# Une étude computationnelle de la polymérisation par (hétéro)arylation directe <br> [A Computational Study of <br> <br> Direct (Hetero)arylation Polymerization] 

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Mémoire

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# Une étude computationnelle de la polymérisation par (hétéro)arylation directe 

[A Computational Study of

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## Terence Blaskovits

Sous la direction de :

Mario Leclerc, directeur de recherche
Paul A. Johnson, codirecteur de recherche

## RÉSUMÉ

En comparaison avec d'autres techniques de couplage-croisé adaptées à la synthèse de polymères conjugués, la polymérisation par (hétéro)arylation directe (PHAD) s'avère avantageuse d'une perspective industrielle et environnementale. En effet, elle permet d'éviter l'utilisation d'agents de transmétallation nécessaires aux méthodes classiques de polymérisation. La réaction de PHAD exploite l'activation de liens aromatiques carbone-hydrogène $(\mathbf{C}-\mathbf{H})$ pour une synthèse efficace de polymères conjugués avec une excellente économie d'atomes. La réaction d'(hétéro)arylation directe permet la formation d'un lien entre deux atomes de carbone d'hybridation $s p^{2}$ à partir d'un lien $\mathbf{C}-\mathbf{H}$ via l'état de transition de la métallation-déprotonation concertée (CMD).

La majorité des polymères conjugués utilisés en électronique organique contient des unités de répétition à base de thiophène. Cet hétérocycle, possédant des propriétés électroniques et stériques désirables, sont fonctionnalisés avec des groupes donneurs ou accepteurs d'électrons, ainsi qu'avec des chaînes aliphatiques à des fins de solubilité. Cependant, l'utilisation du motif thiophène peut mener à des défauts structuraux dans la chaîne polymère puisqu'elle comporte plusieurs liens $\mathbf{C}-\mathbf{H}$ activables en PHAD. Si un lien C-H non-désiré (en position $\beta$ du motif thiophène) est activé plutôt que le lien en position $\alpha$, un défaut en $\beta$ peut alors être incorporé de manière covalente dans la structure polymérique résultante. La présence de défauts en $\beta$ mène à une perturbation de la conjugaison du polymère et de l'organisation du matériau à l'état solide, des facteurs qui peuvent réduire les performances en dispositifs d'électronique organique.

Étant donné l'omniprésence du motif thiophène au sein des polymères conjugués et sa sélectivité parfois problématique, une étude computationnelle du mécanisme de l'arylation directe sur des unités thiophènes modèles a été entreprise dans le cadre de ce projet. En utilisant la théorie de la fonctionnelle de la densité et le cluster couplé, les barrières d'activation pour l'état de transition de la CMD de plusieurs substrats modèles ont été calculées et analysées par la méthode de la distorsion-interaction. L'effet activant d'un halogène sur les liens $\mathbf{C}-\mathbf{H}$ adjacents à celui-ci a été étudié. Les résultats permettront de guider la conception de monomères pour la réalisation de matériaux régioréguliers par PHAD.


#### Abstract

The direct (hetero)arylation polymerization (DHAP) reaction harnesses the single-step activation and arylation of aromatic carbon-hydrogen bonds for the efficient synthesis of conjugated polymers. By avoiding the need for transmetalating agents used in other polymerization techniques, the number of synthesis steps is reduced, the need for expensive and often unstable reagents is minimized and the production of toxic organometallic by-products is eliminated. These factors contribute to a reaction which is more favourable than traditional methods for the preparation of conjugated polymers from an industrial and an environmental perspective.

Most high-performing conjugated polymers for organic electronic applications contain thiophene-based repeating units. These heterocycles possess desirable electronic features and are easily functionalized with electron-accepting or -donating substituents or solubilizing side-chains to tune their electronic and physical properties. However, the issue has arisen over the selectivity of the concerted metalation-deprotonation (CMD) transition state, the key step of the direct arylation mechanism which determines the selectivity of $\mathbf{C}-\mathbf{H}$ bond activation. There are multiple reactive $\mathbf{C}-\mathbf{H}$ bonds on thiophene monomers, and if the undesired bond (the " $\mathbf{C}_{\boldsymbol{\beta}}-\mathbf{H}$ " bond) were to be activated, it would generate a $\beta$-defect in the resulting polymer. This may lead to a disruption in both the $\pi$-conjugation of the polymer and the supramolecular organization of the material in the solid state, factors which can contribute to reduced performance in organic electronic devices.

Given the ubiquity of thiophene-based units in conjugated polymers and the assumed issues regarding selectivity, we used computational techniques to study the direct arylation mechanism on model thiophene substrates possessing various electronic features. Using density functional theory and coupled-cluster methods, activation barriers for the CMD transition states of various $\mathbf{C}-\mathbf{H}$ bonds were calculated and analyzed using the distortion/interaction model. The activating effect of a halide on thiophene was also studied. The results suggest that there are inherent features of selectivity for electron-rich or electron-poor thiophenes, and that the location of the halogen greatly influences coupling selectivity by activating the undesirable $\mathbf{C}_{\boldsymbol{\beta}}-\mathbf{H}$ bond. These findings could guide the design of monomers amenable to high-selectivity DHAP protocols.


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## LIST OF ABBREVIATIONS

## Terms associated with conjugated polymers and quantum chemistry calculations

$\Delta \Delta G^{\ddagger} \quad$ difference in activation free energies
$\Delta E_{d}^{\ddagger} \quad$ distortion component of an electronic transition state energy
$\Delta E_{d-s u b}^{\ddagger} \quad$ substrate distortion component of an electronic transition state energy
$\Delta E_{d-c a t}^{\ddagger} \quad$ catalyst distortion component of an electronic transition state energy
$\Delta E_{i}^{\ddagger} \quad$ interaction component of an electronic transition state energy
$\Delta G \quad$ change in the sum of electronic and thermal free energies
$\Delta G^{\ddagger} \quad$ activation free energy
$\varepsilon \quad$ dielectric permittivity
2Br3EtTh 2-bromo-3-ethylthiophene
BHJ bulk heterojunction
BrCNTh 5-bromo-2-cyanothiophene (5-bromothiophene-2-carbonitrile)
BrMeOTh 5-bromo-2-methoxythiophene
BrTh 2-bromothiophene
$\mathrm{C}_{\text {aryl }}-\mathrm{H} \quad s p^{2}$ carbon-hydrogen bond on an aryl or heteroaryl substrate
$\mathrm{C}_{\alpha}-\mathrm{H} \quad$ carbon-hydrogen bond in the 5-position of a 2-substituted thienyl fragment
$\mathrm{C}_{\beta}-\mathrm{H} \quad$ carbon-hydrogen bond in the 4-position of a 2-substituted thienyl fragment
$\mathrm{C}_{\gamma}-\mathrm{H} \quad$ carbon-hydrogen bond in the 3-position of a 2-substituted thienyl fragment
$\mathrm{C}-\mathrm{X} \quad$ carbon-halogen bond
$\operatorname{CCSD}(\mathrm{T}) \quad$ Coupled cluster with singles, doubles and perturbative triples
CMD concerted metalation-deprotonation
CNTh 2-cyanothiophene (thiophene-2-carbonitrile)

| COSMO | conductor-like screening model (solvation model) |
| :---: | :---: |
| DFT | Density functional theory |
| DHAP | Direct (hetero)arylation polymerization |
| DLPNO | Domain-based local pair natural orbital |
| DPP | diketopyrrolopyrrole |
| $E_{\text {CCSD }}$ | single point (electronic) energy calculated by DLPNO-CCSD (T) |
| EtTh | 2-ethylthiophene |
| $G$ | sum of electronic and thermal free energies calculated by $\operatorname{DLPNO}-\operatorname{CCSD}(\mathrm{T})$ and |
| DFT, respectively |  |
| $G_{\text {CORR DFT }}$ | thermal energy correction calculated by DFT |
| IEFPCM | integral equation formalism polarizable continuum model (solvation model) |
| ITh | 2-iodothiophene |
| kcal mol ${ }^{-1}$ | kilocalories per mole |
| MeOTh | 2-methoxythiophene |
| MeTh | 2-methylthiophene |
| NDI | naphthalene diimide |
| NMR | nuclear magnetic resonance |
| OA | oxidative addition |
| P3HT | poly(3-hexylthiophene) |
| PES | potential energy surface |
| RE | reductive elimination |
| Th | thiophene |
| Thth | thieno[3,2-b]thiophene |
| TS | transition state |
| UV-Vis | ultraviolet-visible |

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El que mucho abarca, poco aprieta.

- Adage espagnol (rapporté par le Dr. Pablo Lebed, post-doc chez le Pr. Dominic Larivière)

I had not considered that chemists and Sanskritists shared a common trait: the love of inventing compound words.

- R. R. Blaskovits (in conversation)


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Finalement, comme à n'importe quel autre moment de ma vie, ce n'est que grâce à mes parents, Janice et Rick Blaskovits, que tout ce que je fais est possible.

## AVANT-PROPOS

The introduction of this thesis is a full reproduction of the chapter Direct (Hetero)Arylation Polymerization for the Preparation Of Conjugated Polymers written for the upcoming $4^{\text {th }}$ edition of the Handbook of Conducting Polymers (T. A. Skotheim, B. C. Thompson, J. R. Reynolds, Eds.) for CRC Press. At the time of the preparation of this thesis, the manuscript has been accepted in its corrected form by the editors of the Handbook of Conducting Polymers and is awaiting publication. I alone wrote the manuscript, which was prepared under the supervision of Professor Mario Leclerc. Only minor formatting changes have been made to the text as it appears here.

Blaskovits, J. T.; Leclerc, M., Direct (Hetero)arylation Polymerization for the Preparation of Conjugated Polymers. The Handbook of Conducting Polymers, 4th Edition. T. A. Skotheim, B. C. Thompson, J. R. Reynolds, Eds. CRC Press. In press.

The second chapter and accompanying computational data is a full reproduction of the research paper Mechanistic Origin of $\beta$-Defect Formation in Thiophene-Based Polymers Prepared by Direct (Hetero)arylation, which has been recently published in Macromolecules. All calculations were undertaken by me under the supervision of Professors Mario Leclerc and Paul Johnson at Université Laval and Professor Alán Aspuru-Guzik at Harvard University. I alone wrote the manuscript and I am the first author of the manuscript. Only minor formatting changes have been made to the text as it appears here. The Supporting Information section of the article is reproduced in Annexes 2 and 3.

Blaskovits, J. T.; Johnson, P. A.; Leclerc, M., Mechanistic Origin of $\beta$-Defect Formation in Thiophene-Based Polymers Prepared by Direct (Hetero)arylation Polymerization. Macromolecules. 2018, 51 (20), 8100-8113.

## INTRODUCTION: DIRECT (HETERO)ARYLATION POLYMERIZATION FOR THE PREPARATION OF CONJUGATED POLYMERS

### 0.1 Outline

The large-scale applications of conjugated polymers are manifold. Unfortunately, in many cases their production is restricted by the costs associated with their synthesis. ${ }^{1}$ The direct (hetero)arylation polymerization (DHAP) reaction, which harnesses the single-step activation and arylation of aromatic carbon-hydrogen bonds, is an attractive alternative for the efficient synthesis of conjugated polymers. This palladium-catalyzed, base-assisted technique allows for the formation of a bond between two $s p^{2}$-carbon atoms via the condensation of the carbonhalogen $(\mathrm{C}-\mathrm{X})$ bond of one arene (or heteroarene) with the carbon-hydrogen $(\mathrm{C}-\mathrm{H})$ bond of another. This contrasts with the traditional cross-coupling techniques which have been adapted to polymer synthesis, which require either ex situ bond pre-functionalization, for example with organotin and organoboron compounds (in the case of Migita-Stille and Miyaura-Suzuki reactions, respectively), or in situ bond modification, such as with organozinc and organomagnesium (for the Negishi and Kumada-Corriu couplings). ${ }^{2-5}$ The former class is illustrated in Figure 1, where the transmetalating functional group could be either $-\mathrm{SnR}_{3}$ or $\mathrm{B}(\mathrm{OR})_{2}$ in the case of ex situ metalation, used primarily for copolymerizations, whereas -ZnX and -MgX are used for in situ metalation of monomers for homopolymerizations.

MIGITA-STILLE CROSS-COUPLING POLYMERIZATION


MIYAURA-SUZUKI CROSS-COUPLING POLYMERIZATION

Figure 1 : DHAP: a shortcut to conjugated polymers. A comparison of the Miyaura-Suzuki, Migita-Stille, and direct (hetero)arylation cross-coupling techniques for the synthesis of a hypothetical polymer.

In bypassing the need for transmetalating agents, the number and complexity of synthesis and purification steps is reduced and expensive and often unstable reagents are no longer needed. The production of toxic organometallic by-products is altogether eliminated, and the quantity of metal residue in the final material and glassware is reduced. ${ }^{6-8}$ For these reasons, DHAP (also called DArP or DAP, for direct arylation polymerization or direct arylation polycondensation) can be seen as a potential means to overcome many of the undesirable costs and challenges associated with the synthesis of conjugated polymers. For example, one study demonstrates that the production costs of a certain polymer could be reduced by $35 \%$ when it is prepared by DHAP, as compared to when it is synthesized by Migita-Stille cross-coupling. ${ }^{9}$

To date, a wide spectrum of substrates can be polymerized by DHAP, and new examples appear frequently. ${ }^{10}$ This chapter presents a brief overview of the direct activation of $\mathrm{C}-\mathrm{H}$ bonds and the proposed mechanisms of direct arylation for small molecules. This is followed by the particularities of expanding palladium-catalyzed direct arylation protocols to the preparation of conjugated polymers, as well as the early examples of the transposition of this reaction from small molecules to polymers. The origins of defects found in polymers synthesized by this method are discussed, principally homocoupling and the undesired activation of secondary $\mathrm{C}-\mathrm{H}$ bonds, termed $\beta$-defects. Understanding and suppressing the formation of such defects is of utmost importance as these defects, even in small quantities, can greatly affect polymer properties and ultimately impede performance in organic electronic devices. ${ }^{11-13}$

For this reason, this chapter presents the optimization of reaction conditions in the context of maximizing molecular weights while limiting the occurrence of defects. Although some generalizable catalytic conditions which balance reactivity and selectivity are emerging, the choice of precatalyst, solvent, base, ligand and additives must still be fine-tuned for each pair of co-monomers. The palette of monomers amenable to DHAP is expanding, although there are still a number of limitations to the reaction. This chapter overviews both the potential of the DHAP reaction and some of the unanswered questions regarding this recently-developed technique.

## 0. 2 Direct C-H Activation and Arylation of Small Molecules

### 0.2.1 History and Development

The mechanism, standard reaction conditions and other synthetic considerations of DHAP are all derived from studies of palladium-catalyzed cross-coupling of small molecules via direct $\mathrm{C}-\mathrm{H}$ bond activation. As with any other coupling reaction which was later adopted by the polymer chemistry community, much of the insight gained regarding mechanisms, selectivity and necessary criteria for a successful reaction originate from small molecule experiments.

Research on arylation via the activation of $s p^{2}$-hybridized $\mathrm{C}-\mathrm{H}$ bonds dates back to the preparation of stilbene derivatives from the palladium-catalyzed arylation of styrene with benzene and other simple arenes. ${ }^{14}$ This seminal work, begun by Moritani and Fujiwara in 1967, was later followed by Itahara's studies of the coupling of various heterocycles (derivatives of thiophene, furan and pyrrole) with benzene via double $\mathrm{C}-\mathrm{H}$ activation in the presence of acetic acid and palladium acetate. ${ }^{15,16}$ This is noteworthy as, already at this point in the development of the reaction, the author of this work discussed the challenge of coupling selectivity (i.e. which $\mathrm{C}-\mathrm{H}$ bonds are activated), a topic which would later became central to the development of the direct arylation reaction for both small molecule and polymer synthesis.

In 1979, based on the earlier observation of Shaw and colleagues that the addition of sodium acetate promotes cyclometalation of $\mathrm{N}, \mathrm{N}$-dimethylaminomethylferrocene, Sokolov, Troitskaya and Reutov proposed a mechanism for palladation in which intramolecular deprotonation of the aryl C-H bond of ferrocene occurs by way of a carboxylate complexed to the palladium center. ${ }^{17,}$ ${ }^{18}$ Later, in 1985, Ryabov, Sakodinskaya and Yatsimirsky studied the stoichiometric orthopalladation of a phenyl substrate ( $N, N$-dimethylbenzamine), which also benefitted from a built-in amine direction group. ${ }^{19}$ From results of detailed kinetic studies, they proposed a similar carboxylate-assisted mechanism. From this point onward, the importance of the base in $\mathrm{C}-\mathrm{H}$ bond activation was studied in detail, and its presence in direct arylation reactions became ubiquitous. ${ }^{20}$ For a time, research into transition-metal-catalyzed direct arylation cross-couplings focused on developing optimal reaction conditions primarily for intramolecular reactions or systems with very specific directing groups so as to control site selectivity. ${ }^{21}$ This period was followed by the expansion of the reaction's scope to intermolecular arylation reactions. ${ }^{22}$ Through the combination of a carbonate base with a carboxylic acid additive, the reactivity of the
catalytic system could be increased while still maintaining high site-selectivity in absence of a directing group. ${ }^{23-27}$

Reactions employing palladium-catalyzed $\mathrm{C}-\mathrm{H}$ activation have since been achieved on a wide variety of simple, substituted and fused arenes and heteroarenes with a high degree of control over substrate- and site-selectivity. ${ }^{28-32}$ This is of particular value to the conjugated polymer community as the vast majority of polymers are prepared from monomers with a wide structural diversity. The activation of aryl and heteroaryl $\mathrm{C}-\mathrm{H}$ bonds has been studied extensively for the functionalization of heterocycles for a wide variety of applications, including for the synthesis of $\pi$-conjugated materials, natural products and pharmaceuticals. ${ }^{8,33-37}$ Included in this range of applications are some substrates that would be intolerant of harsher reaction conditions. ${ }^{38-40}$ The distinct lack of transmetalating agents contributes to the reaction's versatility and general ease of execution.

Standard reaction conditions include a range of solvents, running from non-polar (e.g. xylenes, toluene) to highly polar (e.g. $\mathrm{N}, \mathrm{N}$-dimethylformamide [DMF], $\mathrm{N}, \mathrm{N}$-dimethylacetamide [DMAc]) and a variety of ligands (primarily phosphines) and palladium precatalysts $(\operatorname{Pd}(0)$ and $\operatorname{Pd}(\mathrm{II})$ complexes as well as $\mathrm{Pd}(\mathrm{II})$ salts). The one feature that remains constant throughout small molecule couplings and polymerization reactions via direct $\mathrm{C}-\mathrm{H}$ activation is the necessary presence of a carbonate base (primarily potassium carbonate or cesium carbonate) to mediate the abstraction of the proton from the accessible $\mathrm{C}-\mathrm{H}$ bond. A section later in this chapter is devoted to the role each of these ingredients plays in the quality of polymers prepared by DHAP.

### 0.2.2 Proposed Mechanisms and Implications

The direct arylation mechanism proceeds along the same general lines as the vast majority of other transition-metal-catalyzed cross-coupling reactions: oxidative addition, transmetalation and reductive elimination. What differentiates cross-coupling reactions from one another is the nature of the transmetalation step, which traditionally consists of the transfer of the substrate containing the organometallic (or heteroelement-containing) functional group (a $\mathrm{C}-[\mathrm{M}]$ bond) to the catalyst, forming a $\mathrm{C}-\mathrm{Pd}$ bond. Since it does not involve a $\mathrm{C}-[\mathrm{M}]$ bond on one of its substrates
but rather an aromatic $\mathrm{C}-\mathrm{H}$ bond, it can be said that direct arylation does not proceed so much by transmetalation but rather simply by metalation.

A number of mechanisms have been proposed for direct arylation since the first examples of this reaction appeared in the literature. The three principal mechanisms which have been put forward as replacements for transmetalation are (Figure 2):

- Concerted Metalation-Deprotonation (CMD), in which the $\mathrm{C}-\mathrm{H}$ bond undergoes heterolytic cleavage by means of a carboxylate or carbonate ligand, effectively participating in an acid-base reaction which allows the deprotonated arene to coordinate to the metal center as an X-type ligand. ${ }^{41-43}$
- Aromatic Electrophilic Substitution ( $\mathrm{S}_{\mathrm{E}} \mathrm{Ar}$ ), in which the arene bearing the $\mathrm{C}-\mathrm{H}$ bond acts as an X-type ligand and donates a part of its electron density to the metal center, thereby transferring a positive charge to its aromatic ring (the arenium intermediate), followed by deprotonation and re-establishment of aromaticity; ${ }^{23,44,45}$
- Heck-Type Arylation, in which a $\pi$-bond from the arene coordinates to the metal center, and the palladium and second arene are both inserted into it in a similar fashion as to the double bond in a standard Heck mechanism, followed by $\beta$-H elimination (rather than reductive elimination); ${ }^{46,47}$


Figure 2 : The three most widely-proposed mechanisms for direct arylation.
In most examples, the aromatic electrophilic substitution mechanism has been largely dismissed, primarily due to the fact that high reactivity is observed in experiments where the arene bearing the $\mathrm{C}-\mathrm{H}$ bond has a very electron-poor aromatic system. This would make the transfer of a positive charge to the aromatic ring highly unlikely. ${ }^{42,48}$ Further disregard for this mechanism stems from the fact that density functional theory (DFT) studies of potential transition states have been unable to locate the crucial arenium intermediate. ${ }^{49}$ A high primary kinetic isotope effect is also often observed in direct arylation, which is incongruent with the expectation that deprotonation occurs quickly in a $\mathrm{S}_{\mathrm{E}} \mathrm{Ar}$ mechanism. ${ }^{50}$

On the other hand, many computational studies, beginning with that of Sakaki and colleagues in 2000, have suggested that a concerted base-assisted deprotonation akin to that first proposed by Ryabov et al. in 1985 is the most likely route to the metalation of the aryl C-H-bond. ${ }^{19,49,51}$ It is necessary to note that a few exceptions to this have been observed in very particular conditions, such as when fluorinated ligands and solvents are used. ${ }^{47,52}$ On these occasions, kinetic isotope effects and DFT studies indicate that a Heck-type mechanism is the most likely one involved.

Notwithstanding these select cases, the CMD pathway is now recognized by multiple computational and experimental studies to be the most likely of the three proposed mechanisms.

It is thought to be the process responsible for coupling of a wide variety of substrates, electronrich, electron-poor, phenyl, and heterocyclic derivatives alike. ${ }^{20,}{ }^{53-57}$ A schematic of the CMD mechanism given here (Figure 3) shows the coupling of bromobenzene, the substrate bearing the $\mathrm{C}-\mathrm{X}$ bond, with thiophene, the substrate with the target $\mathrm{C}-\mathrm{H}$ bond.


Figure 3 : The proposed concerted metalation-deprotonation mechanism for the direct arylation of thiophene with bromobenzene.

The reaction begins by the generation of the active $\operatorname{Pd}(0)$ catalyst. This occurs either via the exchange of ligands on a $\mathrm{Pd}(0)$ precatalyst (such as $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ or $\mathrm{Pd}\left(\mathrm{PCy}_{3}\right)_{2}$, where $\mathrm{Cy}=$ cyclohexyl and $\mathrm{dba}=$ dibenzylideneacetone) or via the reduction of a $\mathrm{Pd}(\mathrm{II})$ precatalyst (e.g. $\mathrm{PdCl}_{2}$, $\left.\mathrm{Pd}(\mathrm{OAc})_{2}\right)$, for example via the oxidation of a phosphine ligand or the formation of a $\mathrm{C}-\mathrm{C}$ bond from two $\mathrm{C}-\mathrm{H}$ bonds. ${ }^{58-60}$ Oxidative addition ( $\mathbf{O A}$ ) on the $\mathrm{C}-\mathrm{X}$ bond of bromobenzene leads to the first arylpalladium(II) intermediate 1. Ligand exchange between the halide and a carboxylate ion gives the bidentate complex 2. The CMD transition state consists of the inner-sphere
deprotonation of thiophene by the carboxylate, which simultaneously frees a coordination site on the metal center for the approach of the thienyl substrate. This second part constitutes the metalation of the thiophene. Following the formation of the post-CMD intermediate (3), a number of possible ligand exchanges can occur in order to prepare for reductive elimination. For example, the carboxylic acid may de-coordinate and be replaced by another phosphine ligand (4, as shown) or remain coordinated in a monodentate fashion (5, Pathway 2). In either case, the carboxylic acid is reconverted to its conjugate base by way of an acid-base reaction with the carbonate additive (e.g. cesium carbonate, $\mathrm{Cs}_{2} \mathrm{CO}_{3}$, shown here). During the reductive elimination of the phenyl and thienyl fragments, a new $\mathrm{C}-\mathrm{C}$ bond is formed and the initial $\operatorname{Pd}(0)$ species is regenerated.

