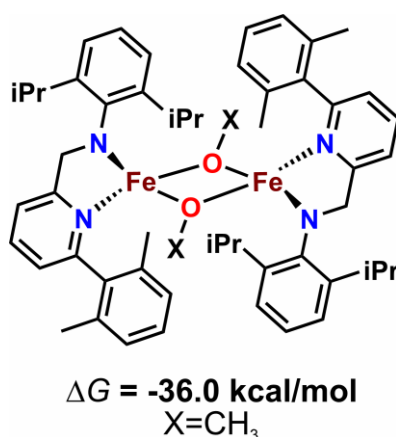


Figure 3.11. Schematic representation of dimeric complex obtained from the neutral precursor.

The computed barrier for ϵ CL initiation on dimer is 19.4 kcal/mol and rises further for δ HL and δ NL (**Figure 3.10** and **Table 3.7**). The optimized structures for TS1 and TS2 on the dimer species, in **Figure 3.12**, show close steric interactions between the side chains of the two δ -alkyl δ -lactones and the catalytic pockets. Such results support the idea that dimeric species can at least initiate polymerization and that the substituted monomers show induction time for the steric interactions occurring with the catalyst. Additionally, after the ring-opening event, a rearrangement of the Int2 occurs, forming a stable four-centre dimer, which is thermodynamically favourable (**Figure 3.13**).

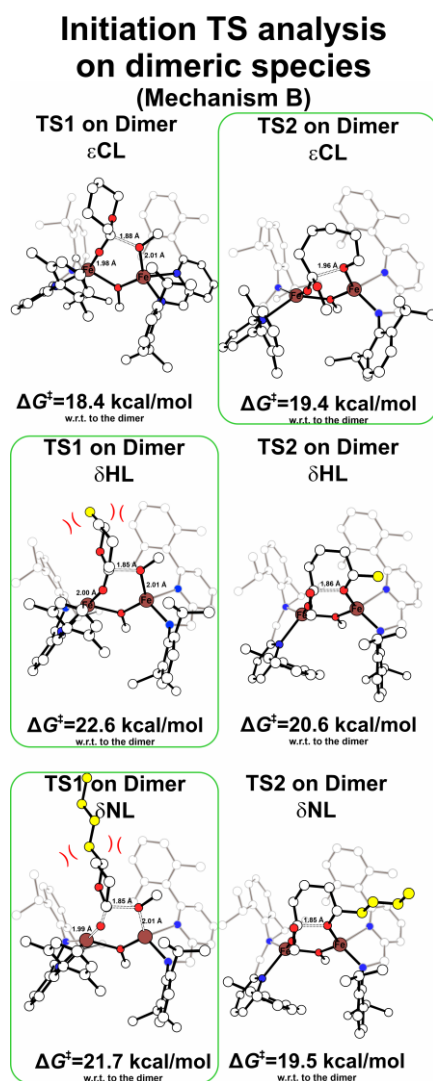


Figure 3.12. DFT optimized TSs for initiation on dimeric species (*Mechanism B*). Steric interactions that raise the barrier are highlighted in red. RDSs are circled in green. Distances in Å, hydrogen atoms are omitted.

Equilibrium between Bent Chain and Linear Chain Conformation for ϵ CL and δ HL monomers