There are a number of variations on this mechanism which have been identified by both experimental and computational studies. For example, in many cases the carboxylate derivative is added to the reaction to increase coupling selectivity and yield, whereas the reaction can proceed successfully with the carbonate base alone. ${ }^{20,55}$ This suggests that the carbonate base can also be responsible for deprotonating the arene. Also, bidentate bis-phosphine ligands have been used, which would limit the number of available coordination sites on the metal center, indicating that more subtle mechanisms may also be at work. ${ }^{58,61}$ The carboxylate or carbonate base could also deprotonate the $\mathrm{C}-\mathrm{H}$ substrate without even being coordinated to the metal center itself. Although this event, termed intermolecular or outer-sphere deprotonation, is possible, inner sphere acid-base interactions (i.e. with a base coordinated to the metal center) have been shown to be the most energetically feasible. ${ }^{62}$

Phosphines are the most widely-used ligands for the direct arylation of small molecules due to their stabilizing influence on palladium catalysts and the great degree of control they can impart on catalyst reactivity. Both the steric and the electronic features of the ligand have a substantial effect on the reactivity of the catalyst. For example, while electron-rich ligands in palladiumcatalyzed cross-coupling reactions tend to increase the rate of the oxidative addition step, they do so at the expense of the transmetalation and reductive elimination steps. ${ }^{63}$ The opposite is the case for electron-poor ligands. Small molecule studies into steric effects in the direct arylation reaction have demonstrated that if there is too little steric congestion around the metal center, the catalyst forms inactive cyclic dimeric or tetrameric species (palladacycles). ${ }^{64}$ However, if the
ligand is too bulky and the coordination sphere is too congested, the coupling reaction may simply not occur. ${ }^{65}$ This may explain why bidentate bis-phosphine ligands employed for small molecule synthesis have not enjoyed similar success in polymerization reactions. ${ }^{66,67}$ Some of the most highly-performing ligands which are used in DHAP reactions, however, contain heteroatoms (oxygen and nitrogen) capable of labile secondary interactions with the metal center. Such interactions have been shown to favor the catalytically active monomeric (noncyclic) palladium species, while still favoring the CMD step by displacing the more labile of the coordinating atoms ( O or N , depending on the ligand) while at the same time maintaining complexation via the phosphorus atom. ${ }^{68}$

Another synthetic possibility is to use a coordinating solvent such as $\mathrm{N}, \mathrm{N}$-dimethylformamide (DMF) or $N, N$-dimethylacetamide (DMAc) as the primary "ligand" for the reaction. These make for conditions which are highly reactive enough that phosphines are not required, although they are sometimes still used to control reactivity. ${ }^{69-71}$ However, the high speed of the reaction and polarity of the environment lead to complications when this approach is used for DHAP. This is discussed later in this chapter.

### 0.3 Direct Arylation Applied to Polymers

### 0.3.1 Early Examples

Electrochemical and oxidative chemical polymerization techniques were widely in use as a means for synthesizing processable conjugated materials before the advent of transition-metal catalyzed polymerization techniques. ${ }^{72-78}$ However, these methods could not be used to prepare either polymers from asymmetrical building blocks or copolymers with any degree of structural regularity. It was only with the adoption of the Kumada-Corriu and Negishi nickel-catalyzed CC cross-coupling reactions into the field of polymer synthesis that the preparation of conjugated homopolymers with high structural regularity became possible. ${ }^{79,80}$ Around the same time, polymerization techniques based on the Migita-Stille and Miyaura-Suzuki palladium-catalyzed cross-coupling reactions, which had been developed a decade earlier, were adapted primarily to the synthesis of conjugated copolymers. ${ }^{81,82}$

In keeping with history, the first report of a polymer synthesized by Pd-catalyzed direct $\mathrm{C}-\mathrm{H}$ activation both occurred with a series of poly(3-alkylthiophene)s, and took place over a decade after the first studies of the C-H activation of heterocycles by Itahara in the 1980's. This first report of a direct arylation polymerization, by Lemaire and colleagues, consisted of the homopolymerization of 2-iodo-3-alkylthiophene using conditions developed for the Heck reaction. ${ }^{83}$ The monomer was chosen for the reason that it possessed both a carbon-halogen ( C X ) bond and an aryl $\mathrm{C}-\mathrm{H}$ bond, the two functional groups necessary for a direct arylation coupling, with the expectation that it would react upon itself and form a homopolymer. The reaction conditions consisted of palladium acetate $\left(\mathrm{Pd}(\mathrm{OAc})_{2}\right)$ as the catalyst, potassium carbonate $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ as the base and tetrabutylammonium bromide (TBAB) as an additive, using DMF as the solvent. This yielded a polymer with a low number-average molecular weight $\left(\mathrm{M}_{\mathrm{n}}\right)$ of 3 kDa and a regioregularity (RR) of $90 \%$ (Figure 4a). Regioregularity, which indicates the degree of selective couplings and structural uniformity of the polymer, is explained in greater detail later in this chapter. The reaction conditions used were chosen because, at the time, the authors believed that the reaction proceeded by a Heck-like carbo-palladation mechanism.





Figure 4 : A few landmarks in DHAP: a) the first homopolymer; b) the first copolymer; c) the first high molecular weight and high regioregularity polymer; d) the first donor-acceptor copolymer.

It was not until 2010 that two reports demonstrated the true possibility of direct $\mathrm{C}-\mathrm{H}$ bond activation as a viable polymerization technique. In the former report, Kumar and Kumar prepared a range of poly(3,4-alkylenedioxythiophene) copolymers from pairs of different 3,4alkylenedioxythiophene monomers, one of which was dibrominated (i.e. it possessed two $\mathrm{C}-\mathrm{Br}$ bonds) and the other of which possessed two aryl $\mathrm{C}-\mathrm{H}$ bonds. ${ }^{84}$ The reaction used mixed-solvent (DMF/ $\mathrm{H}_{2} \mathrm{O}$ ) conditions mediated by a phase transfer agent (TBAB), with $\mathrm{Pd}(\mathrm{OAc})_{2}$ as the catalyst and sodium acetate ( NaOAc ) as the base (Figure 4b). Although the reaction yield $(\mathrm{Y}=$ $50-60 \%$ ) and molecular weights (ranging from 1.3 to 13.7 kDa ) were low, this study served as
both the first indication that co-polymers were also accessible using DHAP protocols, and that the reaction protocol possessed some tolerance for functional groups.

In the second report on polymerization by $\mathrm{C}-\mathrm{H}$ activation of that year, Ozawa and colleagues returned to the preparation of a poly(3-alkylthiophene) with reaction conditions based on those optimized for small molecule direct arylation. ${ }^{25,41,85-87}$ 2-Bromo-3-hexylthiophene was made to react using a palladacycle catalyst (Herrmann-Beller's precatalyst: trans-bis(acetato)bis[o-(di-otolylphosphino)benzyl]dipalladium(II)) chosen for its high thermal stability, a ligand ( $\mathrm{P}(o-$ $\left.\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ ) with secondary coordination sites and cesium carbonate $\left(\mathrm{Cs}_{2} \mathrm{CO}_{3}\right)$ as the base, at a high monomer concentration in a low-polarity coordinating solvent (tetrahydrofuran, THF) at $125{ }^{\circ} \mathrm{C}$ (Figure 4c). In this way, poly(3-hexylthiophene) (P3HT) was synthesized with a regioregularity and molecular weight similar to those achieved for P3HT obtained with other metal-catalyzed cross-coupling reactions ( $\mathrm{RR}>98 \%, \mathrm{M}_{\mathrm{n}}=31 \mathrm{kDa}, \mathrm{Y}=99 \%$ ). It is worthwhile to note that these reaction conditions (and its derivatives) remain among the best for the preparation of poly(alkylthiophene)s. ${ }^{88-90}$

Kanbara and colleagues published the first push-pull copolymer, prepared from 2,7dibromofluorene and tetrafluorobenzene in anhydrous conditions using $\mathrm{Pd}(\mathrm{OAc})_{2}, \mathrm{~K}_{2} \mathrm{CO}_{3}$ and a new ligand $\left(\mathrm{P}(t-\mathrm{Bu})_{2} \mathrm{Me}^{-} \mathrm{HBF}_{4}\right)$ in the highly polar coordinating solvent DMAc (Figure 4d). ${ }^{91}$ The authors chose the monomers carefully, as tetrafluorobenzene has acidic (and therefore reactive) $\mathrm{C}-\mathrm{H}$ bonds for an arene, increasing the likelihood of the selective $\mathrm{C}-\mathrm{H}$ activation of this monomer. This led to a polymer with high regioregularity and molecular weight $\left(\mathrm{M}_{\mathrm{n}}=32\right.$ kDa ).

Shortly thereafter, the groups of Leclerc, Horie and Scherf independently expanded the DHAP reaction to include the synthesis of thiophene-based donor-acceptor copolymers. ${ }^{92-94}$ Following these reports, the DHAP reaction has been improved upon to make possible the synthesis of a wide range of homopolymers, copolymers, random terpolymers and some branched, porous and 3D polymers (Figure 5). A wide range of substrates is now amenable to polymerization via DHAP, and there are a number of examples of polymers prepared by DHAP which show similar or even better performance in photovoltaic devices and field-effect transistors than analog polymers prepared using the Miyaura-Suzuki and Migita-Stille methods. ${ }^{9,94-97}$ In some cases, certain materials that were not possible with pre-existing techniques are now accessible. ${ }^{98}$

Research in the field, driven by the cost-effective and atom-economic nature of the reaction, indicate that DHAP, still a novelty less than a decade ago, has now found a home as a versatile tool in the polymer chemist's arsenal.


Figure 5 : Examples of the diversity of conjugated polymers which have been synthesized by DHAP: poly(alkylthiophene)s, push-pull copolymers, random terpolymers and 3D polymers.

### 0.3.2 Synthetic Considerations of DHAP

The optical and electronic properties of a given conjugated polymer depend on the polymer's molecular weight (the average chain length) and structural regularity (the presence and prevalence of defects). ${ }^{11, ~ 99-107}$ These factors affect the length and availability of extended $\pi$ conjugation channels, which define the material's key intrinsic properties, such as its bandgap and charge mobility. As such, the synthetic goal of DHAP, and of other transition-metal catalyzed reactions for the preparation of conjugated polymers, is to design a catalytic system which is:

- reactive, in that it provides a large number of monomer-linking reactions and therefore high molecular weights;
- selective, such that reactions occur at the desired positions and the resulting polymer has high structural regularity; and
- robust, so that it yields materials reliably from a wide range of monomers and gives reproducible results.

As with any step-growth polymerization, the molecular weight, determined by the degree of polymerization, of a DHAP reaction obeys the Carothers equation for copolymerizations. This is defined below, in which $x_{n}$ is the degree of polymerization (i.e. the average number of repeating units in a polymer chain), $r$ is the ratio of functional groups on the monomers and $p$ is the extent of the reaction (where 0 is the initiation of the reaction and 1 is reaction completion).

$$
x_{n}=\frac{1+r}{1+r-2 r p}
$$

In order to achieve the highest degree of polymerization (the highest value of $x_{n}$ ) at reaction completion $(p \rightarrow 1)$, it is necessary for $r$ to be the closest possible to 1 . In practical terms, this means that the effective monomer concentrations need to be equal. The word effective is used in this context to highlight the fact that not only should equal numbers of moles of monomers be available in the reaction mixture, but that the monomers' functional groups must both be highly reactive and able to withstand modification or degradation in the reaction conditions. In small molecule couplings, this would be the equivalent of requiring both near-quantitative conversion and product yield. For this reason, the only cross-coupling reaction conditions which can be
applied to polymerizations are those with both high selectivity and high reactivity. ${ }^{108}$ The monomers and growing polymer chains must also remain in solution throughout the reaction and the starting monomeric materials must be highly pure, so as not to distort their true concentrations once in the reaction mixture. These are practical challenges which plague many polymerization techniques.

In the case of DHAP, however, the lack of organometallic or heteroelement-containing functional groups (which would either be prepared pre-polymerization or generated in situ for other transition-metal catalyzed polymerizations) leads to more readily purified monomers, reducing the error on experimental monomer ratios. Most importantly, the fact that DHAP also relies on the reactivity of carbon-hydrogen bonds rather than less stable metal-carbon bonds means that there is less of a risk of functional group loss (for example through thermally-initiated bond cleavage) during the reaction. This would otherwise lead to an unbalancing of the monomer ratios.

Both of these features help to reach the synthetic goal outlined above. However, the risk of functional group loss is by no means absent from DHAP. Although relatively stable, carbonhalogen ( $\mathrm{C}-\mathrm{X}$ ) bonds are susceptible to dehalogenation in all Pd -catalyzed polymerization methods, including DHAP. As these bonds undergo oxidative addition, there exists the possibility that the reverse reaction occurs, and that the previously-halogenated monomer (or polymer chain end) vacates its coordination site on the metal center without coupling to another substrate or retrieving its halogen.

In most reactions, dehalogenation during polymerization leads to the loss of available monomers or, if it occurs on a growing polymer chain, to an unreactive end-group. In the case of MiyauraSuzuki or Migita-Stille polymerizations, this simply prevents further growth of that particular chain. However, in DHAP this phenomenon carries an added risk, as the reduction of a $\mathrm{C}-\mathrm{X}$ bond yields an aromatic $\mathrm{C}-\mathrm{H}$ bond, the very target which the catalytic system is meant to activate. This is discussed in greater detail in the next section.

It is important to note here that the vast majority of DHAP protocols reported to date employ bromine ( Br ) as the halogen. While the reactivity of carbon-halogen bonds increases with heavier halides, so too does the cost of the monomers. For this reason, to the best of our knowledge,
there are no examples of DHAP with a chlorinated monomer, due to the requirement for high monomer reactivity, although chlorides are used in small molecule direct arylation. ${ }^{26,} 109$ However, owing to the high reactivity of the carbon-iodine bond, there are a few examples of highly successful polymerizations (high molecular weight, yield and degree of structural regularity) with iodinated monomers. ${ }^{110}$ Other leaving groups used in small molecule couplings, such as triflates, could also be an option for DHAP, but no such examples have been reported to date.

The copolymerization of electron-rich and electron-deficient substrates, primarily derivatives of aromatic six-membered $\left(\mathrm{C}_{6}\right)$ arenes and five-membered heteroarenes (thiophene- or pyrrolebased heterocycles), is central to the DHAP reaction. The incorporation of each structural motif into the polymer structure is possible with a monomer bearing $\mathrm{C}-\mathrm{X}$ bonds on a $\mathrm{C}_{6}$ aryl moiety or either $\mathrm{C}-\mathrm{H}$ or $\mathrm{C}-\mathrm{X}$ bonds on a thienyl moiety. As such, the coupling reactions of interest in DHAP occur primarily between $\mathrm{C}-\mathrm{X}$ bonds on thiophene- or $\mathrm{C}_{6}$ arene-based monomers, and $\mathrm{C}-$ H bonds on thiophene-based monomers. For the most part, aryl $\mathrm{C}-\mathrm{H}$ bonds are not readily activated in DHAP conditions (although the few exceptions to this are detailed later). The activation of the target $\mathrm{C}-\mathrm{H}$ bonds, the importance of the choice of the monomer which bears the $\mathrm{C}-\mathrm{X}$ bond, and the factors which contribute to or interfere with coupling selectivity are central to the success of DHAP. These topics serve as the basis for the remainder of this chapter.

### 0.4 Defects in DHAP-Prepared Polymers

### 0.4.1 Regioregularity

The challenge of coupling selectivity in polymer synthesis as opposed to analogous transformations of small molecule substrates is that the product any undesired secondary reaction which is present in a cross-coupling catalytic system will exist in the resulting polymer material. In other words, what would be considered an impurity in an organic chemistry reaction becomes covalently incorporated into the polymer chain. As a result, there is a great need for a systematic and generalizable understanding of the requirements with regards to both monomer design and catalytic system in order for a defect-free polymer to be obtained. As explained above, this is a crucial factor in the performance of the polymer in various device applications.

As processable conjugated polymers with fine-tuned electronic properties require complex and often asymmetrical monomers, the question of regioregularity soon arose with DHAP. Already with the study of the first push-pull copolymers synthesized via DHAP, the issue of regioregularity was addressed. ${ }^{91,111}$ Regioregularity ( RR ) is defined as the ratio of desirable $\mathrm{C}-\mathrm{C}$ couplings with respect to all of the observed couplings in a given polymer chain. This value can be obtained from ${ }^{1} \mathrm{H}$ NMR analysis of protons either directly on the repeating unit core or the first methylene group $\left(\mathrm{CH}_{2}\right)$ of the aliphatic side-chains, which are often distinguishable from the rest of the aliphatic signals. By comparing the signals of protons on or near repeating units which coupled in the desired fashion with the other signals resulting from chain ends, dehalogenation, homocoupling or other side-reactions, a relatively precise value of regioregularity can be obtained. This is, however, limited to the error of the analytical method, especially regarding the loss of signal resolution in high-temperature NMR experiments and the solubility of the polymer. Small molecules can also be synthesized in order to attribute correctly the polymer NMR signals to various defects.

The two primary defects observed in DHAP-prepared polymers are homocoupling and $\beta$-defects. As demonstrated with the example of a model poly(3-alkylthiophene) chain shown in Figure 6, homocoupling involves the formation of a $\mathrm{C}-\mathrm{C}$ bond from either two $\mathrm{C}-\mathrm{X}$ bonds or two $\mathrm{C}-\mathrm{H}$ bonds. In the example of the homopolymer shown, this leads to a symmetrical defect in which either two side-chains face towards one another (a "head-to-head" defect, HH ) or away from one another ("tail-to-tail", TT), instead of the desired repeating "head-to-tail" (HT) motif. In a copolymer with an -A-B-A-B- structure, homocoupling leads instead to two adjacent units of the same nature, either $-\mathrm{B}-\mathrm{B}-$ or $-\mathrm{A}-\mathrm{A}-$, depending on the nature of the homocoupling. In the case of a copolymer, this fragments the push-pull architecture of the polymer, interfering with its isoelectronic structure and localizing the frontier molecular orbitals. ${ }^{11}$ For both homopolymers and copolymers, homocoupling can also induce problems related to inter-chain interactions and organization in the solid state, which affect device performance.


Figure 6 : Regular and irregular couplings on a hypothetical poly(3-alkylthiophene) chain.
$\beta$-defects, which can also occur on both homo- and co-polymers, involves the activation and cross-coupling of any $\mathrm{C}-\mathrm{H}$ bond other than the one targeted. In thiophene derivatives, for which this process is most likely, the $\mathrm{C}-\mathrm{H}$ bond nearest to the sulfur heteroatom, termed the $\alpha$-position, is the desired coupling position for steric and electronic reasons. It is also the most reactive, yet the bond at the neighboring $\beta$-position is also somewhat reactive. The reactivity of the $\beta$ proton can also be increased through the addition of various functional groups to the heterocycles, and in some cases coupling at this position can even be favored over the $\alpha$-position through a judicious choice of catalysts, ligands, and additives. ${ }^{47,52,66}$

Bond activation and coupling at the $\beta$ position can potentially lead to a number of structural issues, but the presence of $\beta$-defects is often difficult to identify with any degree of confidence. Many reports only suggest $\beta$-defects as a possible source of the small peaks in NMR spectra which could not be attributed to either homocoupling, chain endings or dehalogenation. While homocoupling is found in other polymerization methods, $\beta$-defects are a challenge unique to DHAP, as there are multiple $\mathrm{C}-\mathrm{H}$ bonds on most monomers, and the catalytic system is specifically tailored to activate these bonds. In contrast, in most transition-metal catalyzed polymerization methods, the monomer is functionalized with an organometallic or heteroelement-containing moiety beforehand, which predetermines the coupling position during polymerization.

As it is a reaction whose intricacies are not yet fully understood, polymers obtained from DHAP are often the subject of rigorous studies of defect formation. However, in many cases, it is difficult to assess absolute regioregularity as there is no perfectly regioregular "reference" polymer. Over the course of the development of the DHAP reaction, polymer NMR and UV-visIR spectroscopic signatures have been compared to those of materials prepared by more wellestablished techniques, primarily Migita-Stille and Miyaura-Suzuki protocols. This was done with the assumption that these reactions give the "correct" polymer structure, and that the conjugated backbones of copolymers prepared using these methods are perfectly alternating. However, there is evidence that this is not, in fact, the case. For example, Miyaura-Suzukisynthesized polymers have been shown to contain the product of $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ homocoupling, while results of the Migita-Stille reaction exhibits the by-products both of $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ and $\mathrm{C}-[\mathrm{M}] / \mathrm{C}-[\mathrm{M}]$ homocoupling. ${ }^{107,112}$ One of the goals of the DHAP reaction, therefore, is to allow for the synthesis of materials with regioregularity higher than (or at least comparable to) the same materials prepared by these better understood yet less environmentally benign techniques.

### 0.4.2 Homocoupling

Both $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ and $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ homocoupling are observed in DHAP-prepared polymers. The former phenomenon requires double $\mathrm{C}-\mathrm{H}$ activation, which is proposed to occur via the reduction of the catalyst, where a $\operatorname{Pd}(\mathrm{II})$ precursor is converted into a reactive $\operatorname{Pd}(0)$ species. In other transition-metal-catalyzed cross-coupling techniques, catalyst activation is known to occur via the oxidation of phosphine ligands or double transmetalation of two $\mathrm{C}-[\mathrm{M}]$ bonds, which is documented with organolithium, organoborane and organostannane compounds. ${ }^{59}$, 113-116 Likewise, in DHAP where no transmetalating agent is present, the oxidative coupling of two CH bonds was proposed as a mechanism for the activation of a $\mathrm{Pd}(\mathrm{II})$ catalyst, especially in polar, phosphine free conditions (Figure 7). As homocoupling depends on the quantity of $\operatorname{Pd}(\mathrm{II})$ in the reaction, a reduction in catalyst concentration has been shown to reduce the rate of homocoupling, as has the addition of a ligand. ${ }^{60}$


Figure 7: A proposed mechanism for the activation of a $\mathrm{Pd}(\mathrm{II})$ catalyst via double $\mathrm{C}-\mathrm{H}$ activation and homocoupling.

In many cases, $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ homocoupling first requires dehalogenation of one of the two substrates, effectively making what appears as a homocoupling defect in the final polymer simply the result of a $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{Br}$ cross-coupling during the reaction. In this case, the synthetic challenge is not homocoupling per se as it is the reductive dehalogenation of a $\mathrm{C}-\mathrm{X}$ bond to a $\mathrm{C}-$ H bond. Dehalogenation is a molecular-weight-limiting side reaction, because the loss of a $\mathrm{C}-\mathrm{X}$ functional group unbalances the monomer ratio necessary for a high molecule weight material, as shown by Carothers' equation. Dehalogenation and homocoupling are both widely documented in DHAP, a few key examples of which are presented below. ${ }^{110, ~ 117-121}$

Homocoupling can be reduced when a phosphine is used. As acetate ligands can bridge two palladium centers, it has been proposed that homocoupling may occur if an aryl group or polymer chain on one metal center is transferred to another metal center which has already metalated the $\mathrm{C}-\mathrm{H}$ bond of a separate substrate. ${ }^{122}$ The addition of a bulky phosphine inhibits this by breaking up catalytic intermediates involving two metal centers. This mechanism has been proposed in other palladium-catalyzed coupling reactions. ${ }^{117}$ In one instance, $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling of dithienyl-benzothiadiazole was not suppressed by either a bulky acid (pivalic acid, PivOH) used together with a carbonate base $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right)$ or with a phosphine $\left(\mathrm{P}(\mathrm{Cy})_{3}\right)$ alongside a bulky base (potassium pivalate) when this unit was copolymerized with
dibromocarbazole (Figure 8). ${ }^{117}$ Rather, it was only when the ligand, acid and carbonate base were used together that this homocoupling defect could be eliminated, as determined by ${ }^{1} \mathrm{H}$ NMR analysis. In these optimized conditions, however, $\mathrm{C}-\mathrm{Br} / \mathrm{C}-\mathrm{Br}$ (carbazole) homocoupling was located. Its prevalence was correlated to the reaction temperature, to the point that it could be largely suppressed (though not entirely eliminated) by reducing the reaction temperature from $120{ }^{\circ} \mathrm{C}$ to $80^{\circ} \mathrm{C}$. This indicates that temperature may play an important role in $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ homocoupling or the dehalogenation side reactions which contribute to it.




Figure 8 : A study of the effect of phosphine, acid and base additives on homocoupling in a copolymer of dibromocarbazole and dithienyl-benzothiadiazole.

In a detailed study of homocoupling in the copolymerization of cyclopentadithiophene and dibromobenzothiadiazole, both $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ and $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ homocoupling were observed in phosphine-free polar conditions with $\operatorname{Pd}(\mathrm{OAc})_{2}{ }^{123}$ This was shown to occur regardless of the steric hindrance (methyl groups) placed in the $\beta$-positions of either or both of the monomers. The conclusion was drawn that homocoupling depends primarily on the catalytic system used rather than on steric features of the monomers near the coupling site. The addition of $\mathrm{P}(\mathrm{Cy})_{3}{ }_{3} \mathrm{HBF}_{4}$ to the reaction reduced the NMR signals associated with homocoupling, but the use of HerrmannBeller's precatalyst (still in polar conditions and without a ligand) suppressed it almost completely. A very small quantity of $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling was still noted. Exchanging Herrmann-Beller's precatalyst for $\mathrm{PdCl}_{2}(\mathrm{MeCN})_{2}$ with the $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ ligand provided high molecular weights, but homocoupling was only suppressed (still with the exception of small C$\mathrm{H} / \mathrm{C}-\mathrm{H}$ coupling signals) when the polar solvent (DMAc) was replaced with the less-polar
solvent THF. In this way, by changing the components of the reaction one at a time, both the polar and non-polar reaction conditions were optimized to produce materials that were almost free of homocoupling. This highlights the importance of the choice of the catalyst and ligand in the context of limiting defect formation for a given set of conditions.

Similarly, in the case of a copolymer of 1,4-dibromotetrafluorobenzene and dithienyldiketopyrrolopyrrole (dithienyl-DPP), $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ but not $\mathrm{C}-\mathrm{X} / \mathrm{C}-\mathrm{X}$ homocoupling was observed independently of the polar reaction conditions used (single solvent or mixed solvent conditions; with a ligand or phosphine-free). ${ }^{124}$ The homocoupling-free polymer could only be obtained in toluene, with $\left.\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}\right)$ and $\mathrm{Cs}_{2} \mathrm{CO}_{3}$, albeit with lower molecular weights.

One study revealed a redox balance of oxidative $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling and reductive chain end dehalogenations (conversion of $\mathrm{C}-\mathrm{X}$ to $\mathrm{C}-\mathrm{H}$ ). ${ }^{110,120}$ This led the authors to propose a homocoupling mechanism by which the substrate which undergoes $\mathrm{C}-\mathrm{H}$ bond cleavage enters the coordination sphere of the metal center trans to the substrate which underwent oxidative addition, rather than adjacent (cis) to it, as shown in the general mechanism in Figure 3. If this occurs, the carboxylic acid may rotate to transfer the proton it has acquired via CMD to the initial oxidative addition substrate, hence the dehalogenation. The carboxylate then moves to another coordination site, freeing up a site for another $\mathrm{C}-\mathrm{H}$ bearing group to undergo $\mathrm{C}-\mathrm{H}$ bond cleavage in the process. This is followed by reductive elimination. It is therefore the two substrates which have undergone $\mathrm{C}-\mathrm{H}$ activation which form the new $\mathrm{C}-\mathrm{C}$ bond, leading to the observed $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling. It is possible that this combined homocoupling/dehalogenation reaction occurs in other DHAP copolymerizations, but has not been identified as such. This study is a good example of an occasion where DHAP experiments have given unique insight into the mechanisms involved in direct arylation, whereas previous small molecule experiments have not.

There are very few cases of DHAP with phenyl derivatives bearing the reactive $\mathrm{C}-\mathrm{H}$ bond, due to its relative inertness. The few examples that have been reported all involve phenyl groups whose $\mathrm{C}-\mathrm{H}$ bonds have been rendered relatively acidic due to the incorporation of multiple fluorine atoms. These include some of the earliest reports on DHAP which involved copolymerizations using tetrafluorobenzene and octafluorobiphenyl, as well as later work on tetrafluorobenzene, 5,6-difluoro-2,1,3-benzathiadiazole, and trifluorobenzene derivatives. ${ }^{91,125-}$

The importance of fluorine in activating the aryl $\mathrm{C}-\mathrm{H}$ bonds of 2,1,3-benzathiadiazole was confirmed by the inability of non-fluorinated 2,1,3-benzathiadiazole and electron-rich 5,6-dialkoxy-2,1,3-benzathiadiazole to polymerize in the same reaction conditions as the fluorinated analog. ${ }^{131}$

Aside from these exceptions, for the most part the $\mathrm{C}-\mathrm{H}$ bonds of $\mathrm{C}_{6}$ arenes are not reactive enough for $\mathrm{C}-\mathrm{H}$ activation. If a polymerization requires coupling directly on an arene, this unit is brominated. ${ }^{10,} 108$ There are two advantages to this, as shown in Figure 9. Firstly, if dehalogenation were to occur, the $\mathrm{C}-\mathrm{X}$ bond would be replaced by an unreactive aryl $\mathrm{C}-\mathrm{H}$ bond, rather than a highly reactive heteroaryl $\mathrm{C}_{\alpha}-\mathrm{H}$ bond. This eliminates the risk of cross-coupling between the new $\mathrm{C}-\mathrm{H}$ bond of a dehalogenated unit with a still-halogenated unit, which would lead to a homocoupling defect. Instead, the polymer chain end would simply no longer be able to grow from that end, limiting molecular weights but not causing defects.


Figure 9 : Potential outcomes of the dehalogenation of halogenated arenes and heteroarenes.

Secondly, there is often an intrinsically good selectivity towards the $\alpha$-position of unsubstituted thiophene substrates. ${ }^{12,53,117,132}$ The presence of a halogen in the $\alpha$-position of a thiophene unit, on the other hand, may have an electronically activating effect on the adjacent $\mathrm{C}_{\beta}-\mathrm{H}$ bond, making it more susceptible to the formation of $\beta$-defects, an observation which is discussed in the following section. However, by placing the halogen on a $\mathrm{C}_{6}$ arene, it is unlikely that the adjacent aryl $\mathrm{C}-\mathrm{H}$ bonds are activated due to their high activation energy, unless directing groups or highly electron-withdrawing moieties are involved. ${ }^{57,62,132}$

### 0.4.3 $\boldsymbol{\beta}$-Defects

The issue has arisen over the selectivity of the concerted metalation-deprotonation (CMD) transition state, which determines the selectivity of $\mathrm{C}-\mathrm{H}$ bond coupling. There are often multiple reactive $\mathrm{C}-\mathrm{H}$ bonds on a given thiophene monomer, and if the undesired bond (the $\mathrm{C}_{\beta}-\mathrm{H}$ bond) were to be activated, it would generate a covalently-bound structural defect in the resulting polymer. It is understood that this may lead to a disruption in both the $\pi$-conjugation of the polymer and the supramolecular organization (packing) of the material in the solid state, factors which contribute to reduced performance in organic electronic devices. ${ }^{12,106,133}$

The issue of selectivity poses a challenge primarily for polymers requiring the coupling of thiophene-flanked and fused thiophene monomers. Thiophene-based substrates are thought to be susceptible to unselective couplings given the non-negligible reactivity of $\mathrm{C}_{\beta}-\mathrm{H}$ bonds at the 3position of the heterocycle. In the example given in Figure 10, there are three available protons on dithienyl-DPP and two on a 3 -alkylthiophene monomer. The $\alpha$-proton is the desired coupling position, as a covalent $\mathrm{C}-\mathrm{C}$ with a neighboring repeating unit at this location maximizes both conjugation and co-planarity along the polymer backbone. The $\beta$-proton, if abstracted, would generate a $\beta$-defect, leading to a disruption in both the $\pi$-conjugation of the resulting polymer and the supramolecular organization of the material. Together, these factors contribute to reduced performances in organic electronic devices. ${ }^{12}$ The $\gamma$-proton is adjacent to the DPP core and, as such, is most likely inaccessible to due steric effects. ${ }^{96,134,135}$ In the case of fusedthiophene units described above, the $\gamma$ proton is absent.


Bis-functionalized thiophene monomer


Non-halogenated thiophene-flanked monomer


Non-halogenated fused thiophene monomer


Halogenated thiophene-flanked monomer


Halogenated fused thiophene monomer

Figure 10 : Examples of $\alpha, \beta$, and $\gamma$ aromatic $\mathrm{C}-\mathrm{H}$ bonds on thiophene-based monomers $(\mathrm{R}=$ solubilizing side-chain).

In theory, the activation of a $\mathrm{C}_{\beta}-\mathrm{H}$ bond can lead to three possible events during a DHAP reaction:

- if the $\mathrm{C}_{\beta}-\mathrm{H}$ bond is activated instead of the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond on a chain-end repeating unit, a "bend" could be introduced into the polymer chain, disrupting $\pi$-conjugation and introducing disorder to the polymer;
- if the $\mathrm{C}_{\beta}-\mathrm{H}$ bond is activated in addition to the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond(s) on a unit (i.e. which is already incorporated into the polymer chain), another repeating unit or new polymer chain could grow out of the previous chain in a process termed $\beta$-branching;
- if a $\beta$-branched structure involves the activation of $\mathrm{C}_{\beta}-\mathrm{H}$ bonds on two different polymer chains, a network structure may be formed; this is termed cross-linking.

Cross-linking is statistically the least likely of the three events, and is difficult to characterize. It is thought that cross-linking would lead to an insoluble material. Another observation whose
source is often unclear is that of low reaction yield. Low yield may be due to unreacted monomers removed during polymer washing, which would be indicative of a catalyst which has become deactivated or is not reactive enough. On the contrary, low yield may be due to an overly reactive catalyst, which could interfere with polymer integrity towards the end of the reaction by forming cross-linked structures via the activation of available $\mathrm{C}_{\beta}-\mathrm{H}$ bonds when the reaction mixture grows gelatinous. It is also important to note here that, aside from leading to a loss of valuable material, the formation of insoluble products is of practical concern from an industrial perspective as they are difficult to remove from the desired polymer on a large scale. ${ }^{136}$

This uncertainty is highlighted by a study of the copolymerization of a range of $\mathrm{C}-\mathrm{H}$-bearing bithiophenes or thiophene-flanked electron-poor units primarily with brominated $\mathrm{C}_{6}$ arenes. ${ }^{90,137}$ It was shown that by controlling reaction time, high molecular weights can be achieved while maintaining high regioregularity in low-polarity conditions (toluene or THF, Figure 11). The polymers obtained when the reaction is stopped at a precise time are shown to have comparable or slightly superior properties to Miyaura-Suzuki-prepared analogs with respect to molecular weights, NMR and UV-visible spectra and organic field effect transistor (OFET) performance. However, when the same polymers are left to react for even slightly too long, the material precipitates out of solution and becomes impossible to characterize. This could be attributed either to $\beta$-branching (and potentially cross-linking) or to over-polymerization, in which materials are formed with simply too high molecular weights for solubility to be maintained.


Figure 11: The successful polymerization of a range of unprotected thiophene-flanked units in low-polarity time-controlled conditions.
$\beta$-branching towards the end of a reaction can be rationalized by the fact that as the polymer chain lengthens and monomers are consumed, the number of available $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds in solution diminishes, whereas the number of $\mathrm{C}_{\beta}-\mathrm{H}$ bonds remains constant. In this way, the ratio of available $\beta$ versus $\alpha \mathrm{C}-\mathrm{H}$ bonds becomes very high, increasing the likelihood that, even if activation of a $\mathrm{C}_{\beta}-\mathrm{H}$ bond is not kinetically favored, some of them may react. However, these $\mathrm{C}_{\beta}-\mathrm{H}$ bonds are found along the backbone of the polymer chain surrounded by long linear and branched solubilizing side-chains, which puts them in a very sterically congested environment. This makes them far less kinetically accessible than when they are found on unreacted monomers. ${ }^{95,105}$

Over-polymerization may be explained by the principle that, since DHAP is a step-growth polymerization and relies on the linking of smaller chains to form larger ones, very long chains are formed very rapidly at the end of the reaction. ${ }^{91}$ The molecular weights are essentially doubled, which would explain why an otherwise well-defined and soluble material could suddenly become insoluble.

One study demonstrated the likelihood of $\beta$-branching (and not over-polymerization) being a source of polymer insolubility by placing excessively highly-solubilizing side chains on the monomers of a DPP- and thiazole-based copolymer for which unselective $\alpha / \beta$-couplings were suspected. ${ }^{138}$ The tritriacontan-17-yl butyrate chains used were sufficiently solubilizing to make linear high molecular weight samples of the polymer soluble even in hexane. Nevertheless, it was found that, even with these side chains, a portion of the polymerization product was completely insoluble following standard reaction conditions. The authors proposed that branching structures, and not simply very high molecular weight polymers, were the reason for this.

As this phenomenon likely causes polymer insolubility, one of the major difficulties in addressing $\beta$-branching and its possible sources is that there is virtually no spectroscopic evidence of it. In some studies, all small signals in NMR spectra have been successfully attributed to various homocoupling and dehalogenation defects. This has led some to believe that $\beta$-branching is not an issue in certain cases, and that every spectral discrepancy between a DHAP-prepared polymer and a reference Migita-Stille or Miyaura-Suzuki sample can be
rationalized by homocoupling alone., ${ }^{9,12}$ Other reports have proposed that branching defects may be indistinguishable from homocoupling defects in NMR and UV-Vis spectra. ${ }^{96,121}$

There are two select cases, both involving P3HT, in which it was possible to quantify the degrees of branching from NMR experiments using model compounds to label spectroscopic signals. ${ }^{66,}$ ${ }^{133}$ In these experiments, it was shown that $\beta$-branching in P3HT can be promoted or suppressed, depending on the reaction conditions used. By screening various precatalysts, bases, additives and concentrations of the reagents in DMAc, it was found that by using $\mathrm{PdCl}_{2}$ without a ligand but with added potassium fluoride (KF), a $40 \%$ branched structure could be obtained. However, branching was completely inhibited when $\mathrm{Pd}(\mathrm{OAc})_{2}$ was used in the presence of $\mathrm{K}_{2} \mathrm{CO}_{3}$ and a bidentate nitrogen-based ligand (either 2,2'-bipyridine or tetramethylethylenediamine), although molecular weights were low. In another study, it was shown that through meticulous control of the reaction conditions $\left(\mathrm{Pd}(\mathrm{OAc})_{2}, \mathrm{~K}_{2} \mathrm{CO}_{3}\right.$ and a carboxylic acid in DMAc) and the use of a bulky tertiary carboxylic acid (neodecanoic acid or NDA, see Figure 12 for structure) rather than the smaller tertiary acid (pivalic acid or PivOH, $\left(\mathrm{CH}_{3}\right)_{3} \mathrm{CCOOH}$ ) used in small molecule reactions, $\beta$-branching could be entirely eliminated. ${ }^{25,139,140}$

In many palladium-catalyzed cross coupling reactions, oxidative addition is the rate limiting step, whereas in the Migita-Stille reaction, transmetalation has been observed to be the slowest event of the catalytic cycle. ${ }^{54,141}$ In most cases, the breaking of the $\mathrm{C}-\mathrm{H}$ bond is considered to be the rate-limiting step of the direct arylation reaction. As a result, $\mathrm{C}-\mathrm{C}$ coupling selectivity is believed to be determined by the kinetic accessibility of the various aryl C-H bonds. ${ }^{132}$ Small molecule experiments demonstrate that the use of electron-poor ligands increases the kinetics of the reaction by increasing the electrophilicity of the metal center, favoring metalation of the (hetero)aryl group during CMD. ${ }^{49,142,143}$ The best performing ligands in DHAP, on the other hand, tend to be electron-rich and bulky, implying that their performance stems from the fact they decrease reaction kinetics, which would increase selectivity. A number of studies have shown that by increasing steric bulk around the palladium, more well-defined materials could be obtained. This was noted with studies into the steric bulk of the carboxylate additive, solvent and ligand, as described later in the sections reserved for each component of the reaction mixture.

It was also demonstrated that a similar beneficial steric effect can be obtained when the steric bulk originates from the $\gamma$ position on the thiophene undergoing coupling. ${ }^{89,144}$ In the study of a
polythiophene homopolymer, PQT12, the solubilizing linear $\mathrm{C}_{12}$ chain in the $\gamma$ position of the outer thiophene units of the quaterthiophene monomer provide sufficient steric bulk to prevent activation of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond (Figure 12). While NDA was a necessary additive for the PQT12 synthesized from monomer $\mathbf{A}$ to be well-defined, in the case when monomer $\mathbf{B}$ was used, NDA was not necessary. This indicated that the monomer itself may occupy a similar role to the acid of increasing steric bulk around the catalytic center and suppressing activation of the $\beta$ proton on the thiophene units. In this particular study, the symmetric nature of the monomers ensured that the defects observed were entirely due to $\mathrm{C}_{\beta}-\mathrm{H}$ activation, as any homocoupling side reaction would lead to the same coupling motif as a standard $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{Br}$ cross-coupling.


A without acid:

- lower molecular weight - higher bandgap

A with NDA:

- higher molecular weight - lower bandgap

B without acid:

- higher molecular weight
- lower bandgap
- NDA not necessary

Figure 12: Two synthetic pathways to the preparation of PQT12: when monomer A is used, a bulky carboxylic acid (NDA) is necessary for achieving a well-defined polymer, while when monomer B is used, steric hindrance originates from the $\gamma$-position of the monomer and NDA is not needed.

The first study of the possibility of $\beta$-defects on thiophene derivatives involved the copolymerization of dibromofluorene with bithiophene using $\mathrm{Pd}(\mathrm{OAc})_{2}, \mathrm{~K}_{2} \mathrm{CO}_{3}$ and PivOH in DMAc. ${ }^{111}$ This reaction yielded an insoluble material, potentially indicating unselective $\mathrm{C}-\mathrm{H}$ activations leading to branched structures. In order to test this, the authors performed a small molecule experiment on the coupling of 4-bromotoluene with bithiophene using the same polymerization conditions (Figure 13). While the coupling product of two $\mathrm{C}_{\alpha}-\mathrm{H}$ activations was the primary product, following by single $\mathrm{C}_{\alpha}-\mathrm{H}$ couplings, an unquantified trace amount of branched structures was also identified in the crude reaction mixture, leading to the theory that $\beta$ branching on thiophene units during polymerization leads to the insoluble polymerization
product. To counter this, the authors replaced bithiophene with $3,3^{\prime}, 4,4^{\prime}$ 'tetramethylbithiophene, in order to remove other potentially activated aromatic $\mathrm{C}-\mathrm{H}$ bonds. This approach with modified bithiophene was then successfully extended to a range of copolymers using various brominated monomers.


Figure 13 : Evidence for potential $\beta$-defects from a small molecule experiment.
Following this study, the blocking of $\beta$-positions with methyl groups and longer aliphatic sidechains became a common synthetic strategy to overcome unselective coupling on thiophene derivatives. Although this does lead to more well-defined materials, it also often interferes with the co-planarity of repeating units, leading to non-optimal $\pi$-conjugation along the polymer backbone and diminished polymer packing in the solid state. ${ }^{111,123,137,145}$ Despite this, these results have indicated that $\beta$-coupling is an issue in the synthesis of certain conjugated polymers via $\mathrm{C}-\mathrm{H}$ activation, and that the removal of such bonds makes available polymers which may otherwise be otherwise inaccessible using DHAP.

The coupling at undesired positions is not usually considered problematic for $\mathrm{C}_{6}$ aryl derivatives, whose $\mathrm{C}-\mathrm{H}$ bonds are less reactive as indicated by a higher activation barrier in the CMD transition state. There are, however, a few examples which indicate the presence of branching on nitrogen-containing fused arene groups. In a study of the copolymerization of tetramethylated bithiophene and dibromocarbazole with phosphine-free conditions in DMAc, branching was suggested to be a cause for loss of polymer solubility when it was observed on carbazole units of low molecular weight polymer samples in MALDI-TOF mass spectrometry analyses. ${ }^{111,125,137}$ This observation is supported by the fact that $\mathrm{C}-\mathrm{H}$ bonds at the 3- and 6- positions of carbazole are highly reactive under certain small molecule direct arylation conditions. ${ }^{146}$

DFT calculations of the CMD transition state have been able to predict $\mathrm{C}-\mathrm{H}$ bond reactivity and selectivity of coupling between different thiophenes in small molecule competition reactions. The calculated free energy of activation $\left(\Delta G^{\ddagger}\right)$, which represents kinetic accessibility of $\mathrm{C}-\mathrm{H}$ bonds to reach a CMD transition state geometry, correlates with experimental reactivity vis-à-vis small molecule arylation kinetics. ${ }^{57,132}$ For this reason, DFT calculations have been used to address the issue of $\alpha$-versus $\beta$-selectivity of the $\mathrm{C}-\mathrm{H}$ activation of thiophene-flanked units in DHAP.

The thiophenes flanking electron-poor and electron-rich units are thought to have good intrinsic selectivity for the $\alpha$ - versus $\beta$-selectivity vis-à-vis $\mathrm{C}-\mathrm{H}$ bond activation. ${ }^{12,53,117,132}$ Small molecule experiments in polymerization reaction conditions have confirmed this, in one case showing that for a thiophene-flanked benzothiadiazole substrate, coupling at the $\beta$-position is not observed with stoichiometric or excess quantities of 4-bromotoluene or bromocarbazole in polymerization conditions. ${ }^{12}$ This indicates that on an electron-poor thiophene, coupling is inherently selective for the $\alpha$ position, and blocking of the $\beta$ position, with an alkyl side-chain for example, is not necessary. Surprisingly, some coupling at the $\gamma$ position is observed in these small molecule experiments, although this is only when a large excess of the brominated coupling partner is present, showing that this position is not readily activated. ${ }^{12}$ When the $\beta$ position of dithienyl-benzothiadiazole is blocked, coupling is not observed at the $\gamma$ position. This is corroborated by DFT calculations, which show that the $\mathrm{C}_{\gamma}-\mathrm{H}$ bond has a much higher CMD transition state energy than the $\alpha$-position. ${ }^{117}$

However, following experimental observations correlating the location of the halogen to the quality of the polymerization product, the activating effect of bromine in the $\alpha$-position of a thiophene derivative on the adjacent $\mathrm{C}_{\beta}-\mathrm{H}$ bond was placed under scrutiny. This effect was demonstrated with DFT calculations which compare the CMD transition state energies of $\mathrm{C}_{\beta}-\mathrm{H}$ bonds of various halogenated and non-halogenated thiophene substrates. ${ }^{90,96,147}$

Experimentally, electron-poor units in particular showcase this. In the copolymerization of an electron-poor arene with an electron-poor thiophene-flanked DPP, monomer pairs in which the arene is brominated lead to higher molecular weights and more well-defined polymers than the alternative (Figure 14). ${ }^{121,124,148,149}$ This may be due to either instability of the $\mathrm{C}-\mathrm{Br}$ bond on non-alkylated thiophene derivatives or $\beta$-branching. For instance, $\beta$-alkylated thiophene
derivatives appear less prone to dehalogenation than non- $\beta$-alkylated thiophenes. ${ }^{88}$ In some cases, insoluble or ill-defined material is obtained when the dithienyl-DPP unit is brominated. ${ }^{96}$ In other instances, when the dithienyl-flanked unit is brominated, better results are obtained when the $\beta$-position is blocked with an alkyl group than when it is not. ${ }^{90,150}$

Beta-protected brominated monomers

- Higher
molecular weight
- Lower bandgap
- Fewer structural defects


[Pd]


Unprotected brominated monomers

- Lower molecular weight - Higher bandgap
- More structural defects

[Pd]
$\mathrm{P}(t-\mathrm{Bu})_{2} \mathrm{Me}^{-} \cdot \mathrm{HBF}_{4}$
$\mathrm{PivOH}, \mathrm{K}_{2} \mathrm{CO}_{3}$
THF, $100^{\circ} \mathrm{C}$
[Pd]
$\xrightarrow{\substack{[\mathrm{Pd}] \\ \mathrm{PivOH}, \mathrm{Cs}_{2} \mathrm{CO}_{3} \\ \mathrm{P} \text { (o-OMeC } \\ \hline}}$
Toluene, $120^{\circ} \mathrm{C}$

[Pd]

$\mathrm{P}\left(\mathrm{o}-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ $\xrightarrow{\mathrm{PivOH}, \mathrm{Cs}_{2} \mathrm{CO}_{3}}$
Toluene, $110^{\circ} \mathrm{C}$


Figure 14 : Examples which demonstrate the importance of the location of the bromine.