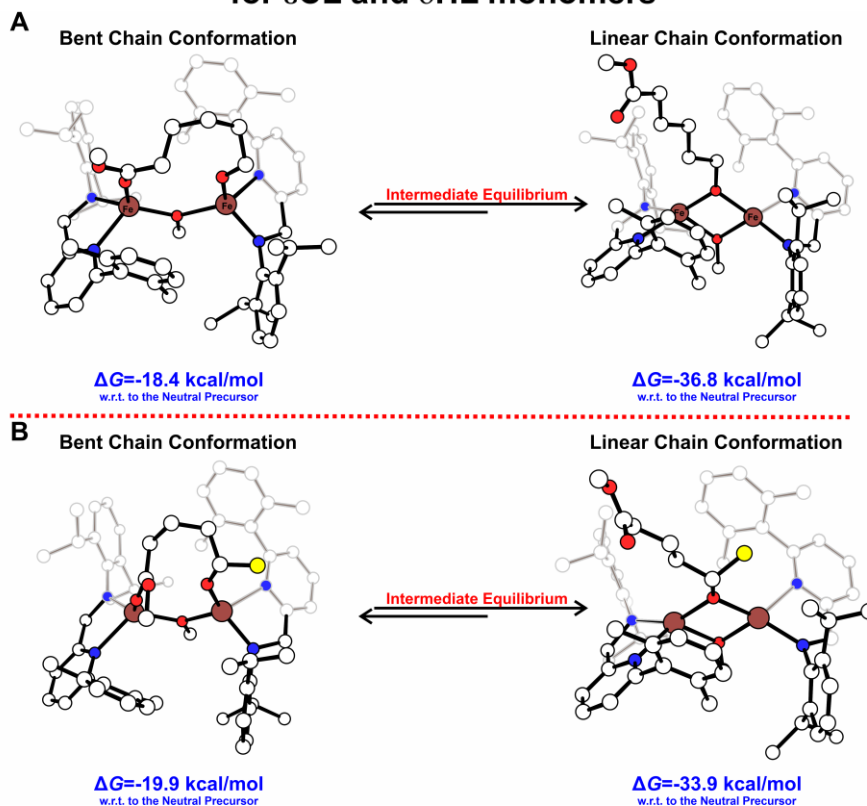


Figure 3.13. DFT optimized structures for Int2 on dimeric species, A for ϵ CL and B for δ HL. Gibbs energies are reported for both chain conformation. Hydrogen atoms are omitted.

The high stability of dimeric alkoxides prompted to explore a third option that bypasses the formation of such species. *Mechanism C* (Scheme 3.8) introduces a concerted TS where nucleophilic attack and amido departure occur simultaneously. The computed barriers for the three monomers are similar to each other and comparable to those of *Mechanism A* (Figure 3.10, red path for *Mechanism C*). This result support the view that aggregates may be off-cycle resting states, while the mechanism proceeds along a path bases on mononuclear active species. The DFT optimized structures are reported in Figure 3.14.

DFT analysis of the concerted TSs for all monomers (Mechanism C)

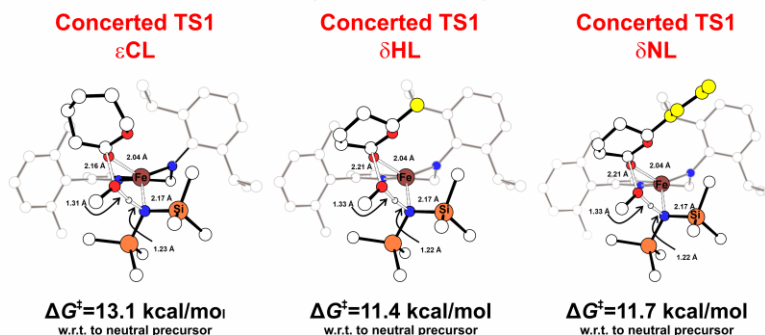


Figure 3.14. DFT optimized concerted TSs (*Mechanism C*) for ϵ CL, δ HL and δ NL. Distances in Å, hydrogen atoms are omitted.

Assessed the possible initiation paths, propagation was modelled following *Mechanism A*. During the propagation, the increasing of repulsive steric interactions is expected between the growing chain and side group of monomers,⁵⁴ and they should be independent to the exact nuclearity of the active species. Notwithstanding this, it is expected that on dimeric species the main monomer/growing chain features revealed on the monomeric pathway would be maintained.⁸⁶

In **Figure 3.15**, DFT optimized structures and Gibbs energies of TS1' and TS2' are reported. Referring to **Figure 3.10** for the full pathway, from initiation to propagation there is a switch in nature of RDSs, passing from TS2 to TS1' for ϵ CL and from TS1 to TS2' for the two δ -alkyl δ -lactones. This switch agrees with literature precedents for LA ROP.^{43,87} With ϵ CL as reference, the computed increase in RDS energies in propagation is about 1.5 and 3.8 kcal/mol for δ HL and δ NL, respectively. These differences reproduce the experimental apparent rate ratio (from **Figure 3.8**) and are reported in **Table 3.8**.