The exceptions, for which brominated electron-poor thiophene-flanked units do lead to highly regioregular and high molecular weight materials, are marked by co-monomers with highly reactive $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds. For example, dibromodithienyl-DPP was successfully copolymerized with co-monomers such as bithiazole, 3,4-dicyanothiophene, thienopyrroledione (TPD), 3,4propylenedioxythiophene and (E)-1,2-bis(3,4-difluorothien-2-yl)ethene. ${ }^{96,135,138,151,152}$ In the
latter example (shown in Figure 15), the copolymerization of the non-fluorinated analog was not successful, further indicating the importance of highly reactive $\mathrm{C}-\mathrm{H}$ bonds on the co-monomer partner for a successful copolymerization. These results suggest that the underlying challenge of obtaining a polymer free of $\beta$-defects is to have a large enough gap in the $\Delta G^{\ddagger}$ values of the $\alpha$ bond of the target $\mathrm{C}-\mathrm{H}$-bearing monomer and the $\mathrm{C}_{\beta}-\mathrm{H}$ bond of the halogen-bearing monomer. ${ }^{90}$, ${ }^{96}$ This issue is, of course, eliminated if there are no available $\beta$-protons on the halogenated monomer.


Figure 15: An example of a $\mathrm{C}-\mathrm{H}$ bearing monomer successfully copolymerized with dibrominated dithienyl-diketopyrrolopyrrole.

A study of donor-acceptor copolymers used this proposition to explain the dramatic differences in copolymers obtained from brominated electron-rich units versus brominated electron-poor units. ${ }^{96}$ In this study, polymers prepared by DHAP from brominated electron-rich units and $\mathrm{C}-\mathrm{H}-$ bearing electron poor units could be obtained with optical and charge transport properties similar to Migita-Stille-prepared analogs. However, the same polymers prepared with the halogens on the electron-poor substrates displayed substantial differences in optical properties and critical reductions in charge transport compared to the Migita-Stille reference polymers and the DHAP polymers prepared via the other synthetic pathway. Larger gaps of $\Delta G^{\ddagger}$ between the $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds on the electron-poor monomer and the $\mathrm{C}_{\beta}-\mathrm{H}$ bond adjacent to the halogen on the electron-rich monomer were observed from DFT calculations. This would theoretically lead to more selective couplings between the monomer pair, which correlated to the experimental observation that more regioregular materials were obtained from this synthetic route. Reciprocally, much smaller gaps in activation energy were found in the case where the electron-poor unit was brominated, which corroborated the ill-defined materials obtained from this route.

### 0.5 Considerations for a Successful Polymerization

### 0.5.1 Optimizing Reaction Conditions

Beyond the optimization of reaction conditions to maximize molecular weight while limiting the formation of defects, there remains a more fundamental challenge: to locate generalized polymerization conditions which make the greatest number of polymers accessible without the need for lengthy optimization for every co-monomer pair.

Achieving high polymer regioregularity involves a balance between reactivity and selectivity. In general terms, control of the reaction is kinetic: by lowering the reaction temperature, using a less reactive catalyst at a lower concentration, performing the reaction in a less-coordinating solvent and increasing the steric bulk around the metal center (with the ligands and/or the carboxylic acid), polymerization is slower but the resulting material often has fewer defects. ${ }^{90,96,}$ ${ }^{105,147}$ For example, the reaction is observed to be much faster with polar coordinating solvents (which act as ligands on the palladium catalyst) than in a less-polar and more weakly coordinating environment with bulkier ligands. ${ }^{108}$ Higher temperatures lead to faster reactions, but often more insoluble material, whereas lower temperatures reactions lead to better-defined polymer structures over a longer period of time. ${ }^{153}$ Similarly, microwave heating will accelerate the reaction, but may lead to insoluble material, possibly due to unselective couplings. ${ }^{154,155}$ Examples of each of these are given in the following section.

Nevertheless, a number of examples exist for polymers which are virtually free of structural defects. ${ }^{9,88-90,120,137,156,157}$ Currently, the best reaction conditions for a given monomer or pair of co-monomers is determined through their careful optimization and evaluation of their impact on polymer weight and regioregularity. In DHAP, the variables to be screened are:

- the solvent (polar versus non-polar, strongly coordinating versus weakly coordinating) and the concentration of the monomer(s) in it;
- the ligand (which is predominantly a phosphine), for its electronic and steric features and its concentration;
- the precatalyst (i.e. the $\operatorname{Pd}(\mathrm{II})$ or $\operatorname{Pd}(0)$ complex or salt) and its concentration (the number of molar equivalents compared to the monomers);
- the primary additives (the carbonate base and, in some cases, the carboxylic acid) as well as any other reaction promoters, such as phase transfer agents; and
- the heating source (oil bath versus microwave heating).

A short section is devoted to each of these features, outlining the trends and recent observations on the impact of each aspect of the reaction with regards to the quality of the resulting polymer.

### 0.5.2 Solvent

Generally speaking, the most widely-used reaction conditions for DHAP have evolved from two series of conditions whose differences stem primarily from the polarity of the solvent used. ${ }^{105,158}$ A highly reactive system in polar solvents was derived from small molecule coupling experiments, while a lower-polarity system was initially optimized for the high molecular weight and regioregular synthesis of P3HT. ${ }^{25,41,53,85,159}$ The particularities of these conditions are as follows:

- High polarity conditions: a highly polar coordinating solvent (e.g. DMAc, DMF, N-methyl-2-pyrrolidone [NMP]) is used (sometimes in a mixture with a lower polarity solvent), primarily with $\mathrm{Pd}(\mathrm{OAc})_{2}$ as the precatalyst, $\mathrm{K}_{2} \mathrm{CO}_{3}$ or $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ as the base, potentially alongside a bulky carboxylic acid ( PivOH , NDA or 1-adamantanecarboxylic acid $[\mathrm{AdCOOH}]$ ), and either without phosphines or in the presence of a bulky, monocoordinating ligand (e.g. $\mathrm{P}(t-\mathrm{Bu})_{2} \mathrm{Me}^{2} \mathrm{HBF}_{4}$ or $\left.\mathrm{P}(\mathrm{Cy})_{3}\right)$
- Lower polarity conditions: a less polar solvent (THF, toluene or dioxane) is used, often with Herrmann-Beller's catalyst or $\mathrm{Pd}_{2} \mathrm{dba}_{3}, \mathrm{Cs}_{2} \mathrm{CO}_{3}$ as the base with the occasional addition of PivOH or NDA, alongside a ligand possessing secondary coordination sites $\left(\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}\right.$ or $\left.\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}\right)$.

Highly polar conditions are more reactive, as the solvent molecules stabilize the catalyst but coordinate weakly to it compared to a phosphine ligand, while in less polar conditions a phosphine restricts catalyst reactivity to a certain degree due to steric effects. ${ }^{65}$ Due to this difference in reactivity, polymerization in high polarity conditions usually is conducted at a lower temperature $\left(<100^{\circ} \mathrm{C}\right)$ and for a shorter time than polymerization in the lower-polarity conditions ( $>100{ }^{\circ} \mathrm{C}$ ). In particular, higher temperatures are needed to activate Herrmann-

Beller's catalyst when the latter is used as the source of Pd. In some cases, the higher reactivity of the catalytic system is trumped by the lower solubility of many conjugated polymer in highly polar solvents. As a result of their long aliphatic side-chains, growing polymer chains remain in solution more readily in lower polarity solvents, leading to slower chain growth, but ultimately longer polymer chains and higher molecular weights. ${ }^{91,127}$

It has been demonstrated that when a polar solvent is used, a balance is needed between the favorable steric hindrance the solvent molecule brings to the catalyst and the facility of the solvent to coordinate the metal center. In one study, various amide solvents which differed with respect to the alkyl and aryl groups on both the N atom and the carbonyl were screened for the synthesis of P3HT. ${ }^{160}$ The highest molecular weight and regioregularity could be achieved with short alkyl-substituted amide solvents ( $\mathrm{N}, \mathrm{N}$-dimethylpropionamide and $\mathrm{N}, \mathrm{N}$-diethylacetamide) than with the more commonly used DMF and DMAc, indicating that more sterically hindered amide solvents could still contribute to a reactive catalytic system while suppressing some undesired couplings. However, longer alkyl groups or bulkier cyclic groups limited reactivity, most likely due to steric effects. Such use of a highly polar amide solvent with steric hindrance ( $\mathrm{N}, \mathrm{N}$-diethylpropanamide) has since been applied to the synthesis of high molecular weight bithiazole copolymers with accessible $\mathrm{C}_{\beta}-\mathrm{H}$ bonds. ${ }^{161}$ Homocoupling side-reactions often observed in highly polar conditions can often be at least partly suppressed with the addition of an alkylated phosphine ligand. ${ }^{94,123}$ The steric bulk reduces the reactivity of the system, however, which can also lead to lower molecular weight polymers. ${ }^{105,111,140,153}$ This is discussed in the following section on ligands.

Solvent mixtures have been used with the goal of combining the polymer-solubilizing effect of a less polar solvent with the catalyst-ligating effect or additive solubilizing effect of another, more polar solvent. This approach has been used for phosphine-free polymerizations, although bromoarene homocoupling was observed when a DMAc/toluene system was used. ${ }^{117}$ In this case, homocoupling was suppressed when a bulky phosphine ligand $\left(\mathrm{PCy}_{3}\right)$ was added, as described earlier. In the polymerization of DPP with 1,4-dibromotetrafluorobenzene, a ligandfree mixed solvent (toluene/DMAc) system provided the highest molecular weight polymers, but with observed $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling, while a less polar system led to a polymer without homocoupling defects, but with lower molecular weight. ${ }^{124}$

Highly polar media have yielded a number of high molecular weight polymers in short reaction times. ${ }^{93,94,111,154,162}$ However, the high reactivity of polar, phosphine-free conditions may lead to a higher degree of homocoupling and dehalogenation than lower polarity systems. ${ }^{123}$ For example, $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling of benzodithiophene (BDT) units was observed even at short reaction times in the preparation of a terpolymer from BDT, dibromobenzothiadiazole and dibromobenzotriazole (Figure 16). ${ }^{163}$ Spectroscopic discrepancies between the material obtained from a DHAP protocol and a Migita-Stille-prepared reference polymer indicated substantial structural defects. When the reaction was undertaken in THF, a lower-polarity solvent, a polymer with properties more similar to the reference material was obtained.


Figure 16 : The synthesis of a terpolymer in high polarity conditions.
Similarly, dehalogenation of 1,4-dibromotetrafluorobenzene and $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling of dithienyl-DPP has also been observed in DMAc/toluene mixed solvent systems for the copolymerization of these two monomers. ${ }^{164}$ When these same monomers were reacted in lower polarity conditions $\left(\mathrm{Pd}_{2} \mathrm{dba}_{3}, \mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}, \mathrm{Cs}_{2} \mathrm{CO}_{3}\right.$ and PivOH in toluene), the polymer produced displayed no observable homocoupling defects, although the molecular weight was reduced considerably ( $16.5 \mathrm{~kg} / \mathrm{mol}$, compared to $30 \mathrm{~kg} / \mathrm{mol}$ in high-polarity conditions).

One possible explanation for the decreased molecular weights observed in certain low-polarity conditions is polymer end-capping with solvent molecules. The $\mathrm{C}-\mathrm{H}$ bond activation of aromatic solvents was observed in the preparation of a copolymer of naphthalene diimide (NDI) and bithiophene in toluene. ${ }^{9,165}$ It was shown that polymer molecular weights were positively correlated to the starting monomer concentration: increasing the monomer concentration incrementally from 0.05 M to 0.5 M consistently improved polymer number average molecular
weights from 9 to $35 \mathrm{~kg} / \mathrm{mol}$. From the observation that NDI chain-ends were almost exclusively capped with tolyl groups, it was proposed that increased monomer concentrations lead to an increased rate of step growth between monomer and oligomers, while lower monomer concentrations favor the kinetics of coupling reactions between the brominated arene with the solvent. Polymerization in a solvent with less reactive $\mathrm{C}-\mathrm{H}$ bonds (chlorobenzene) led to higher molecular weight materials. However, it was also observed that the use of non-aromatic solvents (DMAc and THF) favors the nucleophilic substitution of chain-end bromine with hydroxyl or pivalate groups from the acid or base additive. ${ }^{166}$

A further study of the susceptibility of a range of aromatic solvents to $\mathrm{C}-\mathrm{H}$ activation and their effect on the molecular weight of NDI copolymers demonstrated that the solvent with the least accessible aryl $\mathrm{C}-\mathrm{H}$ bonds (mesitylene) gave the highest molecular weight polymers ( $58 \mathrm{~kg} / \mathrm{mol}$, see Figure 17). Likewise, the least-substituted solvents (toluene and 1-chloronaphthalene) gave the lowest molecular weight materials ( 9.0 and $8.1 \mathrm{~kg} / \mathrm{mol}$, respectively). The role of solvent end-capping in limiting molecular weights in this study was confirmed with small molecule coupling experiments of a brominated NDI unit under polymerization conditions. In the absence of a partner co-monomer with available $\mathrm{C}-\mathrm{H}$ bonds, the NDI unit undergoes coupling with an aromatic solvent molecule. The best solvents for polymerization reacted least readily with NDI, while the solvents which afforded the lowest molecular weight polymers coupled with NDI in high yield.

$\qquad$


Figure 17 : The impact of aromatic solvent end-capping on polymer molecular weight.

The first copolymer synthesized by DHAP used a mixed-solvent (DMF/ $\mathrm{H}_{2} \mathrm{O}$ ) system. However, later studies which reported obtaining P3HT with very high regioregularity and molecular weight using dry solvents in inert conditions and at high temperature began a trend of performing DHAP in completely anhydrous and pressurized conditions (a superheated solvent is a closed flask). ${ }^{85,91}$ This was considered to be a necessity to ensure the proper functioning of the catalytic system until recently, in which biphasic conditions (toluene/ $\mathrm{H}_{2} \mathrm{O}$ ) were used to prepare a wide range of donor-acceptor copolymers with results comparable to or better than those in anhydrous and airfree conditions (Figure 18). ${ }^{167}$ This approach bears a number of advantages. Most notably, it removes the need for dry solvents and an inert atmosphere as well as increases the accessibility of the base due to the increased solubility of many carbonate salts in water. As the growing polymer chain is only soluble in the organic phase, the reaction occurs at the liquid-liquid interface. In order to favor this, a phase transfer agent was also added, in a similar fashion to the Miyaura-Suzuki cross-coupling reaction. Results were dependent on the nature of the phase transfer agent: tetrabutylammonium chloride provided better results than the bromide analog. Also similar to Miyaura-Suzuki protocols was an observation that debromination occurs more readily in biphasic conditions. This could be explained by the greater availability of protons (from water) than in pure organic solvents.


Figure 18 : Isoindigo-based copolymers prepared in biphasic DHAP conditions.

### 0.5.3 Ligand

As described earlier, the choice of ligand depends on the polarity of the solvent used. From the earliest studies involving low-polarity solvents, it was observed that $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ and $\mathrm{P}(o-$ $\left.\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ give the highest molecular weight and regioregularity polymers in low polarity
conditions, while in higher polarity conditions with coordinating solvents, the reaction can proceed either with a tri(alkyl)phosphine or without any ligand at all.

The incorporation of tri(aryl)phosphines into polymer chains has been observed in the palladiumcatalyzed cross-coupling synthesis of polyanilines and polyphenylenes. ${ }^{168,}{ }^{169}$ Non-negligible quantities of phosphorus impurities have been found in Miyaura-Suzuki-prepared conjugated polymers, as have traces of aryl groups from phosphines. ${ }^{6,127}$ Phosphine-free reaction conditions eliminate the risk of contaminating the final polymer material with the ligand and reduce the cost of polymerization by removing a component of the reaction mixture. ${ }^{105}$ However, as described earlier, homocoupling is prevalent in highly polar phosphine-free conditions, and these unselective couplings can be suppressed with varying degrees of success through the addition of a bulky phosphine.

The most widely-used ligands in this regard are $\mathrm{PCy}_{3}$ and $\mathrm{P}(t-\mathrm{Bu})_{2} \mathrm{Me}^{-} \mathrm{HBF}_{4}$. Substantial steric hindrance is therefore necessary, and yet there are examples in which phosphines that are too sterically demanding inhibited the reaction. For example, the copolymerization of tetrafluorobenzene or octafluorobiphenyl with other phenyl derivatives required the presence of a sterically demanding phosphine $\left(\mathrm{P}(t-\mathrm{Bu})_{2} \mathrm{Me}^{2} \mathrm{HBF}_{4}\right)$, whereas in the presence of other, even more bulky phosphines $\left(\mathrm{P}(t-\mathrm{Bu})_{3} \cdot \mathrm{HBF}_{4}\right.$ or SPhos), the reaction does not occur (Figure 19). ${ }^{91}$, 125 The significance of the ligand in suppressing $\beta$-defects in polar conditions was also shown in a study which promoted various degrees of branching in P3HT through the choice of ligand used. Of the reaction conditions tested, the ligand-free system led to the highest degree of branching, while the bidentate ligands $2,2^{\prime}$-bipyridine and tetramethylethylenediamine (TMEDA) suppressed $\beta$ branching entirely.



Figure 19: The copolymerization of tetrafluorobenzene and dibromofluorene with various ligands.

In low polarity conditions, $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ and $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ most consistently provide the best materials. Although these ligands are similar with respect to their chelating potential, they are not interchangeable. ${ }^{127,170}$ In fact, trends have emerged which suggest that $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ works best for poly(alkylthiophene)s, while $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ is most suitable for DHAP involving bromoarenes. ${ }^{108}$ The importance of secondary interactions between the metal center and the oxygen or nitrogen atoms was highlighted by the observation that ligands with only similar steric or electronic features to $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ and $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ did not provide the polymer in similar molecular weights, regioregularity or yield. ${ }^{85}$ Neither phosphines with orthotolyl groups (with provide a similar steric effect to methoxy or dimethylamine groups in the ortho positions) nor para-methoxyphenyl or ortho-fluorophenyl groups (with similar ortho/para activating effects) were successful. This indicates that these ligands are more than the sum of their steric and electronic features, and do rely on secondary coordinating effects in the vicinity of the phosphorus atom. It is interesting to note that, despite the beneficial effect of the polydentate nature of these phosphines, bidentate bis-phosphine ligands have not been effective for the synthesis of P3HT. ${ }^{66,67}$

The crucial role of the ligand's chelating ability vis-à-vis the catalyst was further confirmed by studies of palladium complexes ligated by an aryl group, an acetate and the phosphine P (o-
$\left.\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3} .{ }^{68}$ Although in the solid state this complex could be in either a monomeric or dimeric form, in solution two monomeric species are present in equilibrium. One of these tetracoordinated palladium species involves a bidentate acetate ligand, while the other consists of a chelating phosphine (Figure 20). The hemilabile nature of the phosphine promotes the formation of this monomeric form of the catalyst, which reacts readily with $\mathrm{C}-\mathrm{H}$ bearing substrates via CMD to form cross coupling products. On the other hand, when the $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ ligand of the starting complex is replaced with $\mathrm{PPh}_{3}$, the monomeric form of the catalyst is less reactive unless bulkier aryl groups or polar solvents are used, demonstrating that the phosphine is responsible for breaking up the polymeric (or dimeric) form of the catalyst in low polarity conditions. In another study of this equilibrium, it was shown that steric bulk around the metal center from either the aryl group or the carboxylate ligand is necessary to convert the cyclic (dimeric or tetrameric) form of the catalyst to the reactive monomeric form in solution. ${ }^{64}$
$1 / 2$




Figure 20 : The role of $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ in the equilibrium between the dimeric and monomeric forms of a palladium catalyst.

In one study, the degree of steric hindrance on the oxygen atom of $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ was modulated in an effort to further increase the cross-coupling selectivity promoted by this ligand. ${ }^{96}$ It was found that for the synthesis of donor-acceptor copolymers, the increased steric bulk suppressed side-reactions (particularly homocoupling) such that materials with optical and charge-transport properties comparable to Migita-Stille analogs could be obtained. This approach was only beneficial when the electron-rich units were halogenated, however, and the bulkier ligands could not give well-defined materials when the electron-poor units bore the $\mathrm{C}-\mathrm{X}$ bonds.

It was observed that the phenomenon of redox-balanced oxidative $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling and reductive $\mathrm{C}-\mathrm{X}$ dehalogenation can be avoided when a diamine ligand (e.g. TMEDA) is included in the reaction mixture in addition to the standard ligand $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ (Figure 21). ${ }^{110,120}$ While one nitrogen atom coordinates to the metal center, the other competes with the carboxylate for the necessary interaction with the proton of the $\mathrm{C}-\mathrm{H}$ bond, thereby rendering a CMD event trans to the oxidative addition substrate less likely. If this trans CMD were to occur according to the proposed mechanism described earlier, it would lead to dehalogenation of the oxidative addition substrate by way of a carboxylate-assisted proton transfer from the CMD substrate. Following this, the deprotonated carboxylate ligand would free its coordination site cis to the CMD substrate to allow a second CMD event and subsequent reductive elimination, thereby leading to the observed $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling. A similar suppression of homocoupling was observed when $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ and $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ were used in concert. From this, it was suggested that one ligand is responsible for the reactivity of the catalytic system, and the other maximizes selectivity by suppressing the proposed trans mechanism. This system has also been shown to eliminate the production of insoluble products in polymers prepared from dibromoDPP, indicating that $\beta$-defects which could originate from brominated electron-poor thiophenes described above could in fact be suppressed. ${ }^{152}$ Without the use of combined ligands, the proposed branching phenomena limited yield and molecular weight of the recoverable polymer fraction.


Figure 21 : The suppression of homocoupling using a mixed ligand system.

N-heterocyclic carbene ligands have been used in high polarity conditions to prepare P3HT
(Figure 22) with a high regioregularity ( $94 \%$ ) and molecular weight ( $26.9 \mathrm{~kg} / \mathrm{mol}$ ), albeit in low
yield ( $57 \%$ ). A high molar mass dispersity was observed, likely due to slow catalyst initiation. The precatalyst Pd-IPr, chosen for its strong coordination to palladium, which was used alongside PivOH and $\mathrm{K}_{2} \mathrm{CO}_{3}$, also led to the synthesis of the selenophene analog of P 3 HT , albeit with a low molecular weight as a result of the low solubility of the polymer in the polar solvent.


Figure 22 : The use of an N-heterocyclic carbene in the DHAP of P3HT.

### 0.5.4 Catalyst

The catalysts used in DHAP are primarily $\mathrm{Pd}(\mathrm{II})$ salts (e.g. $\mathrm{Pd}(\mathrm{OAc})_{2}, \mathrm{PdCl}_{2}$ ) or organometallic complexes of $\mathrm{Pd}(\mathrm{II})$ (Herrmann-Beller's precatalyst, $\left.\mathrm{PdCl}_{2}(\mathrm{MeCN})_{2}\right)$ or $\mathrm{Pd}(0)\left(\operatorname{Pd}\left(\mathrm{PCy}_{3}\right)_{2}\right.$, $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ and its chloroform adduct). While $\mathrm{Pd}(\mathrm{II})$ sources tend to be less costly and more air stable, they may also be an origin of homocoupling defects during the in situ conversion of the $\operatorname{Pd}(\mathrm{II})$ precatalyst to the active $\operatorname{Pd}(0)$ species. As described earlier, this is proposed to proceed via two subsequent CMD transition states, followed by reductive elimination to generate an oxidative $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ homocoupling defect. ${ }^{60} \mathrm{Pd}(0)$ precatalysts, on the other hand, have their reactive 0 oxidation state stabilized by bulky L-type ligands. Once in solution, these catalysts need only undergo ligand exchange to become active. Due to their susceptibility to oxidation, some $\operatorname{Pd}(0)$ precatalysts may not be bench-stable, in which case they would need to be handled under inert (i.e. glovebox and Schlenk line) conditions.

As the solvent molecules serve as ligands in high polarity conditions, most reactions using DMAc or DMF as the solvent involve simple Pd (II) salts. ${ }^{10}$ A detailed study of polar reaction
conditions using $\mathrm{Pd}(\mathrm{OAc})_{2}$ indicated that lowering the catalyst load leads to a reduced presence of defects in P3HT. ${ }^{139}$ The best regioregularity ( $96 \%$ ) and highest molecular weight (24.2 $\mathrm{kg} / \mathrm{mol}$ ) could be obtained at a catalyst concentration as low as $0.0313 \mathrm{~mol} \%$. However, to maintain a constant effective concentration of the catalyst in solution in this study, the solvent volume was reduced considerably. In order to compensate for the limited polymer solubility, much higher reaction temperatures $\left(160^{\circ} \mathrm{C}\right)$ were necessary. The beneficial effect of reducing catalyst concentration is echoed in other studies. ${ }^{60,167}$

Although the role of the starting ligands of more complex organometallic catalysts used in lower polarity reactions is unclear, it is likely that they are involved in catalyst reactivity. This is suggested by the dissimilar polymeric materials obtained for the same reaction with different precatalysts. For instance, the dba ligands of $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ are easily displaced with other ligands is solution, while the metal centers of Herrmann-Beller's precatalyst (shown in Figure 4c) are already ligated by a phosphine and acetate base, such that it may proceed directly to a CMDready species.