Propagation TS analysis on mononuclear species (Mechanism A)

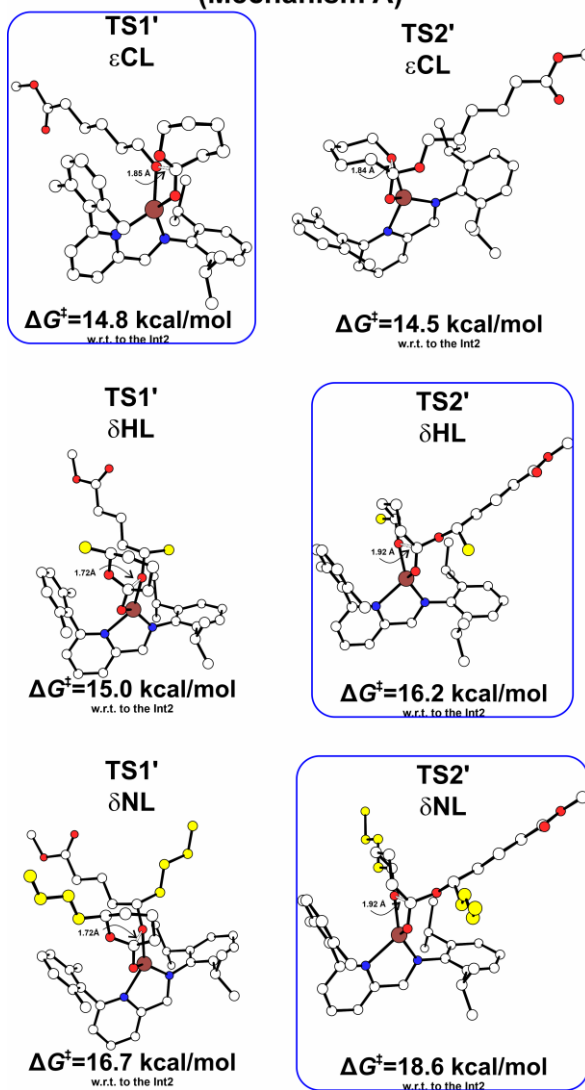


Figure 3.15. DFT optimized TSs for propagation on mononuclear species (*Mechanism A*). Steric interactions that raise the barrier are highlighted in red. RDSs are circled in blue. Distances in Å, hydrogen atoms are omitted.

Table 3.8. Experimental Gibbs energies (kcal/mol) derived from the experimental k_{app} ratio

($k_{\text{app.}(\delta\text{HL})}/k_{\text{app.}(\varepsilon\text{CL})}$ and $k_{\text{app.}(\delta\text{NL})}/k_{\text{app.}(\varepsilon\text{CL})}$), and DFT activation barrier energies for monomeric and dimeric initiations and monomeric propagation using B3LYP computational methodology.

	$\Delta\Delta G(\delta\text{HL}-\varepsilon\text{CL})$	$\Delta\Delta G(\delta\text{NL}-\varepsilon\text{CL})$
Experimental	1.4	2.6
Monomeric Initiation	-0.4	/
Dimeric Initiation	3.2	2.3
Monomeric Propagation	1.8	3.8

- a) Calculated from the $k_{\text{app.}}$ ratio reported in Figure 3.8 by using the Arrhenius equation and compared to the $\Delta\Delta G_{\text{calc.}}^{\ddagger}$. The reference used is the εCL and for the $\Delta\Delta G_{\text{calc.}}^{\ddagger}$, the activation energies of the initiation on the monomeric and dimeric specie and the propagation on the monomeric species have been considered.

Methodological robustness on selected critical points of MEP, including TSs and intermediates, was assessed through a benchmark that compares single-point refinements on B3LYP optimized structures. Single-point calculations have been performed using M06L⁸² including D3 dispersion^{70,71}, TPSSh⁸⁴ in conjunction with D3BJ dispersion⁷² and $\omega\text{B97X-D}^{85}$. Results are reported in **Table 3.9**.

B3LYP-D3BJ and TPSSh-D3BJ shows consistent activation energies across all the path and monomers, M06L-D3 results are slightly increased and $\omega\text{B97X-D}$ predicts lower barrier, especially for dinuclear species, which could be related to its long-range hybrid nature. Notwithstanding this, all of them reproduces the increase in the activation barrier from εCL to δHL and δNL .

Table 3.9. Free energies (ΔG in kcal/mol) for critical points of lactone MEPs, obtained with different functionals in single-point energy refinement calculations, reported with respect to the neutral monomeric precursor and compared to B3LYP-D3BJ.