For example, the polymerization of dibromocarbazole and EDOT (3,4-ethylenedioxythiophene) was observed to occur more slowly with $\mathrm{PdCl}_{2}$ than with $\mathrm{Pd}(\mathrm{OAc})_{2}$, but gave a polymer with a higher molecular weight (reaching $80 \mathrm{~kg} / \mathrm{mol}) .{ }^{126} \mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ was used with $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ to prepare high molecular weight terpolymers from phenanthridinone, phenanthridine and dithienyl-DPP, and with $\mathrm{PCy}_{3} \cdot \mathrm{HBF}_{4}$ to prepare high molecular weight copolymers of dithienylDPP and dithienyl-benzothiadiazole. ${ }^{156,} 171$ The use of $\mathrm{PdCl}_{2}(\mathrm{MeCN})_{2}$ and $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$ together have led to a range of well-defined polymers containing TPD units, including a copolymer with a dialkylbithiophene in a lower molecular weight ( $37 \mathrm{~kg} / \mathrm{mol}$ ) but higher regioregularity than was obtained Herrmann-Beller's precatalyst with the same ligand (56 $\mathrm{kg} / \mathrm{mol}){ }^{92,170}$

Herrmann-Beller's precatalyst requires high reaction temperatures in order to become reactive, as well as the presence of bulky phosphines with chelating ability to break up the palladacycles and favor its monomeric form. It has been used in concert with $\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}$ to synthesize some of the most regioregular poly(alkylthiophene)s reported to date (as shown in Figure 4c and 12). ${ }^{85,88,89}$ When used with $\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}$, protocols employing Herrmann-Beller's precatalyst have also been adapted to the synthesis of a wide range of copolymers containing thiophene
derivatives and in particular brominated electron-poor thiophene-flanked units. ${ }^{22,108,135,150,151}$ On the other hand, the use of $\operatorname{Pd}(\mathrm{OAc})_{2}$ as the precatalyst has been identified as the best precatalyst for the copolymerization of brominated electron-rich units with various thiophene derivatives. ${ }^{90,96}$

As with any other metal-catalyzed reaction, the purity of the precatalyst is crucial. The chloroform adduct of $\mathrm{Pd}_{2} \mathrm{dba}_{3}$ is formed via recrystallization, which removes bulk impurities. ${ }^{172}$ Optimized conditions which use $\mathrm{Pd}_{2} \mathrm{dba}_{3} \cdot \mathrm{CHCl}_{3}$ have given high molecular weight and welldefined materials in high yield for some polymers, particularly ones involving bromoarenes. In other cases, $\mathrm{Pd}_{2} \mathrm{dba}_{3} \mathrm{CHCl}_{3}$ has led to polymers accompanied by large quantities of insoluble material. This may be due, however, to the fact that the particular target polymers were fluorinated. ${ }^{127,157,173-175}$

Supported catalysts are attractive from the perspective of potential reaction scale-up, as they can be retrieved followed the reaction and reused. They are also less likely to contaminate the reaction product with residual metals than homogenous catalysts. ${ }^{176}$ On the subject of catalyst contamination, a study which employed elemental analysis of a DHAP-prepared polymer prepared using a homogenous catalyst also showed that the final material contains much fewer palladium impurities than the same polymer prepared by Miyaura-Suzuki cross-coupling. ${ }^{6}$

A few studies have demonstrated the potential of supported catalysts for DHAP. For example, P3HT was synthesized using $\mathrm{Pd} / \mathrm{C}$ with a molecular weight of $16.3 \mathrm{~kg} / \mathrm{mol}$ and a regioregularity of $97 \%$ with $\mathrm{K}_{2} \mathrm{CO}_{3}$ and PivOH in high polarity conditions (NMP as the solvent), while Pearlman's catalyst $\left(\mathrm{Pd}[\mathrm{OH}]_{2} / \mathrm{C}\right)$ gave P3HT with higher molecular weights $(18.9 \mathrm{~kg} / \mathrm{mol}, \mathrm{RR}=$ $96 \%) .{ }^{177}$ The modification of reaction conditions through the addition of a phosphine ligand $\left(\mathrm{P}(\mathrm{Cy})_{3} \cdot \mathrm{HBF}_{4}\right)$, the increase of reaction temperatures higher than $100{ }^{\circ} \mathrm{C}$ and the use of DMAc instead of NMP each led to the formation of a large quantity of insoluble material. Another study compared the use of $\operatorname{Pd}(0)$ and $\mathrm{Pd}(\mathrm{II})$ catalysts supported on mesoporous silica for the synthesis of a copolymer from dibromoisoindigo and EDOT (Figure 23). ${ }^{167}$ The supported $\mathrm{Pd}(\mathrm{II})$ catalyst gave results superior to optimized conditions using $\mathrm{Pd}(\mathrm{OAc})_{2}$ as a heterogeneous precatalyst (84 vs $79 \mathrm{~kg} / \mathrm{mol}$ ), while the $\operatorname{Pd}(0)$ supported catalyst yielded only oligomers.

$\mathrm{Pd}(\mathrm{OAc})_{2}$ $\left(\mathrm{Cs}_{2} \mathrm{CO}_{3}, \mathrm{TBAB}\right)$ $\mathrm{M}_{\mathrm{n}}=79 \mathrm{~kg} / \mathrm{mol}, \mathrm{Y}=94 \%$

Mesoporous silica-supported Pd(II) $\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right.$, TBAC $)$
$M_{n}=84 \mathrm{~kg} / \mathrm{mol}, \mathrm{Y}=91 \%$
Mesoporous silica-supported $\operatorname{Pd}(0)$
$\left(\mathrm{K}_{2} \mathrm{CO}_{3}\right.$, TBAC)
$\mathrm{M}_{\mathrm{n}}=5 \mathrm{~kg} / \mathrm{mol}, \mathrm{Y}=35 \%$

Figure 23 : An example of the use of supported catalysts in DHAP.
One report demonstrated the use of a ruthenium catalyst (with the (cymene)ruthenium dichloride dimer as precatalyst) for the copolymerization of pyrrole with dibromofluorene (Figure 24). ${ }^{178}$ $\mathrm{C}_{\mathrm{a}}-\mathrm{H}$ bond activation and arylation was guided by the use of an $N$-substituted 2-pyrimidinyl directing group on the pyrrole monomer, in which the heteroatoms of the pyrimidinyl group served as ligands for the metal center. The role of the directing group was confirmed by the attempt to polymerize a pyrrole in which the 2-pyrimidinyl moiety was replaced with a phenyl group, which led to a largely insoluble product. This was likely due to unselective couplings on pyrrole. The directing group was removed post-polymerization with a strong base at high temperature, adding another step to the preparation of the final material. The use of directing groups to guide $\mathrm{C}-\mathrm{H}$ bond activation is widely used in direct arylation of small molecules (particularly in the early studies of intramolecular arylation), but to date this is the only example of the engineering of a substrate directing group with the purpose of guiding polymerization siteselectivity.


Figure 24 : Ruthenium-catalyzed DHAP with a monomer bearing a directing group.

### 0.5.5 Base, Acid and Other Additives

As indicated above, homocoupling defects which are often observed when polymerization occurs in polar solvents can be reduced with the addition of a phosphine due to the increased steric bulk around the catalyst center. In a similar way, the carboxylic acid may impart steric hindrance to the catalytic system and suppress undesired $\mathrm{C}_{\beta}-\mathrm{H}$ bond activation.

In a systematic study where many primary, secondary, tertiary and cyclic carboxylic acids were screened for their effect on the preparation of P 3 HT , the highest regioregularity and lowest rate of $\beta$-defects were achieved with tertiary acids. ${ }^{140}$ Of the various aliphatic carboxylic acids studied (linear, ramified and cyclic), only tertiary acids suppressed $\beta$-branching entirely (although the use of the smallest tertiary acid, pivalic acid, did lead to $1 \%$ of $\beta$-defects). Neodecanoic acid (NDA, see Figure 12 for structure), a mixture of isomers of a tertiary $\mathrm{C}_{12}$ acid, provided the best results when both regioregularity and molecular weight were considered. This led to the hypothesis that these acids inhibited the kinetic accessibility of the proton adjacent to the hexyl side-chain (i.e. at the 4-position of the thiophene).

For the most part, higher regioregularity and molecular weights are deemed to be indicators of coupling selectivity, although in many cases the interference of homocoupling on the physical and optical properties of the polymer sample cannot be ruled out. In order to separate the impact of homocoupling from that of unfavorable $\alpha / \beta$-selectivity, in another study a mono-brominated but otherwise symmetrical monomer was homopolymerized to prepare the poly(alkylthiophene) PQT12 (Figure 12). ${ }^{89}$ In this way, the potential outcome of a homocoupling side-reaction was made redundant, and variations in polymer structure (as identified from differential scanning calorimetry and thin film UV-vis measurements) could only be attributed to coupling at the $\beta$ position. From these results, it was shown that the same bulky acid additive (NDA) suppressed the side-reactions at the $\beta$ position which led to the observed variations in polymer structure. It was also demonstrated that a similar steric effect to NDA could be introduced to the catalytic system via alkyl chains in the $\gamma$ position of the thiophene unit, as described earlier. This induced steric effect was thought to be sufficient to render activation of the adjacent $\beta$ proton kinetically unfavorable. As such, when a $\gamma$-substituted monomer was used, NDA was not necessary to achieve a well-defined material. The steric effect of side chains at the $\gamma$ position was also suggested by a study in which 3,3 '-dialkylbithiophene was successfully used to produce a
processable material with similar molecular weights to a tetramethylated ( $\beta$ - and $\gamma$-methylated) bithiophene, whereas non-alkylated bithiophene led to a large quantity of insoluble product. ${ }^{144}$ More recently, a similar protocol using a single isomer of NDA (2,2-diethylhexanoic acid) has been applied to the synthesis of a range of donor-acceptor copolymers which were shown to be structurally indistinguishable from their Migita-Stille-prepared analogs (which are absent of $\beta$ defects). ${ }^{95}$

As described in the introduction, research in DHAP is driven primarily by its coherence with industrial requirements. One limit of DHAP in this regard is the widespread use of cesium carbonate $\left(\mathrm{Cs}_{2} \mathrm{CO}_{3}\right)$, an expensive reagent, as the base in the reaction. While $\mathrm{K}_{2} \mathrm{CO}_{3}$ was used in the earliest studies of DHAP, cesium has been shown to be the counter ion leading to the highest coupling yields in small molecule experiments. ${ }^{23,83}$ Due to its large ionic radius, its carbonate salt is more soluble in organic solvents than other carbonates. This makes the carbonate anion more available either to perform the CMD step (in the absence of a carboxylate) or to neutralize the carboxylic acid formed following proton abstraction (when a carboxylate is used). Despite the greater solubility of $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ over other carbonate salts, its solubility at the concentration needed for polymerization remains limited. This leads to large solid pieces of the salt accumulating at the bottom and sides of reaction vials, which has the double consequence of interfering with magnetic stirring and restricting the polymerization to the surface area of the solid-liquid interface. ${ }^{167}$ As a result, the grain size of the base affects batch-to-batch variation considerably, even at the millimolar scale.

A recent study overcomes this limitation by performing the reaction in biphasic conditions using a large excess ( 40 equivalents) of $\mathrm{K}_{2} \mathrm{CO}_{3}$, a much cheaper carbonate (Figure 18). ${ }^{167}$ In this protocol, which is reminiscent of Miyaura-Suzuki coupling conditions, the base is dissolved in the aqueous phase, while the growing polymer chain remains in solution in the organic phase. The polymerization reaction occurs therefore at the interface of the two phases, making the base more readily available to assist in the CMD. This approach was successfully demonstrated on electron-rich and electron-poor substrates, and both phenyl and thienyl derivatives, and led to polymers with equally good or better properties than the same polymers prepared to date by any other cross-coupling method.

### 0.5.6 Heating Source

DHAP protocols involve much higher monomer concentrations than other polymerization techniques, and higher monomer concentration is often linked to a higher degree of polymerization. However, there is a limit to this, in that very high monomer concentrations (i.e. very low solvent volumes) lead to gelation of the polymer, which inhibit the reaction and prevent further chain growth. One approach which has managed to overcome this physical limitation is to use microwave protocols, in which higher reactivity can be obtained at a given reactant concentration than is possible than with conventional (oil bath) heating.

For example, a report of the optimized conditions for the synthesis of poly[(3,4-ethylenedioxythiophene-2,5-diyl)-(9,9-dioctylfluorene-2,7-diyl)] (PEDOTF) using oil bath heating yielded a polymer with a Mn of 39 kDa after 6 hours at $100{ }^{\circ} \mathrm{C}$ with a monomer concentration of 0.3 M (Figure 25). ${ }^{179}$ In comparison, optimized conditions using microwave heating after only 0.5 hours yielded the same polymer with Mn values of $56 \mathrm{kDa}, 74 \mathrm{kDa}$ and 147 kDa , depending on the initial monomer concentration ( $0.3,0.2$ and 0.1 M , respectively). ${ }^{154}$ However, the limitations of polymer solubility led to a drop of molecular weight at a concentration of 0.05 M , with a near-quantitative recoverable fraction of 36 kDa . Interestingly, in this example, the material prepared using a microwave protocol also yielded higher power conversion efficiency in solar cell devices and increased hole mobility in field effect transistors than the material prepared using conventional heating, which was in turn superior to the Miyaura-Suzuki analog. ${ }^{6}$ This divergence of device performance for the three polymers may be due to molecular weight differences, or to the fact that brominated terminal groups were absent from the microwave-synthesized polymer, but present in the oil bath-heated DHAP and MiyauraSuzuki polymers.


Figure 25 : A comparison of microwave and oil bath heating in DHAP.

On the other hand, by increasing kinetics through microwave heating, $\mathrm{C}-\mathrm{H}$ bonds in the undesired $\beta$-position may also be more easily activated as well. As there are no $\mathrm{C}_{\beta}-\mathrm{H}$ bonds on the EDOT unit, this did not occur in the abovementioned case. However, in another study involving monomers with unprotected $\mathrm{C}_{\beta}-\mathrm{H}$ bonds on thienyl moieties, ill-defined structures and insoluble fractions obtained from microwave protocols were believed to be a result of coupling at the $\beta$-position. ${ }^{155}$ Due to the limited number of results obtained from such protocols, the use of microwave heating remains inconclusive.

### 0.6 Conclusions and Outlook

To date, the DHAP reaction has shown to balance the environmental and industrial requirements for large-scale polymer production with a wide synthetic scope. Indeed, DHAP can be applied to the preparation of a broad range well-defined and high-performance homopolymers, co-polymers and three-dimensional materials. The burgeoning library of building blocks amenable to DHAP polymerization demonstrates the reaction's versatility.

DHAP has benefitted from the rich chemistry developed for small molecule synthesis. Information gathered from the last three decades of research into the mechanisms and optimal reaction conditions for transition-metal catalyzed $\mathrm{C}-\mathrm{H}$ activation and arylation has allowed DHAP to evolve rapidly. The polar and non-polar solvent conditions, bulky carboxylic acids, carbonate bases and polydentate phosphines that have been transposed from small molecule studies have contributed to polymerization conditions which provide materials with high molecular weight, regioregularity and yield.

While the risk of monomer decomposition through the loss of organometallic (or heteroelementcontaining) functional groups is absent in DHAP, there are still many challenges associated with dehalogenation and homocoupling side-reactions. In general terms, homocoupling is less prevalent in low polarity reaction conditions when a bulky ligand (such as $\mathrm{P}\left[o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right]_{3}$ or $\mathrm{P}\left[o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right]_{3}$ ) or a mixture of ligands capable of secondary interactions with the metal center are used. ${ }^{85, ~ 89, ~ 108, ~ 127, ~} 170$ The homocoupling and other side-reactions observed in more reactive high-polarity conditions, on the other hand, can be suppressed with the addition of a monocoordinating ligand (such as $\left.\mathrm{P}(\mathrm{Cy})_{3}\right) .{ }^{118}$ However, the fact that the reaction tends to occur more
rapidly and at lower temperatures in phosphine-free polar conditions makes these reaction conditions industrially advantageous. ${ }^{105}$

The role and pervasiveness of $\beta$-defects, on the other hand, is not fully understood due to the few examples of spectroscopic evidence for it. ${ }^{66,133}$ In many cases, sudden loss of polymer solubility in what is otherwise a well-defined material is given as a symptom of $\beta$-branching and crosslinking. ${ }^{90,91,111,138}$ There are, however, some instances where $\beta$-defects have been eliminated entirely through careful optimization of reaction conditions. In both higher- and lower-polarity conditions, the steric effect introduced by a bulky carboxylic acid additive (PivOH, NDA) increases coupling selectivity and reduces homocoupling. ${ }^{9,25, ~ 85, ~ 90, ~ 95, ~ 118, ~} 140$ Solvent end-capping has been observed when aromatic solvents are used, while the use of polar non-aromatic solvents can lead to nucleophilic substitution on the $\mathrm{C}-\mathrm{Br}$ chain end-group. Recent insights regarding DHAP in biphasic conditions and continuous flow systems make it particularly attractive from an industrial perspective, due to their robust batch-to-batch variation and potential for reaction scale-up. ${ }^{167,180}$

By looking at the evolution of other cross-coupling reactions which have been adapted to the preparation of conjugated polymers, one can imagine potential future directions for DHAP. For instance, although traditional palladium-catalyzed cross couplings reactions are largely regarded as step-growth when used as polymerization methodologies, under certain conditions they can exhibit features of chain-growth through the design of the initiator species. This has been observed for Miyaura-Suzuki polymerization with highly reactive and sterically hindered Pd catalysts and for Migita-Stille polymerization with PEPPSI-IPr-type catalysts. ${ }^{181-183}$

Other transition metal catalyzed polymerization techniques have been adapted to express a living character. For example, in the Kumada Catalyst-Transfer Polymerization (KCTP) reaction, the nickel catalyst is understood to remain complexed to the $\pi$-system of the growing polymer chain throughout the reaction. Following the formation of a $\mathrm{C}-\mathrm{C}$ bond between the polymer chain endgroup and a monomer, the catalyst migrates to the $\mathrm{C}-\mathrm{Br}$ bond on the new chain end to begin the next coupling reaction. ${ }^{184}$ The development of such a catalytic system for DHAP would open the door to the preparation of block copolymers via direct $\mathrm{C}-\mathrm{H}$ activation and the control of polymer chain length.

Finally, a recently-developed variation of DHAP consists of the oxidative coupling of two aromatic $\mathrm{C}-\mathrm{H}$ bonds via two consecutive base-assisted $\mathrm{C}-\mathrm{H}$ bond activations, rather than the oxidative addition on a carbon-halogen bond followed by a single $\mathrm{C}-\mathrm{H}$ bond activation. First reported in 2013, this technique has been used to prepare homopolymers from monomers bearing two reactive $\mathrm{C}-\mathrm{H}$ bonds (Figure 26). ${ }^{185}$ The oxidative direct $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ arylation polymerization reactions studied to date are catalyzed by a $\mathrm{Pd}(\mathrm{II})$ catalyst $\left(\mathrm{Pd}(\mathrm{OAc})_{2}\right.$ or $\left.\mathrm{PdCl}_{2}\right)$. As there is no carbon-halogen bond involved or oxidative addition step involved in the reaction, the reduction of the Pd catalyst is mediated by either a copper(II) or silver(I) salt $\left(\mathrm{Cu}(\mathrm{OAc})_{2}\right)$ or $\mathrm{Ag}_{2} \mathrm{CO}_{3}$, respectively) as the oxidizing agent, sometimes in the presence of oxygen gas $\left(\mathrm{O}_{2}\right)$. Although this new and streamlined form of DHAP is, for the most part, currently limited to the synthesis of homopolymers from monomers with directing groups (primarily esters and amides), it carries the potential for the preparation of polymers without resorting to halogenated starting materials and by-products. ${ }^{186-188}$ Recently, this method was used to obtain copolymers by means of a sulfonyl directing group adjacent to the target $\mathrm{C}-\mathrm{H}$ bonds. ${ }^{189}$ In another report, the polymerization of a family of polybenzodiimidazoles was even catalyzed by $\mathrm{Cu}(\mathrm{OAc})_{2}$ in the presence of $\mathrm{Ag}_{2} \mathrm{CO}_{3}$ and $\mathrm{O}_{2}$, thereby entirely eliminating the need for a Pd catalyst. ${ }^{190}$ These features provide even more environmentally-friendly DHAP protocols for the synthesis of conjugated polymers than those presented in this chapter.


$$
M_{n}=7 \mathrm{~kg} / \mathrm{mol}
$$



Figure 26 : The first examples of oxidative direct $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ arylation polymerization.

Regardless of the future directions of DHAP, whether it is new catalyst design or double $\mathrm{C}-\mathrm{H}$ bond activation, the progress made in the last decade demonstrates its great synthetic and practical potential. Some of the most well-defined and highly performing polymers for organic electronics can already be prepared with this method, indicating that the true extent of its usefulness in the preparation of complex $\pi$-conjugated polymers and macromolecules is yet to be revealed.

## CHAPTER 1: BRIEF OVERVIEW OF COMPUTATIONAL APPROACHES USED AND OBJECTIVE OF THE PROJECT

### 1.1 Objective of the project

As discussed in the Introduction, detailed experimental results pertaining to the source(s) of $\beta$ defect formation in polymers prepared by direct (hetero)arylation polymerization remain elusive. To elucidate the likelihood of $\mathrm{C}_{\beta}-\mathrm{H}$ bond activation during the course of a polymerization, the computational techniques described in the present chapter will be used to explore the arylation reaction pathways for the $\mathrm{C}_{\alpha}-\mathrm{H}$ and $\mathrm{C}_{\beta}-\mathrm{H}$ bonds of a range of model thiophenes. By changing both the thiophene undergoing oxidative addition ( $\mathrm{C}-\mathrm{Br}$ bond cleavage) and the thiophene undergoing proton abstraction and arylation (via the CMD mechanism), the competing reactivities of the various $\mathrm{C}-\mathrm{H}$ bonds of a wide scope of potential coupling partners can be modeled. From the resulting energy profiles of the reaction pathways, the coupling selectivity can be understood in terms of the electronic and steric character of each substrate.

Steric effects are introduced to the coupling partners by means of methyl and ethyl side-chains in the thiophene 3-position (i.e. adjacent to the 2-position desired for coupling), while the introduction of methoxy $(\mathrm{MeO})$ and carbonitrile $(\mathrm{CN})$ groups in the 5-position enrich or deplete the electron density of the thiophene. These strong electron-withdrawing and donating groups will coarsely mimic the electronic character of thiophene-based monomers (such as those containing amide, imide and ketone functions), while the short alkyl chains grant insight into the effect of longer aliphatic side-chains (i.e. ethylhexyl, dodecyl and other linear and branched chains) on monomer reactivity. This will give a general (albeit rough) set of design principles to maximize the selectivity of $\mathrm{C}-\mathrm{H}$ bond activation and arylation at the $\alpha$ position of "monomerlike" substrates. The results of these computational experiments are detailed in the following section (Chapter 2).

### 1.2 Molecular Hamiltonian

The molecular (Coulomb) Hamiltonian (not considering fine structure effects) is defined by:

$$
\widehat{H}=\widehat{T}_{N}+\widehat{T}_{e}+\widehat{U}_{e N}+\widehat{U}_{e e}+\widehat{U}_{N N}
$$

where the right-hand terms are the nuclear kinetic energy, electronic kinetic energy, electronnuclear potential energy, electron-electron potential energy and nuclear-nuclear potential energy operators, respectively. Each of these terms can be expanded in the following way:

$$
\begin{aligned}
& \widehat{H}=-\sum_{A} \frac{\hbar^{2}}{2 M_{A}} \nabla_{A}^{2}-\sum_{i} \frac{\hbar^{2}}{2 m_{e}} \nabla_{i}^{2}-\sum_{i} \sum_{A} \frac{Z_{A} e}{4 \pi \varepsilon_{0}\left|R_{A}-r_{i}\right|}+\sum_{i} \sum_{j>i} \frac{e^{2}}{4 \pi \varepsilon_{0}\left|r_{j}-r_{i}\right|} \\
&+\sum_{A} \sum_{B>A} \frac{Z_{A} Z_{B}}{4 \pi \varepsilon_{0}\left|R_{B}-R_{A}\right|}
\end{aligned}
$$

in which $M_{A}$ is the mass of nucleus $A, R_{A}$ is the position of nucleus $A, Z_{A}$ is the charge of nucleus $A, m_{e}$ is the mass of an electron, $r_{i}$ is the position of electron $i$ and $e$ is the charge of an electron. Nuclei and electrons are denoted with the indices A, B and i, j, respectively.