	Initiation						Propagation		Methodology
	TS1	TS2	Int2	Dimer precursor	TS1 dimer	TS2 dimer	TS1'	TS2'	
εCL	4.2	2.5	-11.0	-36.0	-17.6	-16.6	3.8	3.5	B3LYP-D3BJ/PCM
	8.1	5.5	-9.5	-31.9	-13.2	-14.2	5.7	4.5	M06L-D3/PCM
	4.5	2.7	-8.2	-31.7	-12.6	-12.1	4.7	4.7	TPSSh-D3BJ/PCM
	5.1	2.7	-10.1	-34.9	-17.6	-16.6	4.5	3.6	$\omega\text{B97XD/PCM}$

δHL	3.8	1.2	-8.0	-36.0	-13.3	-10.6	7.0	8.2	B3LYP-D3BJ/PCM
	6.2	5.0	-6.6	-31.9	-7.8	-12.1	9.6	10.9	M06L-D3/PCM
	4.0	1.5	-5.6	-31.7	-9.2	-11.1	7.3	9.5	TPPSh-D3BJ/PCM
	4.7	1.2	-6.9	-34.9	-13.6	-16.7	6.2	8.8	ω B97XD/PCM
δNL	/	/	-8.5	-36.0	-14.3	-16.4	8.1	10.1	B3LYP-D3BJ/PCM
	/	/	-7.6	-31.9	-9.2	-14.1	11.0	13.2	M06L-D3/PCM
	/	/	-6.3	-31.7	-10.3	-12.6	8.1	11.0	TPPSh-D3BJ/PCM
	/	/	-7.7	-34.9	-14.8	-18.4	6.9	9.6	ω B97XD/PCM

Promolecular NCI analysis provides a qualitative picture of the origin of the higher TS2' energy barriers for δ -alkyl δ -lactones. Indeed, NCI analysis shows a *quasi*-repulsive region between the side pendant group of the incoming monomer and the growing chain itself. This situation is more pronounced for δNL than for δHL and similar monomer-chain repulsions have been implicated in organocatalytic systems.⁵⁴ Interactions are shown in **Figure 3.16**.

Non Covalent Interaction Analysis on TS2' (Mechanism A)

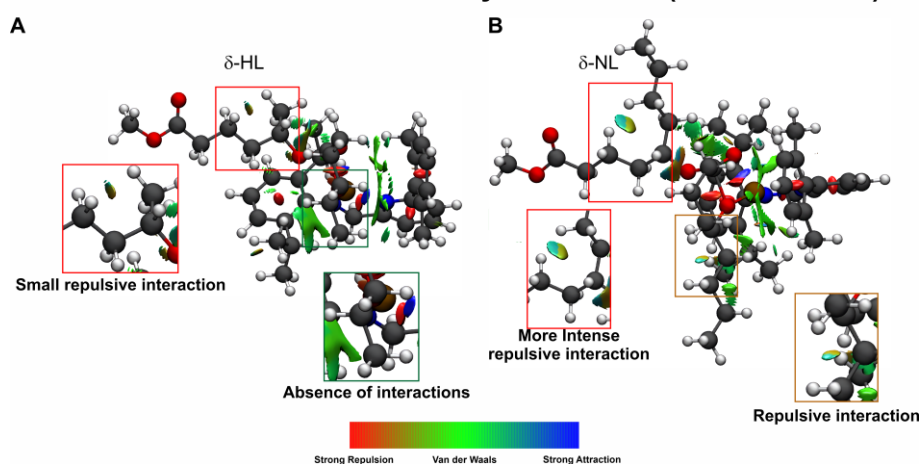


Figure 3.16. NCI analysis of optimized TS2's on mononuclear species (*Mechanism A*) for δHL (A) and δNL (B). NCI surfaces at $s = 0.3$ a.u. and colour scale $-3 < \rho < 3$ a.u. for promolecular densities.

Overall, the computational picture rationalises those features defining Fe(II) catalyst on ϵ CL, δ HL and δ NL. First, the light-blue precipitate and the induction time are consistent with the initial formation of polynuclear iron alkoxides, that gradually reorganize or redissolve during the polymerization. Additionally, the formation of these aggregates does not block catalysis since the initiation could potentially proceed either starting from a mononuclear alkoxide or through a concerted path that avoid the most stable dimeric species. The activation barriers are governed by monomer-chain steric interactions and rise with side-chain length, reproducing the experimental rates.