The nuclear-electron Coulomb interaction is attractive (and therefore negative), whereas the nuclear-nuclear and electron-electron terms are repulsive and positive definite. Each of these three terms contains two variables: the position of each of the particles involved in the Coulombic interaction. The Born-Oppenheimer approximation improves the tractability of such a calculation by considering the nuclei to be stationary. This is usually an acceptable approximation given than nuclear motion (such as vibration) is much slower than electronic motion, and so the electrons in a system can adapt quasi-instantaneously to changes in nuclear coordinates.

In this approximation, however, the electron-electron repulsion term still contains two variables which cannot be considered independently of one another. Therefore, for any system larger than a hydrogenoid (1 electron) structure, the result cannot be known exactly, and further approximations (as described in the following sections) must be made to take into account the interaction of electrons and their spins. In the Born-Oppenheimer approximation, the nuclearnuclear repulsion term becomes a constant which is added at the end of a calculation of electronic energy at a given geometry. In this way, the electronic energy can be evaluated with different nuclear coordinates in order to find the lowest energy geometry of a molecule.

### 1.3 Orbitals and Slater Determinants

An orbital $(\varphi)$ is defined as a one-electron wave function obtained from solutions to the Schrödinger equation for a single electron system, such as the hydrogen atom. Combinations of
one-electron orbitals are used to approximate complex systems with multiple electrons, as described above. A set of hydrogenoid orbitals can be written as the determinant of a matrix composed of electrons $\left(r_{x}\right)$ placed in one-electron orbitals $\left(\varphi_{x}\right)$. For instance, shown below are examples of matrices for a two- and three-electron system.

$$
\left[\begin{array}{ll}
\varphi_{1}\left(r_{1}\right) & \varphi_{1}\left(r_{2}\right) \\
\varphi_{2}\left(r_{1}\right) & \varphi_{2}\left(r_{2}\right)
\end{array}\right]\left[\begin{array}{lll}
\varphi_{1}\left(r_{1}\right) & \varphi_{1}\left(r_{2}\right) & \varphi_{1}\left(r_{3}\right) \\
\varphi_{2}\left(r_{1}\right) & \varphi_{2}\left(r_{2}\right) & \varphi_{2}\left(r_{3}\right) \\
\varphi_{3}\left(r_{1}\right) & \varphi_{3}\left(r_{2}\right) & \varphi_{3}\left(r_{3}\right)
\end{array}\right]
$$

The determinants of matrices comprised of one-electron orbitals and one-electron wave functions are Slater determinants (shown here for the same examples):

$$
\begin{gathered}
\Phi_{\left(r_{1}, r_{2}\right)}=\operatorname{det}\left[\begin{array}{ll}
\varphi_{1}\left(r_{1}\right) & \varphi_{1}\left(r_{2}\right) \\
\varphi_{2}\left(r_{1}\right) & \varphi_{2}\left(r_{2}\right)
\end{array}\right]=\varphi_{1}\left(r_{1}\right) \varphi_{2}\left(r_{2}\right)-\varphi_{1}\left(r_{2}\right) \varphi_{2}\left(r_{1}\right) \\
\Phi_{\left(r_{1}, r_{2}, r_{3}\right)}=\operatorname{det}\left[\begin{array}{lll}
\varphi_{1}\left(r_{1}\right) & \varphi_{1}\left(r_{2}\right) & \varphi_{1}\left(r_{3}\right) \\
\varphi_{2}\left(r_{1}\right) & \varphi_{2}\left(r_{2}\right) & \varphi_{2}\left(r_{3}\right) \\
\varphi_{3}\left(r_{1}\right) & \varphi_{3}\left(r_{2}\right) & \varphi_{3}\left(r_{3}\right)
\end{array}\right]=\varphi_{1}\left(r_{1}\right)\left(\varphi_{2}\left(r_{2}\right) \varphi_{3}\left(r_{3}\right)-\varphi_{2}\left(r_{3}\right) \varphi_{3}\left(r_{2}\right)\right)-\cdots
\end{gathered}
$$

Each Slater determinant is equivalent to an arrangement of electrons in a set of molecular orbitals $\left(\Phi_{\left(r_{1}, r_{2}, \ldots\right)}\right)$. Therefore, from the above example, the simplest representation of a twoelectron wave function can be given as:

$$
\Phi_{\left(r_{1}, r_{2}\right)}=\varphi_{1}\left(r_{1}\right) \varphi_{2}\left(r_{2}\right)-\varphi_{1}\left(r_{2}\right) \varphi_{2}\left(r_{1}\right)
$$

In other words, the Slater determinant is a representation of a molecular orbital diagram. This representation obeys the Pauli principle, in that if any two rows or columns of the matrix are exchanged, the Slater determinant changes its sign. As a result, if two rows or columns are identical (i.e. two electrons occupy the same state) the Slater determinant is identically equal to 0 . This can be extended to any size of chemical system with any number of electrons.

A basis set is a collection of these hydrogenoid orbitals (solutions to the 1-electron Schrodinger equation, as described above) A larger basis set means that a greater number of such orbitals are placed around each atom to better describe the molecular orbitals formed from the atomic orbitals of adjacent atoms, according to a linear combination of atomic orbitals approach. For instance, a heavy atom, such as bromine, requires a large number of $p$ and $d$ atomic orbitals to be placed around it to effectively describe the polarization of the atom's electronic density within a molecule. By increasing the size of the basis set, the computational cost is increased and the result becomes closer to the exact result within the method (termed the complete basis set limit).

Within the Hartree-Fock method, the result eventually stabilizes to the Hartree-Fock limit, after which point the addition of more basis functions will no longer improve the result. To move beyond this limit, it is necessary to take into account the contributions of other Slater determinants (such as in multiconfigurational methods) or to add a model which takes into account electronic correlation (as is the case for DFT, described below).

Within a given basis set, the wave function of a system, $|\Psi\rangle$, can be written as a linear combination of all the possible Slater determinants $\left|\Phi_{i}\right\rangle$ :

$$
|\Psi\rangle=\sum_{i} C_{i}\left|\Phi_{i}\right\rangle
$$

The coefficient $C_{i}$ is the overlap of the physical wave function with a given Slater determinant:

$$
C_{i}=\left\langle\Phi_{i} \mid \Psi\right\rangle
$$

A full configuration-interaction (CI) calculation is comprised of every possible Slater determinant within a given basis. This gives an "exact" answer for the energy of a system, for the basis set used. However, beyond systems of only a few electrons, full-CI calculations are prohibitively expensive. Approximations are required is general.
In the Hartree-Fock model, the wave function is approximated as one Slater determinant (i.e. one orbital diagram):

$$
\left|\Psi_{H F}\right\rangle=|\Phi\rangle
$$

The energies calculated using this method are a good first approximation for systems in which electrons interact only weakly and thus are essentially described using one molecular orbital diagram. Such systems are called weakly correlated. However, this is not the case for systems whose accurate description requires many molecular orbital diagrams. Such systems are called strongly correlated. Many chemically relevant situations fall into the latter category, such as transition states, organometallic complexes and systems with many transition metals.

To improve the accuracy of quantum chemical calculations while still maintaining tractability, the goal of post-Hartree-Fock methods is to «correct » the HF approximation so that the energy obtained from a calculation approaches reality without resorting to a full-CI calculation. Every improvement to the HF picture can be described as follows,

$$
E_{\text {exact (CI) }}-E_{\text {Hartree-Fock }}=E_{\text {correlation }}
$$

where corrections aim to reduce the difference between the CI energy and the HF energy by estimating the correlation energy, originating from electrons interacting with one another. Post-

Hartree-Fock methods only have a chance of converging if Hartree-Fock is a reasonable first approximation to the answer.

### 1.3.1 Coupled Cluster

Coupled Cluster is one such correction to the HF approximation. We define a cluster operator $(\hat{T})$ which will generate all the excitations of the Hartree-Fock Slater determinant

$$
\widehat{T}=\widehat{T_{1}}+\widehat{T_{2}}+\widehat{T_{3}}+\cdots+\widehat{T_{N}}
$$

where $\widehat{T}_{1}$ is a singles cluster operator, $\widehat{T}_{2}$ is a doubles cluster operator, and so on. In coupled cluster singles and doubles (CCSD), this is simplified to:

$$
\widehat{T}=\widehat{T_{1}}+\widehat{T}_{2}
$$

Acting on the Hartree-Fock Slater determinant, the cluster operators generate all single and double excitations:

$$
\begin{gathered}
\widehat{T}_{1} \Psi_{0}=\sum_{a, i} t_{i}^{a} \Psi_{i}^{a} \\
\widehat{T_{2}} \Psi_{0}=\sum_{a, b, i, j} t_{i, j}^{a, b} \Psi_{i, j}^{a, b}
\end{gathered}
$$

In the Slater determinant $\left|\Phi_{i}^{a}\right\rangle$ an electron is excited from the $i$ th occupied orbital to the $a$ th unoccupied orbital. Each possible single electron excitation Slater determinant is multiplied by the amplitude $t_{i}^{a}$, which is the contribution of the given excitation $\left|\Phi_{i}^{a}\right\rangle$ to the total system (i.e. the overlap of $\left|\Phi_{i}^{a}\right\rangle$ with the real wave function $|\Psi\rangle$ ). The amplitudes themselves are obtained numerically from a set of coupled non-linear equations.

A visualization of the excited Slater determinants is given in Figure 27.


Figure 27 : Schematic orbital representation of the reference (HF) wave function and arbitrary single, double, triple and quadruple excitations.
(Source: Andrew S. Ichimura: «Post Hartree-Fock» ; NSF Computational Nanotechnology and Molecular Engineering Pan-American Advanced Studies Institute Workshop, 2004)

Triple and quadruple excitations are usually not included in coupled cluster calculations due to their lesser impact on correlation energy and the exponentially higher resources needed to compute them.

The coupled cluster singles and doubles wave function $\left(\left|\Psi_{C C S D}\right\rangle\right)$ is defined as the exponential of the cluster operator acting on the Hartree-Fock Slater determinant:

$$
\left|\Psi_{C C S D}\right\rangle=\exp \left(\hat{T}_{1}+\hat{T}_{2}\right)\left|\Psi_{H F}\right\rangle
$$

The CCSD wavefunction is not optimized variationally as this would be intractable. Rather, a set of Slater determinants are projected against the Hamiltonian acting on the CCSD wavefunction:

$$
\begin{aligned}
& \left\langle\Phi_{0}\right| H e^{\left(T_{1}+T_{2}\right)}\left|\Phi_{0}\right\rangle=E \\
& \left\langle\Phi_{i}^{a}\right| H e^{\left(T_{1}+T_{2}\right)}\left|\Phi_{0}\right\rangle=0
\end{aligned}
$$

$$
\left\langle\Phi_{i j}^{a b}\right| H e^{\left(T_{1}+T_{2}\right)}\left|\Phi_{0}\right\rangle=0
$$

Here, the Hartree-Fock ground state as well as single and double excitations have been projected from the left. This leads to a set of coupled non-linear equations for the cluster amplitudes that are solved iteratively. The cluster amplitudes are analogous to the $C_{i}$ coefficients described earlier, in that they provide the contribution of a given excitation to the total wave function.

A full configuration-interaction calculation contains all possible Slater determinants within a given basis. These are made up of a linear combination of the Slater determinants for all single excitations of the electron from each occupied spin-orbital to each virtual orbital:

$$
\left|\Psi_{C I S D}\right\rangle=\left|\Psi_{H F}\right\rangle+\sum_{a, i} C_{i}^{a}\left|\Phi_{i}^{a}\right\rangle+\sum_{a, b, i, j} C_{i, j}^{a, b}\left|\Phi_{i, j}^{a, b}\right\rangle
$$

The full CI wave function contains excitations to all orders, but is often truncated to only single and double excitations (CISD, as shown above), as higher order excitations (triples, quadruples, etc.) are expensive to evaluate but likely contribute very little to the total enery of the system. The coupled cluster singles and doubles method affords an electronic energy which approaches that of a full-CI calculation at a reduced computational cost. As a result, CI with singles and doubles (CISD) scales as $\mathrm{O}\left(\mathrm{n}^{6}\right)$, whereas CCSD scales on the order of $\mathrm{n}^{6}$. The computational cost of $\operatorname{CCSD}(\mathrm{T})$ is around $\mathrm{n}^{7}$. This can be reduced using the DLPNO approximation, which lowers the cost to the order of a single point energy calculation with a hybrid functional.

### 1.3.2 Density Functional Theory

While post-Hartree-Fock methods are built upon a simplified expression of the wave function of a system, Density Functional Theory (DFT) approximates the energy of a system using the electronic density without resorting to calculating its wave function directly. In this way, electronic structure calculations are made computationally more accessible.

The molecular Hamiltonian is defined below (using atomic units) for a system containing $i$ electrons in the Born-Oppenheimer approximation (i.e. that nuclei are much more slow moving than electrons and so their kinetic energy is zero, and the internuclear repulsion is a constant to be added at the end) :

$$
\widehat{H}=-\frac{1}{2} \sum_{i} \nabla_{i}^{2}+V_{e x t}+\sum_{i>j} \frac{1}{\left|r_{i}-r_{j}\right|}
$$

The first term expresses the kinetic energy of the electrons, the second term the external potential and the third term the electron-electron repulsions. The external potential ( $V_{\text {ext }}$ ) is the electrostatic attraction between the positively charged nuclei and the negatively charged electrons. As such, the external potential is defined by the static arrangement of nuclei.

The terms of the Hamiltonian above can all be redefined as functionals of the electron density:

$$
E[\rho]=T[\rho]+V_{e n}[\rho]+V_{e e}[\rho]
$$

where $T[\rho], V_{e n}[\rho]$ and $V_{e e}[\rho]$ are the electronic kinetic energy, the electron-nucleus potential energy and the electron-electron potential energy as functionals of the density. The integration of the electron density $(\rho(r))$ over all space gives the number of electrons:

$$
\int \rho(r) d r=N
$$

In almost all cases, there exists a duality between the density of the electron cloud around the nuclei and the external potential (the charge and position of the nuclei) which is exerted upon the electrons. For one electron density cloud $(\rho(r))$, there exists one specific arrangement of nuclei which exerts the external potential on $N$ electrons:

$$
\rho(r) \leftrightarrow N, V_{\text {ext }}
$$

$V_{e n}[\rho]$ can therefore be defined as follows:

$$
V_{e n}[\rho]=\int V_{e x t}(r) \rho(r) d r
$$

The number of electrons and the external potential define the Hamiltonian, which determines the wave function, from which the properties of the system are computed:

$$
\rho(r) \rightarrow N, V_{\text {ext }} \rightarrow \widehat{H} \rightarrow \Psi \rightarrow \text { properties }
$$

This is encapsulated in the Hohenberg-Kohn theorem, which states that the energy of a system is a functional of the electron density, and that this density obeys a variational principle, meaning that the physical density of the system is that which minimizes the energy expression. According to this theorem, from the electron density alone all other properties of the system can be determined.
To determine electron density, a Slater determinant (the Kohn-Sham Slater determinant, $\Phi_{K S}$ ) is introduced. The Kohn-Sham Slater determinant is comprised of non-interacting electrons placed in a set of non-physical orbitals such that it produces the physical ground state density of the real
system. From this Kohn-Sham Slater determinant, it is possible to calculate an auxiliary kinetic energy, that is, the kinetic energy of the system of non-interacting electrons:

$$
T_{a u x}[\rho]=\left\langle\Phi_{K S}\right| \widehat{T}\left|\Phi_{K S}\right\rangle
$$

The electron-electron interaction term $\left(\widehat{V}_{e e}\right)$ is approximated with a classical expression for the electrostatic interaction of a charge distribution $(J[\rho])$ :

$$
J[\rho]=\int \frac{\rho(r) \rho\left(r^{\prime}\right)}{\left|r-r^{\prime}\right|} d r d r^{\prime}
$$

These expressions are first approximations, and their differences from the exact result (the physical electronic kinetic energy $T$ and the electron-electron repulsive potential energy $V_{e e}$ ) are combined into the so-called exchange-correlation energy:

$$
E_{X C}[\rho]=\left(T-T_{a u x}[\rho]\right)+\left(V_{e e}-J[\rho]\right)
$$

This term therefore accounts for exchange (the Pauli principle) and correlation (interelectronic repulsion). This $E_{X C}[\rho]$ correction is added to the other components described above to give the Kohn-Sham energy density functional:

$$
E_{K S}[\rho]=\min _{\Phi_{K S}}\left\langle\Phi_{K S}\right| \widehat{T}\left|\Phi_{K S}\right\rangle+J[\rho]+\int V_{e x t}(r) \rho(r) d r+E_{X C}[\rho]
$$

As in the standard Slater determinant for the Hartree-Fock method described above, the KohnSham Slater determinant is an antisymmetric product of one-electron orbitals ( $\psi_{i}$ ), albeit nonphysical ones. This gives a set of one-electron Kohn-Sham equations which use, instead of the molecular Hamiltonian operator, a one-electron Kohn-Sham operator ( $\hat{f}_{K S}$ ):

$$
\hat{f}_{K S} \psi_{i}=\varepsilon_{i} \psi_{i}
$$

The Kohn-Sham equations are solved self-consistently to minimize (using the variational principle) the energy of the Kohn-Sham Slater determinant to give the orbital energies $\left(\varepsilon_{i}\right)$. The sum of the set of non-physical orbitals obtained from this self-consistent solution gives the same density as the real system:

$$
\rho(r)=\sum_{i=1}^{N_{\text {orbs }}}\left|\psi_{i}(r)\right|^{2}
$$

$E_{X C}[\rho]$ is by definition unknowable, given that it accounts for all the effects that make the real system different from that of non-interacting electrons in the Kohn-Sham determinant. If the

Hartree-Fock method is a realistic approximation for the system (i.e. one Slater determinant dominates the electronic picture), the approximations of $E_{X C}[\rho]$ are generally acceptable and DFT yields a reasonable result.

Many functionals have been developed which attempt to account for $E_{X C}[\rho]$. Such models include local density approximations (LDAs, which depend solely on electronic density at point in space and are based on a homogeneous electron gas), generalized gradient approximations (GGAs, which account for the non-homogeneity of the electron density by including gradients of the density), meta-generalized gradient approximations (meta-GGAs, which, in addition to the gradient of the density, include its Laplacian), hybrid functionals (in which the exchange is computed with the occupied Kohn-Shan orbitals and the density) and double-hybrid functionals (where, in addition to the Kohn-Sham orbitals, unoccupied Kohn-Sham orbitals are also included).

### 1.4 Application of DFT and DLPNO-CCSD(T) to This Project

The starting materials, intermediates and transition states of a chemical reaction pathway exist on a potential energy surface (PES), which has as many coordinates (dimensions) as the molecules have degrees of freedom (i.e. bond lengths, bond angles and dihedral angles). One use of computational organic chemistry is to locate the key chemical structures on the PES using quantum mechanical calculations to locate and compare the energy profile of possible reaction pathways from reactant(s) to product(s). To do so, an iteration of energy calculations are performed to identify the lowest energy (or « optimized ») geometry of each structure on the PES.

While there are always rotational and vibrational excited states present in a real system, to simplify calculations the absolute minimum of the system is calculated without the statistical contribution of excited states. Instead, a "correction" is then added at the end of the calculation which accounts for the thermal contribution to the total energy of a given optimized geometry.

Beginning with an initial guess for each structure which is submitted for calculation, a selfconsistent field (SCF) is calculated, the molecular geometry is adjusted according to a gradient, and the SCF of the new geometry is evaluated. This continues until a stationary point is located.

A stationary point is defined as a structure for which the first derivative of the energy with respect to each degree of freedom is 0 .

Every minimum and transition state is a stationary point. An intermediate or starting material is a minimum in the potential energy surface, meaning that any change in its geometry will only increase the structure's energy, while a transition state is a point on the PES which is a minimum with respect to every coordinate except one. It is therefore a saddle point. In the schematic example given in Figure 28, the reaction pathway is represented in only three dimensions for simplicity. The horizontal axes represent the degrees of freedom of the chemical structure and the vertical axis represents the potential energy. Both the reactant and the product are minima on the PES, and the transition state is a saddle point between the two minima.


Figure 28 : Schematic diagram of a potential energy surface.
(Source: www.chm.bris.ac.uk)
For this project, geometries were optimized using DFT. The thermal energy correction to the free energy (i.e. the rotational, vibrational and translational energies) of each compound was extracted from the optimized geometry $\left(G_{C O R R}\right)$. A single-point electronic energy calculation ( $E_{C C S D}$ ) was then performed on the optimized geometry using domain-based local pair natural orbital coupled cluster with singles, doubles and perturbative triples (DLPNO-CCSD(T)). This
method was not used for structure optimizations due to the prohibitive computational cost of such an approach. In addition, geometries optimized using $\operatorname{CCSD}(\mathrm{T})$ would be essentially the same as those obtained from DFT optimization.

In this way, the total free energy of each substrate $(G)$ was comprised of the electronic energy evaluated from an explicit treatment of the wave function ( $\operatorname{DLPNO}-\operatorname{CCSD}(\mathrm{T})$ ) and the thermal energy from a DFT calculation:

$$
G=E_{C C S D}+G_{C O R R}
$$

From this, the free energy barriers of each step of the reaction ( $\Delta G_{\text {reaction step }}$ ) were calculated by subtracting the sum of free energies of all the reactants for a given reaction step from the sum of free energies of the products:

$$
\Delta G_{\text {reaction step }}=\sum G_{\text {products }}-\sum G_{\text {reactants }}
$$

All results reported in the following chapter are the result of this two-method calculation.
To account in part for the effect of solvent on the energy profile of the reaction mechanism, the implicit integral equation formalism polarizable continuum model (IEFPCM) was used during DFT geometry optimizations. ${ }^{191-193}$ As an explicit consideration of solvent molecules would significantly increase calculation time and complexity, the polarizable continuum model approximates the effect of solvent on the total free energy of the calculated structures (which are otherwise determined in the gas phase).

This model provides the electrostatic ( $\mathrm{G}_{\mathrm{ES}}$ ) and dispersion-repulsion $\left(\mathrm{G}_{\mathrm{DR}}\right)$ free energy, and the cavitation energy $\left(\mathrm{G}_{\mathrm{CAV}}\right)$, which together constitute the free energy in solution $\left(\mathrm{G}_{\mathrm{SOL}}\right)$ :

$$
G_{S O L}=G_{E S}+G_{D R}+G_{C A V}
$$

A cavity is created around the molecular structure, its form determined by placing spheres slightly larger than the van der Waals radii of each atom centered on each nucleus. The exact shape of the cavity is also determined by the connectivity of the atoms and global charge of the structure, in addition to the atom type. The shape of this cavity and its interaction with the molecular geometry determines the cavitation energy. The dispersion-repulsion energy is evaluated by adding the approximate radius and shape of solvent molecules around the structure, forming a solvent accessible surface, which is larger than the cavity. The space between the van der Waals cavity of the structure and the solvent accessible surface is the solvent excluding
surface. The electrostatic free energy is obtained by assessing the charges of the structure at this surface.

## CHAPTER 2: MECHANISTIC ORIGIN OF $\beta$-DEFECT FORMATION IN THIOPHENEBASED POLYMERS PREPARED BY DIRECT (HETERO)ARYLATION

### 2.1 Résumé

Une étude computationnelle de la réaction de l'arylation directe a été entreprise afin d'élucider l'origine des couplages non-sélectifs en position $\beta$ observés au sein de polymères à base d'unités thiophène préparés par polymérisation par (hétéro)arylation directe ( PHAD , ou DHAP en anglais). La réactivité et la sélectivité de l'activation du lien $\mathrm{C}-\mathrm{H}$ vis-à-vis le mécanisme de la métallation-déprotonation concertée ont été étudiées sur des thiophènes modèles avec la théorie de la fonctionnelle de la densité (DFT) et la méthode du cluster couplé avec excitations simples et doubles avec triples perturbés, approximée avec la méthode de l'orbitale naturelle de paires locales à base de domaine (DLPNO-CCSD(T)). Il est démontré que l'effet électronique de différents substituants contrôle la régiosélectivité observée expérimentalement. Des unités thiophène riches ou pauvres en électrons ayant plus d'un lien $\mathrm{C}-\mathrm{H}$ possèdent une sélectivité intrinsèque pour l'activation du lien en position $\alpha$, tandis que la présence d'un atome de brome en position $\alpha$ réduit considérablement cette sélectivité en activant le lien $\mathrm{C}_{\beta}-\mathrm{H}$ adjacent. Par conséquent, le monomère halogéné est responsable pour la faible sélectivité parfois rapportée en PHAD. L'effet du substrat qui subit l'addition oxydante est rapporté pour la première fois et quelques principes de conception pour les monomères ont été établis afin d'atteindre une polymérisation par PHAD à haute sélectivité.