3.5 On going study on ring opening copolymerization of *L*-LA and ϵ CL catalysed by Iron catalyst

Poly lactide is a thermoplastic polyester with enhanced biodegradability and biocompatibility. One of its drawbacks is the brittleness, which limits the application of this polymer in various fields. On the other hand, polyCL shows high elasticity and thermal proprieties, but scarce mechanical strength. The copolymerization is a good strategy to modulate the properties and wide the range of applications.^{7,88–90} The most effective route to copolymerize these monomers is through ROP mediated by metal catalyst, which enables control over composition, sequence, molar mass and so on. In this context, the iron catalyst studied above revealed the ability to copolymerize the two monomers, by adding first ϵ CL and then LA monomer, obtaining a di-block copolymer. When the order is reversed, on PLLA homopolymer is obtained, a behaviour frequently observed in literature.^{91–95} Only few exceptions have been found in literature to this behaviour.^{96,97} In this on-going study, the aim is to identify through DFT the reasons behind this general trend, focusing on the iron catalyst analysed above. It is generally reported in literature that such result is the consequence of the formation of a strong intermediate after lactide insertion, which makes not possible to the ϵ CL to be polymerized.

3.6 Conclusion

The results deliver a coherent mechanistic framework that spans from stereocontrol in *rac*-LA and reactivity in ROP of low strain lactones. For achiral Al catalysts, stereoselectivity arises from monomer guiding wrapping modes which creates a chiral environment at the active site. Buried Volume ($\%V_{\text{Bur}}$) analysis and ASM-NEDA analysis show that the preferred pathways are those minimising deformation of both catalyst and monomer fragments in RDSs. The computational analysis rationalises ESC and CEC in reproducing the microstructure of the obtained polymer.

For Fe(II) pyridylamido systems, kinetic analysis and experimental evidence regarding induction time and the formation of a light blue precipitate which dissolve during polymerization were used to gain insight into the mechanism governing the ROP. DFT enables exploring different mechanisms, including monomeric, dimeric assisted and concerted initiation pathways, reproducing the experimental results. The activation barriers rise with side chain length because of monomer-chain destabilizing steric interactions, accounting for the decreasing activity passing from ϵCL to δHL to δNL .

The analysis performed on Al and Fe systems yields possible rules for catalyst and process design. For achiral Al systems, wrapping dynamics can be tuned to steer the balance between ESC and CEC while retaining high activity and stereoregularity. For Fe(II) pyridylamido catalysts, polynuclearity is not an intrinsic drawback but a structural feature that can be exploited to tune catalytic activity and, potentially, selectivity. Indeed, steric adjustments of the catalytic skeleton can be made to stabilise reactive polynuclear species active in polymerization.

On the computational side, DFT, coupled to Buried Volume ($\%V_{\text{Bur}}$) analysis, ASM-NEDA and NCI analysis, can provide important and interesting insights for mechanisms, identifying RDSs, discriminating competing pathways and decomposing stereoelectronic effects occurring during the catalysis. Used prospectively, these tools could yield quantitative descriptors than enable screening of

ligands, monomers and nuclearities giving the opportunity to predict rates, stereocontrol new catalysts and materials aligned the sustainability principles.^{98,99}

3.7 Acknowledgment

The study presented in this chapter, in particular in **Section 3.3**, is an adaptation of a work already published, including text, tables and figures:

1) Moccia, S.; D'Alterio, M. C.; **Romano, E.**; De Rosa, C.; Talarico, G. Stereoselectivity Control Interplay in Racemic Lactide Polymerization by Achiral Al-Salen Complexes. *Macromol. Rapid Commun.* **2025**, *46*, 2400733. <https://doi.org/10.1002/marc.202400733> (CC by 4.0)

The study on Fe(II) pyridylamido catalyst for the polymerization of challenging monomers, presented in **Section 3.4**, has been published and here adapted, including text, tables and figures, from the paper:

2) Gravina, G.; **Romano, E.**; Liporace, A.; D'Alterio, M. C.; Talarico, G.; Pellecchia, C. Sustainable Polymerization of Natural Lactones via Iron Catalysis: An Integrated Experimental and Computational Study. *ACS Sustain. Chem. Eng.* **2025**, *13*, 19613-19624. <https://doi.org/10.1021/acssuschemeng.5c07947> (CC by 4.0)

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