### 2.2 Abstract

A computational study of the direct arylation reaction was undertaken to understand the origin of non-selective $\beta$-couplings observed in thiophene-based polymers prepared by direct (hetero)arylation polymerization (DHAP). The reactivities and selectivities of $\mathrm{C}-\mathrm{H}$ bond activations were studied for the concerted metalation-deprotonation mechanism on model thiophene substrates using density functional theory (DFT) and domain-based local pair natural orbital coupled cluster with singles, doubles and perturbative triples (DLPNO-CCSD(T)). Substituent effects are shown to control experimentally observed regioselectivities. Electron-rich or deficient thiophene substrates with multiple $\mathrm{C}-\mathrm{H}$ bonds possess an intrinsic selectivity for bond activation at the $\alpha$-position, while halogens in the $\alpha$-position substantially reduce coupling selectivities by activating the adjacent $\mathrm{C}_{\beta}-\mathrm{H}$ bonds. Therefore, the halogenated monomer is responsible for the reported poor selectivities in DHAP. The effect of the substrate undergoing oxidative addition is also reported for the first time along with design principles for monomeric units amenable to high-selectivity DHAP polymerizations.

### 2.3 Introduction

The direct (hetero)arylation polymerization (DHAP) reaction harnesses the single-step activation and arylation of aromatic carbon-hydrogen bonds for the efficient synthesis of conjugated polymers. ${ }^{10}$ This palladium-catalyzed technique accesses the stepwise formation of a bond between two $s p^{2}$-hybridized carbons via the coupling of the carbon-halogen $(\mathrm{C}-\mathrm{X})$ bond of one arene (or heteroarene) with the carbon-hydrogen ( $\mathrm{C}-\mathrm{H}$ ) bond of another. Bypassing transmetalation agents (such as the organotin, organoboron and organozinc derivatives necessary for Migita-Stille, Miyaura-Suzuki and Negishi polymerizations, respectively) reduces the number of synthetic steps, eliminates the need for expensive or unstable reagents, and avoids the production of stoichiometric quantities of toxic organometallic by-products. Thus from industrial and environmental perspectives, DHAP is more favorable than traditional coupling protocols involving organometallic or heteroelement-containing components.

The challenge of adapting any cross-coupling reaction to the synthesis of conjugated polymers is that products of undesired secondary reactions in the catalytic system will remain in the resulting polymer material. In other words, what would be considered an impurity in an organic chemistry reaction becomes a covalently-incorporated defect in the polymer chain. DHAP is no exception to this: the side-reactions which lead to easily separable impurities in small molecule direct arylation protocols contribute to polymeric materials with chemical structures which diverge from ideal (or "defect-free") polymers. For this reason, much DHAP research focuses on the suppression of defects to obtain materials that exhibit optoelectronic properties which meet (or surpass) those of polymers prepared by other cross-coupling techniques. ${ }^{10,95,105,108,158}$

Figure 29 shows the most common defects for the well-characterized polymer poly(3hexylthiophene) (P3HT). One such defect is homocoupling, which can originate from either the coupling of two $\mathrm{C}-\mathrm{Br}$ bonds (often preceded by dehalogenation of one of the two carbon-halide bonds) or double activation of two $\mathrm{C}-\mathrm{H}$ bonds. In homopolymers, this can lead to "head-tohead" or "tail-to-tail" defects (Figure 29, b and c) rather than the desired regioregular "head-totail" motif (a), while in copolymers it leads to the linking of two of the same units ( $-\mathrm{A}-\mathrm{A}-$ or -$\mathrm{B}-\mathrm{B}-$ ) rather than the alternating repeating ( $-\mathrm{A}-\mathrm{B}-$ ) motif. This side-reaction is identified from NMR and UV-Vis spectroscopy, and recent studies have endeavored to eliminate it by optimizing reaction conditions. ${ }^{107,112}$

Ideal structure


Figure 29 : Defects observed in DHAP-prepared polymers shown on a model P3HT chain.

Another less well-understood side-reaction is $\beta$-defect formation, in which cross-coupling occurs on a $\mathrm{C}_{\text {aryl }}-\mathrm{H}$ bond other than the one targeted (Figure 29, d). This defect is unique to DHAP as the catalytic system is intended to activate $\mathrm{C}-\mathrm{H}$ bonds, while in other cross-coupling polymerization techniques the placement of the organometallic (or heteroelement-containing) group during monomer synthesis predetermines the location of coupling. There are often multiple $\mathrm{C}_{\text {aryl }}-\mathrm{H}$ bonds on a given monomer, but these bonds do not necessarily all interfere with polymerization. The $\mathrm{C}_{\text {ary }} 1-\mathrm{H}$ bonds of most phenyl derivatives (such as carbazole, fluorene, isoindigo and benzothiadiazole) are not reactive enough for DHAP. ${ }^{53,132}$ For this reason, when one of these units serves as a monomer in a copolymerization, it is almost exclusively used in is halogenated form.

Thiophene-based substrates, on the other hand, have more than one energetically accessible $\mathrm{C}-\mathrm{H}$ bond in standard coupling conditions, and are therefore susceptible to non-selective couplings. This is crucial in DHAP, as most conjugated polymers are synthesized by cross-couplings involving thiophene-based building blocks. Thienyl fragments, while providing reactive $\mathrm{C}-\mathrm{H}$ bonds for polymerization, also act as spacers between otherwise bulky repeating units, reducing torsion within the polymer chain and increasing co-planarity. In addition, thiophenes are easily
functionalized with electron-accepting or electron-donating functional groups, or with sidechains to fine-tune the electronic properties and solubility of the polymer., ${ }^{9,85,89,90,96,110,163,167}$

Most high-performance copolymers are synthesized from monomers which either contain thiophenes fused to other aromatic fragments or consist of arenes flanked with thienyl groups. Thiophene-flanked monomers possesses three pairs of available $\mathrm{C}_{\text {ary }}-\mathrm{H}$ bonds: the $\mathrm{C}-\mathrm{H}$ bond adjacent to the sulfur atom, (the $\alpha$-position), the neighboring $\mathrm{C}_{\beta}-\mathrm{H}$ bond, and the $\mathrm{C}_{\gamma}-\mathrm{H}$ bond, adjacent to the monomer core linked to the thiophene. Examples of units often used with flanking thiophenes include diketopyrrolopyrrole, benzothiadiazole, alkylphenylene and naphthalene diimide. ${ }^{90,156,158,194}$ When a monomer of this type is halogenated, the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond is replaced by a halogen, which is typically bromine in DHAP due to the reactivity of the $\mathrm{C}-\mathrm{Br}$ bond and synthetic ease of bromination reactions. Thiophenes can also be fused to other aromatic cores, such as benzodithiophene, cyclopentadithiophene, dithienothiophene, dithienosilole and thienoisoindigo. ${ }^{93,95,96,110,145,195-197}$ These units differ from thiophene-flanked units in that they do not possess $\mathrm{C}_{\gamma}-\mathrm{H}$ bonds.

In DHAP, the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond is the desired coupling position, as $\alpha$ - linkages maximize co-planarity between repeating units and contribute to optimal $\pi$-orbital overlap and extended conjugation. However, if an available $\beta$-proton on a monomer or oligomer chain were to be cleaved during polymerization, a $\beta$-defect may occur. This leads to a disruption of the $\pi$-conjugation and supramolecular organization of the polymer chain. As such, even a small fraction of $\beta$-defects can contribute to drastically reduced performances in organic electronic devices. ${ }^{133}$ For instance, branching leads to poorer short circuit currents and fill factors in bulk heterojunction (BHJ) organic photovoltaic devices, indicating the poor quality of the BHJ morphology. ${ }^{12}$
$\beta$-defects must therefore be eliminated to maximize the optoelectronic properties of organic materials prepared by DHAP. Unfortunately, there is very little spectroscopic evidence for $\beta$ defect formation. ${ }^{66,89,133}$. While $\mathrm{C}-\mathrm{C}$ coupling at the $\beta$-position instead of the $\alpha$ - position of a thiophene substrate would lead to a bend in the polymer, the activation of a $\mathrm{C}_{\beta}-\mathrm{H}$ bond in addition to an $\alpha$-bond may lead to multiple chains becoming interconnected, forming a branched and insoluble structure. ${ }^{138}$ This leads to loss of yield and the added difficulty of removing insoluble material on an industrial scale. ${ }^{136}$

One solution employed to overcoming unselective coupling was to replace $\mathrm{C}-\mathrm{H}$ bonds in the $\beta$ position of thiophene substrates with alkyl side-chains. ${ }^{11,137}$ This approach has led to more welldefined materials, demonstrating that $\beta$-coupling is an impediment to the synthesis of highquality conjugated polymers via DHAP. However, this approach is not feasible for the synthesis of high-performance semi-conductor materials because co-planarity of the repeating units is no longer possible, and the reduced $\pi$-orbital overlap leads to poor charge transport. ${ }^{111,123,137,145}$
$\beta$-defect formation can be suppressed by increasing steric hindrance around the catalyst by way of alkyl chains near the target $\mathrm{C}-\mathrm{H}$ bond on the monomer, large or bidentate ligands, or bulky carboxylic acid additives. ${ }^{68,105,108,120,140,152}$ There are still a number of cases which demonstrate that even in optimized reaction conditions DHAP does not lead to polymers with properties resembling those of analog materials prepared by traditional coupling techniques. ${ }^{36,90,97,105,111,}$ 134, 198 Furthermore, in certain copolymerizations the choice of the monomer bearing the bromines can substantially influence polymer yield, molecular weight, solubility and optoelectronic properties, which suggests that the halide may promote $\beta$-defect formation. ${ }^{96,121,}$ 138

Direct arylation involves the metalation of an aryl or heteroaryl C-H bond with a palladium ( Pd ) catalyst, while other palladium-catalyzed cross-coupling reactions rely on aryl group transfer to the catalyst by transmetalating another organometallic (or heteroelement-containing) functional group. Several mechanisms have been put forward to explain this metalation event, including electrophilic aromatic substitution ( $\mathrm{S}_{\mathrm{E}} \mathrm{Ar}$ ), Heck-type carbo-palladation followed by anti $\beta-\mathrm{H}$ elimination, and $\mathrm{C}-\mathrm{H}$ oxidative insertion followed by double reductive elimination. ${ }^{23,} 44-47,62$ However, concerted metalation-deprotonation (CMD) is broadly accepted as the step of the catalytic cycle to replace transmetalation. ${ }^{42,48-50,54,55}$ This base-assisted mechanism explains the requirement of a mild carbonate or carboxylate for the reaction to proceed. ${ }^{25,51,62}$ Studies of the direct arylation of thiophenes reveal that a concerted mechanism is universally favored. Moreover, the CMD pathway offers the best explanation for the experimentally observed regioselectivities for many small molecules. ${ }^{53,132,199}$

Given both the ubiquity of thiophene-based units in conjugated polymers and the intrinsic issues regarding $\mathrm{C}-\mathrm{H}$ bond selectivity in DHAP, the CMD direct arylation mechanism was studied using model thiophenes with density functional theory using the M06 functional and domain-
based local pair natural orbital coupled cluster with singles, doubles and perturbative triples (DLPNO-CCSD(T)).

### 2.4 Results and Discussion

### 2.4.1 Direct arylation of 2-bromothiophene

The proposed catalytic cycle for direct arylation of 2-bromothiophene (BrTh) via the CMD transition state (TS) is shown in Figure 30. The mechanism begins with the oxidative addition (OA) of the BrTh $\mathrm{C}-\mathrm{Br}$ bond onto a $\operatorname{Pd}(0)$ catalyst. Ligand exchange leads to a bidentate carboxylate complex. This is followed by the deprotonation of the $\mathrm{C}_{\text {ary }} 1-\mathrm{H}$ bond of another substrate (another BrTh in this example) by the carboxylate base and simultaneous formation of a Pd-C bond, hence the CMD. The carboxylic acid may de-coordinate from the metal center and undergo an acid-base reaction with a carbonate base. Finally, the new carbon-carbon bond is formed via the reductive elimination (RE) TS, which regenerates the $\operatorname{Pd}(0)$ catalyst.


Figure 30 : The proposed mechanism for carboxylate-assisted direct arylation cross-coupling of two 2-bromothiophene substrates via the concerted metalation-deprotonation (CMD) pathway.

Only the coupling of the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond (the 5-position of the thiophene unit, with the proton in blue) is shown for clarity.

A number of variations on this mechanism have been proposed. For instance, it is possible for deprotonation to occur via a base which is not itself complexed to the metal center. However, this "outer-sphere" deprotonation is less energetically feasible than $\mathrm{C}-\mathrm{H}$ bond cleavage with a base coordinated to the Pd via an oxygen atom ("inner-sphere" deprotonation). ${ }^{62}$ Also, while deprotonation of the $\mathrm{C}-\mathrm{H}$ bond can occur with a carbonate base alone, carboxylate is shown in this example and is used for this study due to the observation that bulkier carboxylates increase coupling reactivity and selectivity in small molecule experiments. Carboxylate additives also tend to provide the best catalytic reactivity in copolymerizations. ${ }^{25, ~ 89, ~ 90, ~} 108$ When carboxylates are used, the carbonate salt is included in the polymerization reaction medium primarily to recycle the carboxylate, as shown in Figure 30.

Small molecule studies, particularly employing bidentate ligands, have also led to the proposition of variations on the direct arylation mechanism. ${ }^{58,60,61,66,67,200}$ While diamine ligands in some instances have been shown to improve coupling selectivity when used alone or alongside other ligands, they do not provide the necessary reactivity for obtaining high molecular weight polymers. ${ }^{66}$ Bidentate (bis)phosphine ligands have also not provided the desired reactivity or selectivity in DHAP. ${ }^{66,67}$ As such, a model mono-dentate phosphine ligand and carboxylate base were used in this study.

Due to the central role of the thiophene motif in DHAP and the experimental observations regarding the role of brominated thiophene substrates, the full catalytic cycle for the direct arylation of two $\mathbf{B r T h}$ units was computed. The computed potential energy surface is shown in Figure 31 and optimized geometries are given in Table 1. As there are three available $\mathrm{C}-\mathrm{H}$ bonds on BrTh, there are three possible CMD TSs and subsequent pathways to arylation, which give insight into the observed coupling selectivity of thiophene-based substrates.


Figure 31 : Catalytic cycle for the direct arylation of 2-bromothiophene (BrTh) in the $\alpha(5-), \beta(4-)$ and $\gamma(3-)$ positions with another 2bromothiophene substrate via the concerted metalation-deprotonation pathway. For clarity, transition states and intermediates 5-10 are reproduced in Table 1. Gibbs free energies are in ${\mathrm{kcal} \mathrm{mol}^{-1} \text { and are presented relative to the starting complex (Int-1) and were }}_{\text {a }}$ calculated using DLPNO-CCSD(T)/DefBas4-COSMO( $\varepsilon=7.25$ )//M06/6-31+G(d,p)-LANL2DZ-IEFPCM( $\varepsilon=7.25$ ). (orange = phosphorus, turquoise $=$ palladium, burgundy $=$ bromine ) .

Table 1 : Intermediates and transition states of the three potential coupling pathways in the direct arylation of 2-bromothiophene.
Calculated using DLPNO-CCSD(T)/DefBas4-COSMO $(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+G(\mathrm{~d}, \mathrm{p})-\operatorname{LANL} 2 \mathrm{DZ}-\operatorname{IEFPCM}(\varepsilon=7.25)$. (orange = phosphorus, turquoise $=$ palladium, burgundy $=$ bromine)

|  | CMD TS (kcal mol ${ }^{-1}$ ) | Post-CMD Intermediate | Pre-RE Intermediate | RE TS (kcal mol ${ }^{-1}$ ) |
| :---: | :---: | :---: | :---: | :---: |
| 星 |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

The OA TS is not shown as there is only one possible $\mathrm{C}-\mathrm{Br}$ bond which can undergo oxidative addition in the reaction, and will not affect coupling selectivity. Following OA of BrTh, successive ligand exchanges (Int-2 and Int-3) lead to the stabilized bidentate complex, Int-4. The CMD TSs for the three $\mathrm{C}-\mathrm{H}$ bonds on the incipient BrTh were located. The $\mathrm{C}-\mathrm{H}$ bond at the 5-position ( $\alpha$ ) of 2bromothiophene has the lowest activation free energy $\left(\Delta G^{\ddagger}\right)$ of the three possible $\mathrm{C}-\mathrm{H}$ bonds ( 25.7 kcal $\mathrm{mol}^{-1}$, in blue). The $\Delta G^{\ddagger}$ of the $\gamma$-position (the $\mathrm{C}-\mathrm{H}$ bond adjacent to the bromine, with the potential energy surface in green) is lower than that of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond ( $26.3 \mathrm{vs} .28 .3 \mathrm{kcal} \mathrm{mol}^{-1}$ ) and comparable to that of the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond $\left(\Delta \Delta G^{\ddagger}=0.7 \mathrm{kcal} \mathrm{mol}^{-1}\right)$, consistent with the hypothesis that bromination increases the reactivity of adjacent $\mathrm{C}-\mathrm{H}$ bonds. ${ }^{90,150}$

Following the CMD step, the Post-CMD intermediate is converted to a Pre-RE intermediate by the exchange of now-protonated carboxylate with another phosphine. The reductive elimination (RE) TS leads to the formation of the final cross-coupling product. CMD, Post-CMD, Pre-RE and RE geometries are given in Table 1. TS energies and bond lengths are similar for all three reductive elimination pathways (2.01-2.02 $\AA$ for the evolving $\mathrm{C}-\mathrm{C}$ bonds and 2.05-2.07 for the $\mathrm{Pd}-\mathrm{C}$ bonds), indicating that the presence of the bromine has little effect on the final stage of the coupling mechanism. Following the Post-CMD intermediate, the $\gamma$ coupling pathway becomes the lowest in energy prior to and during the reductive elimination (Pre-RE and RE), though the free energy differences between the three pathways is small $\left(-10.1 \mathrm{kcal} \mathrm{mol}^{-1}\right.$ for Pre-RE intermediate in the $\gamma$ pathway and $-9.6 \mathrm{kcal} \mathrm{mol}^{-1}$ in the $\alpha$ pathway). The RE TS free energies are much lower than the CMD free energies (e.g. $12.6 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\boldsymbol{\alpha}$-RE versus $25.7 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\boldsymbol{\alpha}$-CMD, Table 1). As such, the CMD step is rate- and regioselectivity-determining. ${ }^{47,53,132}$ The final products are $37-39 \mathrm{kcal} \mathrm{mol}^{-1}$ lower in free energy than the reactants, showing that the reaction is irreversible.

The use of pivalate as the base was shown to have little effect on $\mathrm{C}-\mathrm{H}$ bond activation energies other than lowering the activation free energies of all three $\mathrm{C}-\mathrm{H}$ bonds by $0.2-0.5 \mathrm{kcal} \mathrm{mol}^{-1}$ relative to an acetate-assisted TS, explaining the greater success of direct small molecule arylation using pivalate rather than acetate. ${ }^{25}$ Results for CMD TSs using pivalate are given in Annex 2 (Figure 41 and Table 4). Acetate was used as the base for the rest of this study to reduce computational cost.

In a similar fashion, the effect of the ligand on the $\mathrm{C}-\mathrm{H}$ activation barrier was explored. Because of the increased difficulty of converging geometries with a large number of degrees of freedom, such as would be the case with bulky phosphines such as tricyclohexylphosphine $\left(\mathrm{PCy}_{3}\right)$, it was desirable to
employ the smallest possible phosphine $\left(\mathrm{PH}_{3}\right)$ in this study. Although $\mathrm{PH}_{3}$ is not a ligand used experimentally in cross-coupling reactions, it is expected that because the phosphine remains coordinated to the metal center throughout the coupling mechanism, its impact on catalyst reactivity should remain constant. For instance, it has been shown in recent work on computational catalyst design that approximations of ligand structure preserve the linear free energy scaling relationships observed with more complex and experimentally "realistic" ligands for $\mathrm{C}-\mathrm{C}$ cross-coupling reaction profiles. ${ }^{201}$ To confirm that the ligand has a limited effect on the observed trends of $\mathrm{C}-\mathrm{H}$ coupling selectivity, the CMD steps at the three available $\mathrm{C}-\mathrm{H}$ bonds $(\alpha, \beta$, and $\gamma$ ) of bromothiophene were evaluated using the ligands trimethylphosphine $\left(\mathrm{PMe}_{3}\right)$ and tricyclohexylphosphine $\left(\mathrm{PCy}_{3}\right)$. The results, given in Table S , clearly express the same trends with regards to difference in relative activation energy $\left(\Delta \Delta \mathrm{G}^{\ddagger}\right.$ ) for the three $\mathrm{C}-\mathrm{H}$ activation pathways of bromothiophene ( $\Delta \mathrm{G}^{\ddagger}$ for $\mathrm{C}_{\alpha}-\mathrm{H}<\mathrm{C}_{\gamma}-\mathrm{H}<$ $\mathrm{C}_{\beta}-\mathrm{H}$ ). Given the limited effect of phosphine structure on this trend, $\mathrm{PH}_{3}$ was used as the ligand in the model catalyst for the remainder of the study to maintain a reasonable computational cost.

### 2.4.2 Electronic substituent effects

Previous studies have focused on the $\mathrm{C}-\mathrm{H}$ bond reactivity of independent substrates for small molecule coupling reactions but not the possible competing reactivities of two coupling partners. ${ }^{53,57,62,132,199}$ Other work has compared the CMD activation energies of multiple $\mathrm{C}-\mathrm{H}$ bonds on pairs of truncated co-monomers to take into account competing reactivities during polymerization, but has exclusively used a phenyl group as the aryl on the starting catalyst. ${ }^{96}$



Figure 32 : Model thiophenes used in this study. 2D model of the CMD transition states available in the cross-coupling of the model thiophene units, where R and R ' are the electronically activating substituents (CN, H and OMe ) on the brominated thiophene and the CMD thiophene, respectively.

We explored the electronic properties for both the catalyst and the incident thiophene by installing electron-withdrawing and electron-donating groups ( $\mathrm{R}=\mathrm{CN}$ and OMe , respectively) at the thiophene 2-position. In this way, the model thiophenes CNTh and MeOTh (Figure 32) simulate the electrondonating and -withdrawing character of electron-poor and electron-rich monomers. We compared these results to thiophene ( $\mathbf{T h}$ ) to understand the substituent effects on $\alpha$ - versus $\beta$ - selectivity. The brominated derivatives of each substrate (BrCNTh, BrTh, and BrMeOTh) were used as oxidative addition substrates to generate the three possible catalyst complexes prior to the CMD event (Int-11, Int-4 and Int-16, respectively), as shown in Figures 32 and 33. The activation free energies at the $\alpha$ (blue) and $\beta$ - (red) positions of each CMD substrate were calculated with each catalyst. The oxidative addition substrate is also present during the reaction and therefore the activation of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond adjacent to bromine was also determined (green). ${ }^{12,202}$


Figure 33: A schematic of activation free energies for the CMD of electron-rich (MeOTh), unsubstituted ( $\mathbf{T h}$ ) and electron-poor ( $\mathbf{C N T h}$ ) thiophenes using catalysts of the same electronic classes. Locations for $\mathrm{C}_{\alpha}-\mathrm{H}$ activation are marked in blue, $\mathrm{C}_{\beta}-\mathrm{H}$ in red, and $\mathrm{C}_{\beta}-\mathrm{H}$ on oxidative addition (brominated) thiophenes in green. Full results are detailed in Table 2. Calculated using DLPNO$\operatorname{CCSD}(\mathrm{T}) / \mathrm{DefBas4}-\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})-L A N L 2 D Z-I E F P C M(\varepsilon=7.25)$.

As has been demonstrated experimentally and computationally, both electron-donating and electronaccepting substituents activate the $\alpha$-proton relative to the reference $\mathbf{T h}$ (for a given starting catalyst). ${ }^{53,}$
${ }^{57}$ For example, $25.3 \mathrm{kcal} \mathrm{mol}^{-1}$ is observed for the CMD TS energy of Th with the catalyst Int-11, while the $\alpha$-CMD for CNTh and MeOTh have reduced $\Delta G^{\ddagger}$ values of 24.6 and $22.9 \mathrm{kcal} \mathrm{mol}^{-1}$, respectively. This trend is observed regardless of the catalyst used. We utilized the distortion/interaction model to explain the difference in activation energies. ${ }^{203}$ The distortion energy $\left(\Delta E_{d}^{\ddagger}\right)$ is required to distort the reactants (the substrate and the catalyst complex) into their respective CMD TS geometry ( $\Delta E_{d-s u b}^{\ddagger}$ and $\Delta E_{d-c a t}^{\ddagger}$ ) without allowing them to interact. The interaction energy $\left(\Delta E_{i}^{\ddagger}\right)$ is the difference between the distortion energy and the electronic activation energy and is comprised of the stabilizing interactions of the reactants, such as charge transfer, dispersive and electrostatic effects.


Figure 34: Substrate distortion energies $\left(\Delta \boldsymbol{E}_{\boldsymbol{d}-\text { sub }}^{\ddagger}\right)$, catalyst distortion energies $\left(\Delta \boldsymbol{E}_{\boldsymbol{d}-\boldsymbol{c a t}}^{\ddagger}\right)$ and interaction energies ( $\Delta \boldsymbol{E}_{\boldsymbol{i}}^{\ddagger}$ ) for the concerted metalation-deprotonation of MeOTh, $\mathbf{T h}$ and $\mathbf{C N T h}$ with the catalysts Int-11, Int-4 and Int-16. Full results are detailed in Table 2. Calculated using DLPNO$\operatorname{CCSD}(\mathrm{T}) / \mathrm{DefBas4}-\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})-\mathrm{LANL} 2 \mathrm{DZ}-\operatorname{IEFPCM}(\varepsilon=7.25)$.

Nucleophilic CMD substrates (MeOTh) have more favorable $\Delta E_{i}^{\ddagger}$ and higher $\Delta E_{d-s u b}^{\ddagger}$, while electronpoor thiophenes (CNTh) have both a small $\Delta E_{i}^{\ddagger}$ and lower $\Delta E_{d-s u b}^{\ddagger}$. Therefore, it is not possible to predict the reactivity of a thiophene substrate-based on the nucleophilicity or electrophilicity of the
substrate alone. ${ }^{53,132}$ The increase in substrate distortion and interaction energies with increased nucleophilicity on the CMD substrate is observed for both the $\mathrm{C}_{\alpha}-\mathrm{H}$ and $\mathrm{C}_{\beta}-\mathrm{H}$ bonds, regardless of the catalyst (Figure 34; all additional distortion/interaction results are provided in the Table 2). The increase in $\Delta E_{i}^{\ddagger}$ and $\Delta E_{d}^{\ddagger}$ affect the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond much more than the $\mathrm{C}_{\beta}-\mathrm{H}$ bond. $\Delta E_{i}^{\ddagger}$ for the activation of the $\mathrm{C}_{\alpha}-\mathrm{H}$ in particular increases steeply with higher electron density on the thiophene, such that the difference in $\alpha$ versus $\beta \mathbf{C}-\mathrm{H}$ activation energy ( $\Delta \Delta G^{\ddagger}$ ) increases from $2.0 \mathrm{kcal} \mathrm{mol}^{-1}$ with $\mathbf{C N T h}$ (with Int-4 as catalyst) to $3.0 \mathrm{kcal} \mathrm{mol}^{-1}$ with $\mathbf{T h}$, and to $4.3 \mathrm{kcal} \mathrm{mol}^{-1}$ with MeOTh. Regardless of the catalyst, this contributes to the electron-rich CMD substrate (MeOTh) showing the greatest selectivity for the $\alpha$-coupling position.

The $\Delta E_{d-s u b}^{\ddagger}$ for CNTh with Int-16 is $25.1 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathrm{C}_{\alpha}-\mathrm{H}$ and $27.8 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathrm{C}_{\beta}-\mathrm{H}$ activation while the $\Delta E_{i}^{\ddagger}$ is very similar for both $\left(-25.7 \mathrm{kcal} \mathrm{mol}^{-1}\right.$ for $\mathrm{C}_{\alpha}-\mathrm{H}$ and $-25.2 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\left.\mathrm{C}_{\beta}-\mathrm{H}\right)$. The $\Delta E_{d-s u b}^{\ddagger}$ values for MeOTh with the same catalyst are almost equivalent ( $33.8 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathrm{C}_{\alpha}-\mathrm{H}$ ) and $33.2 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathrm{C}_{\beta}-\mathrm{H}$ ) while the gap in interaction energy is much larger ( $-36.9 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathrm{C}_{\alpha}-\mathrm{H}$ and $-30.1 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathrm{C}_{\beta}-\mathrm{H}$ ). Therefore, substrate distortion energy controls regioselectivity for the $\alpha$-position of electron-poor thiophenes, while interaction energy controls the regioselectivity for electron-rich thiophenes. While the metal-carbon bond distances are the same for the $\alpha$ and $\beta$ CMD of CNTh (2.22 $\AA$ ), there is a substantial difference between the $\mathrm{Pd}-\mathrm{C}_{\text {aryl }}$ bond lengths in the $\alpha$ and $\beta$ CMD TSs of MeOTh (e.g. $2.15 \AA$ and $2.19 \AA$, respectively). The shorter $\mathrm{Pd}-\mathrm{C}_{\text {aryl }}$ bond distances in the TS geometry show that the lower $\Delta E_{i}^{\ddagger}$ values are attributable to stronger interactions between the developing thienyl anion and the vacant binding site on palladium. All TS bond lengths are given in Table 2.

The electron-poor oxidative addition substrate on the catalyst (Int-11) leads to lower CMD substrate $\mathrm{C}-\mathrm{H}$ activation energies. For example, the $\Delta G^{\ddagger}$ of the $\alpha$ and $\beta \mathrm{C}-\mathrm{H}$ bonds of MeOTh with the electronpoor catalyst Int-11 are 22.9 and $27.7 \mathrm{kcal} \mathrm{mol}^{-1}$. This increases to 25.1 and 29.4 with the intermediate catalyst Int-4 and again to 25.8 and 29.9 for the electron-rich catalyst Int-6. The lower C-H activation energies with the more electron-deficient catalyst are driven by a lower $\Delta E_{d-s u b}^{\ddagger}$ (e.g. 33.0/31.0, 33.7/32.3 and 33.8/33.2 $\mathrm{kcal} \mathrm{mol}^{-1}$ for the activation of $\mathrm{C}_{\alpha}-\mathrm{H} / \mathrm{C}_{\beta}-\mathrm{H}$ of MeOTh with Int-11, Int-4 and Int-6, respectively) and higher interaction energy. For each CMD substrate, the $\Delta E_{i}^{\ddagger}$ values are most negative with the electron-poor catalyst. This may occur by the electron-poor OA substrate drawing
electron density away from the metal center, making it more susceptible to the approach of the deprotonated thienyl anion, in a similar fashion to electron-poor ligands that increase the rate of transmetalation in certain cross-coupling reactions. ${ }^{63}$

The $\Delta G^{\ddagger}$ values of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond for each brominated thiophene are substantially lower than the $\mathrm{C}_{\beta}-\mathrm{H}$ bond of its non-brominated counterpart, with $\Delta G^{\ddagger}$ reduced by $3.0,3.5$ and $4.3 \mathrm{kcal} \mathrm{mol}^{-1}$ for the CNTh/BrCNTh, Th/BrTh and MeOTh/BrMeOTh pairs, respectively. The activation barriers of the $\mathrm{C}-\mathrm{H}$ bonds on the brominated substrates $\left(24.0 \mathrm{kcal} \mathrm{mol}^{-1}\right.$ for $\mathbf{B r C N T h}, 26.3$ for $\mathbf{B r T h}$ and 25.6 for BrMeOTh) are similar to the $\alpha$-CMD event on the non-brominated substrates, such that the presence of bromine on thiophene substrates with available $\mathrm{C}_{\beta}-\mathrm{H}$ bonds may lead to competition with the $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds of non-brominated thiophenes. ${ }^{89, ~ 90, ~} 147$

As shown in Figure 34, the distortion energy of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond and corresponding $\mathrm{C}-\mathrm{H}$ bond length elongation (Table 2) are substantially reduced when bromine is in the $\alpha$-position (e.g. $24.0 \mathrm{kcal} \mathrm{mol}^{-1}$ and $0.23 \AA$ for $\mathbf{B r C N T h}$ ) as opposed to when there is simply another $\mathrm{C}-\mathrm{H}$ bond in that position (e.g. $27.5 \mathrm{kcal} \mathrm{mol}^{-1}$ and $0.27 \AA$ for CNTh). The $\mathrm{C}_{\beta}-\mathrm{H}$ bond lengths of the brominated and non-brominated thiophene substrates in the ground state are the same (1.08-1.09 A. Table 6). This difference in bond length between the ground state and TS is due to the inductive electron-withdrawing character of the adjacent halogen, as shown by the deeper energy level of the $\sigma \mathrm{C}_{\beta}-\mathrm{H}$ orbital and lower $\mathrm{C}_{\beta}-\mathrm{H}$ out-ofplane bending frequency of the brominated thiophenes relative to non-brominated thiophenes (Table 6). The smaller variation in $\Delta E_{i}^{\ddagger}$ indicates that the weaker interactions observed between an electrondeficient substrate and catalyst may be mitigated by the electron-donating resonance effect of the halide into the thiophene $\pi$-system.

The hypothesis that resonance effects drive $\Delta E_{i}^{\ddagger}$ is supported by the observation that the substituent in the 2-position ( $\mathrm{CN}, \mathrm{H}$ and OMe ) has a much higher impact on the $\Delta E_{i}^{\ddagger}$ of $\mathrm{C}_{\alpha}-\mathrm{H}$ (the 5-position) than on $\mathrm{C}_{\beta}-\mathrm{H}$ (the 4-position), as described above. Although spatially nearer to the substituent, the 4-position is not affected by resonance effects from the substituent in the 2-position. For example, with the catalyst Int-4, $\mathrm{C}_{\alpha}-\mathrm{H} \Delta E_{i}^{\ddagger}$ increases from -25.4 to -30.4 and $-37.1 \mathrm{kcal} \mathrm{mol}^{-1}$ for CNTh, Th and MeOTh, while $\mathrm{C}_{\beta}-\mathrm{H} \Delta E_{i}^{\ddagger}$ changes only from -25.5 to -26.8 and $-29.4 \mathrm{kcal} \mathrm{mol}^{-1}$ for the same three substrates. Similarly, the $\sigma \mathrm{C}_{\beta}-\mathrm{H}$ orbital energies of CNTh, Th and MeOTh are all the same ( -10.8 eV ), while the $\sigma \mathrm{C}_{\alpha}-\mathrm{H}$ orbital energies change substantially with different substituents in the 2-position (Table 6).

By comparing $\Delta E_{d-s u b}^{\ddagger}$ of the CMD TSs for the three substrate $\mathrm{C}-\mathrm{H}$ bonds of $\mathbf{B r T h}$ described earlier, the substrate activated in the $\gamma$ position was found to have the lowest $\Delta E_{d-s u b}^{\ddagger}\left(27.0 \mathrm{kcal} \mathrm{mol}^{-1}\right.$, compared to $28.3 \mathrm{kcal} \mathrm{mol}^{-1}$ for the $\alpha$-position and $30.2 \mathrm{kcal} \mathrm{mol}^{-1}$ for the $\beta$-position) due to its spatial proximity to the halogen (Figure 35). These distortion energies are lower than the corresponding bonds on non-brominated $\mathbf{T h}$, which indicates a more electron-deficient substrate. However, the interaction energy at the $\beta$ - and $\gamma$-positions of BrTh ( -27.8 and $-27.4 \mathrm{kcal} \mathrm{mol}^{-1}$, Figure 35) are greater than those of the $\beta$-positions of $\mathbf{T h}\left(-26.8 \mathrm{kcal} \mathrm{mol}^{-1}\right)$, indicative of an electron-donating effect.


Figure 35: A comparison of the activation energies, substrate distortion energies and interaction energies of thiophene and bromothiophene. Calculated using DLPNO-CCSD(T)/DefBas4$\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})-L A N L 2 D Z-I E F P C M(\varepsilon=7.25)$. Full results are detailed in Table 4.

The latter part of the direct arylation catalytic cycle (after the CMD TS) was evaluated for the $\mathrm{C}_{\beta}-\mathrm{H}$ bonds of CNTh and BrCNTh to assess if the activating effect of bromine determines the outcome of coupling (Figure 36). From the potential energy surface and bond lengths of the intermediates (Int-12 through Int-15) and RE TSs of both substrates, it is shown that the presence of the halogen does not at any point destabilize the intermediates or reductive elimination TS, but rather controls the lower energy pathway throughout the mechanism. The $3 \mathrm{kcal} \mathrm{mol}^{-1}$ difference in $\mathrm{C}-\mathrm{H}$ activation energies between BrCNTh and CNTh ( 24.0 and $27.0 \mathrm{kcal} \mathrm{mol}^{-1}$, respectively) is approximately maintained through to the RE. The RE TS is slightly stabilized for $\operatorname{BrCNTh}\left(\Delta \mathrm{G}^{\ddagger}=13.9 \mathrm{kcal} \mathrm{mol}^{-1}\right)$ compared to $\mathbf{C N T h}\left(\Delta \mathrm{G}^{\ddagger}\right.$
$=14.4 \mathrm{kcal} \mathrm{mol}^{-1}$ ), with smaller C-C bond lengths in the calculated TS geometry ( 1.96 versus $1.99 \AA$ ). The evolution of the potential energy surface of the brominated and non-brominated substrates highlights that the increased kinetic accessibility of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond to a CMD event induced by the halogen lowers the free energy of the subsequent intermediates, ultimately contributing to a higher rate of coupling at this position.


Figure 36: The latter part of the arylation pathway of CNTh and BrCNTh with catalyst Int-11. All Gibbs free energies are in $\mathrm{kcal} \mathrm{mol}^{-1}$ (to scale) and are presented relative to the starting complex. Calculated using DLPNO-CCSD(T)/DefBas4-COSMO( $\varepsilon=7.25$ )/M06/6-31+G(d,p)-LANL2DZ$\operatorname{IEFPCM}(\varepsilon=7.25) .($ orange $=$ phosphorus, turquoise $=$ palladium, burgundy $=$ bromine, blue $=$ nitrogen $)$

### 2.4.3 Experimental implications

These calculations explain the dramatic divergence of properties observed in some copolymers whose synthesis differed only with respect to the monomer bearing the halogen (some examples of which are shown in Figure 37). ${ }^{\text {9, } 90,108, ~ 121, ~ 124, ~ 138, ~} 150$ In the synthetic route leading to higher molecular weight and lower bandgap materials (indicative of fewer structural defects on the polymer chain), the $\mathrm{C}-\mathrm{H}$ -
bearing monomers have both $\alpha$ and $\beta \mathrm{C}-\mathrm{H}$ bonds, with an inherent selectivity for coupling at the $\alpha$ position, while the brominated monomers do not have available $\mathrm{C}-\mathrm{H}$ bonds in the $\beta$-position. In the other route, the brominated monomers include $\mathrm{C}_{\beta}-\mathrm{H}$ bonds, which according to our results are susceptible to a CMD event. ${ }^{89}$

Beta-protected brominated monomers $\vdots$

- Higher molecular weight
- Lower bandgap
- Fewer structural defects





Unprotected brominated monomers

- Lower molecular weight
- Higher bandgap
- More structural defects

[Pd]
$\mathrm{P}(t-\mathrm{Bu})_{2} \mathrm{Me} \cdot \mathrm{HBF}_{4}$


THF, $100^{\circ} \mathrm{C}$
$\mathrm{P}(o-\mathrm{OMeC}$
C $\mathrm{H}_{4}$
Toluene, $120^{\circ} \mathrm{C}$



Figure 37 : Examples from the literature which demonstrate that polymer regioregularity is dependent on the location of the halogen. Thiophene-based monomers with available $\mathrm{C}-\mathrm{H}$ bonds in both the $\alpha$ and $\beta$ positions (blue and red, respectively) lead to more well-defined materials than monomers with a $\mathrm{C}_{\beta-}$ H bond adjacent to the bromine (green). R is a solubilizing alkyl side-chain.

The $\mathrm{C}_{\beta}-\mathrm{H}$ bonds of the electron-poor substrate $\mathbf{B r C N T h}$ are the most activated by the presence of bromine in the $\alpha$-position. This explains the difficulties encountered in the polymerization of certain brominated electron-poor thiophene-based units. ${ }^{96,121,147}$ The $\mathrm{C}_{\beta}-\mathrm{H}$ bonds of $\mathbf{B r M e O T h}$ and $\mathbf{B r T h}$ are
less reactive, which may help to understand the highly regioregular polymers obtained via thiophenethiophene coupling when the electron-rich monomer is brominated. ${ }^{90,95,96}$

Decreased $\mathrm{C}-\mathrm{H}$ bond activation energy with an electron-withdrawing OA substrate (Int-11) may explain certain recent examples in which brominated electron-poor thiophene-flanked units have led to well-defined polymers, despite the reactivity of their $\mathrm{C}_{\beta}-\mathrm{H}$ bonds. For example, dibrominated DPP (an electron-withdrawing unit) was successfully copolymerized with 3,4-dicyanothiophene, thienopyrroledione, 3,4-propylenedioxythiophene, bithiazole and (E)-1,2-bis(3,4-difluorothien-2yl)ethene. ${ }^{151,152}$ These co-monomers are all very electron-rich or electron-poor, indicating that they have highly reactive $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds, as shown by these calculations. This, paired with the increased reactivity of the catalyst due to the strongly electron-withdrawing OA substrate, may lead to CMD substrate $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds which are far more reactive than the $\mathrm{C}_{\beta}-\mathrm{H}$ bond on the brominated OA substrate.

### 2.4.4 Steric substituent effects

A greater selectivity for $\mathrm{C}_{\alpha}-\mathrm{H}$ bonds is likely present when there is steric congestion around the active catalyst species ${ }^{89}$ For instance, steric hindrance brought about by bulky carboxylate bases (i.e. pivalate, neodecanoate) can eliminate the formation of branched structures in P3HT, and can lead to overall more regioregular polymers than less hindered bases, such as acetate. ${ }^{25,140}$ It has also been proposed that steric effects originating from alkyl groups at the $\gamma$ position of thiophene monomers bearing $\mathrm{C}-\mathrm{H}$ bonds at both the $\alpha$ - and $\beta$-positions can disfavor activation of the adjacent $\mathrm{C}_{\beta}-\mathrm{H}$ bond. ${ }^{89,144}$

The approach of modifying both the nature of the OA and CMD substrates was used to study the effect of the steric bulk of thiophene substrates on $\mathrm{C}-\mathrm{H}$ activation. By introducing methyl and ethyl groups to the 3-position of each substrate, four potential CMD TSs become available for each catalyst: $\alpha$ and $\beta$ $\mathrm{C}-\mathrm{H}$ activation on sterically unhindered thiophene ( $\mathbf{T h}$ ), and $\alpha$-activation for $\beta$-methylated ( $\mathbf{M e T h}$ ) and $\beta$-ethylated (EtTh) thiophene (Figure 38). Similar starting materials (Int-4, Int-17 and Int-18) were each used as catalyst to assess the potential role of the OA substrate bulk on the $\mathrm{C}-\mathrm{H}$ activation of the CMD substrate.


Figure 38 : General schematic for the cross-coupling of model thiophenes with various degrees of steric bulk adjacent to the coupling positions, where R is the alkyl group on the catalyst thiophene and R' is the alkyl group on the CMD substrate. Full results are detailed in Table 3. Calculated using DLPNO-CCSD(T)/DefBas4-COSMO( $\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})-L A N L 2 D Z-I E F P C M(\varepsilon=7.25)$.

The evolution of the activation free energy for the three CMD units is similar for all three starting catalysts: the $\Delta G^{\ddagger}$ drops upon methylation at the $\beta$-position of the CMD substrate (for instance from $26.8 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathbf{T h}$ to $25.0 \mathrm{kcal} \mathrm{mol}^{-1}$ for MeTh when unhindered thiophene Int-4 is the OA unit) and then rises when the $\beta$-methyl is replaced by an ethyl group (EtTh), but not as high as with Th (e.g. $25.9 \mathrm{kcal} \mathrm{mol}^{-1}$ with Int-4). This suggests that methylation in the $\beta$-position, as done in various experimental studies to avoid potential $\beta$-defects, not only removes a potential site for undesired $\mathrm{C}-\mathrm{H}$ activation, but also activates the adjacent $\mathrm{C}_{\alpha}-\mathrm{H}$ bond. ${ }^{111,137,204}$ This is likely due to inductive electrondonating effects, as evidenced by the stabilization of $\Delta E_{i}^{\ddagger}$ by approximately $4 \mathrm{kcal} \mathrm{mol}^{-1}$ from $\mathbf{T h}$ to MeTh, regardless of the catalyst (Table 3). While $\Delta E_{d-s u b}^{\ddagger}$ is also increased by $1-2 \mathrm{kcal} \mathrm{mol}^{-1}$ due to
the steric congestion around the site of $\mathrm{C}-\mathrm{H}$ activation, the effect is not as pronounced as the beneficial effect of $\Delta E_{i}^{\ddagger}$. However, upon increasing the steric bulk around the CMD substrate (from MeTh to EtTh), the further increase of the substrate and catalyst distortion grows more important than the inductive activating effect of the alkyl group.

The OA substrate has little effect on activation barriers for both MeTh and EtTh. For instance, the CMD TS $\Delta \mathrm{G}^{\ddagger}$ for MeTh is $25.0 \mathrm{kcal} \mathrm{mol}^{-1}$ with $\mathbf{I n t}-4,24.8 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathbf{I n t} \mathbf{- 1 7}$ and $25.1 \mathrm{kcal} \mathrm{mol}^{-1}$ for Int-18, with comparable catalyst and substrate distortion energies (Table 3). This indicates that steric congestion around the CMD substrate plays a more important role in reaction kinetics than steric effects on the OA unit. However, steric effects originating from the OA unit do affect $\alpha$ - versus $\beta$ selectivity on unsubstituted Th. While the difference in $\alpha$-versus $\beta$-reactivity on thiophene is 3.0 kcal $\mathrm{mol}^{-1}$ when the catalyst Int-4, this is lowered to 2.4 with Int-17 and $1.6 \mathrm{kcal} \mathrm{mol}^{-1}$ with Int-18. While the activation barriers of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond on $\mathbf{T h}$ change little ( $29.8,28.9$ and $29.7 \mathrm{kcal} \mathrm{mol}^{-1}$ for increasing hindrance on the catalyst), the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond activation energy increases from 26.8 and 26.5 with Int-4 and Int-17 to 28.1 with Int-18. This indicates that steric effects near the catalytic center may not always be beneficial on unsubstituted thiophene substrates.

The computational method used was expanded to one final model system. By truncating 2-bromo-3hexylthiophene, the monomer used for the synthesis of P3HT, to 2-bromo-3-ethylthiophene (2Br3EtTh), a difference in activation energies of $3.0 \mathrm{kcal} \mathrm{mol}^{-1}$ was observed between the $\alpha$ and $\beta \mathrm{C}-$ H bonds ( 25.7 versus $28.7 \mathrm{kcal} \mathrm{mol}^{-1}$, with Figure 39). A breakdown of the energy contributions indicates that this difference is largely due to higher interaction energy in the $\alpha$-position (Table 4), which may be explained by the favorable electronic effects of the nearby halogen without the steric penalty of being directly adjacent to the alkyl chain. This is confirmed by the smaller $\mathrm{Pd}-\mathrm{C}_{\text {aryl }}$ bond length for the $\alpha$ CMD pathway ( $2.18 \AA$ versus $2.23 \AA$ for $\beta$ CMD) in the TS geometry. This difference in $\alpha / \beta$-activation energies confirms the excellent regioregularity obtained with P 3 HT in optimized DHAP conditions. ${ }^{85, ~ 88, ~} 153$


Figure 39 : The activation energies of model monomers for the synthesis of a poly(3-alkylthiophene). Full results are detailed in Table 4. Calculated using $\operatorname{CCSD}(\mathrm{T}) / \operatorname{DefBas} 4-\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-$ $31+G(d, p)-L A N L 2 D Z-I E F P C M(\varepsilon=7.25)$.

### 2.5 Conclusion

We undertook a detailed computational study of the coupling of model thiophene and bromothiophenes, central motifs to the direct (hetero)arylation polymerization reaction. By studying the full mechanism of the coupling of two bromothiophenes, it was possible to confirm from the evolution of the potential energy surface that regioselectivity is governed by the CMD TS energy. While the $\mathrm{C}_{\alpha}-$ H bond is the most kinetically accessible, the $\mathrm{C}_{\beta}-\mathrm{H}$ bond adjacent to the halogen is also activated. From these initial results, a series of model thiophenes with electron-donating, electron-withdrawing and sterically hindered groups were studied as both the oxidative addition and concerted metalationdeprotonation substrates.

A generalized understanding of coupling selectivity was obtained by evaluating the reactivity of $\alpha$ and $\beta \mathrm{C}-\mathrm{H}$ bonds on a range of thiophene substrates with respect to different coupling partners. The results demonstrate that, for the most part, non-halogenated thiophenes possess a good intrinsic selectivity for $\mathrm{C}-\mathrm{H}$ activation at the $\alpha$-position. The limits to coupling selectivity observed with certain co-monomer pairs is therefore not due to poor intrinsic $\alpha$ - versus $\beta$-selectivity on an electron-rich or electron-poor thiophene, but rather a result of the activating effect of bromine on the $\mathrm{C}_{\beta}-\mathrm{H}$ bond of the oxidative
addition substrate. Additional results pertaining to steric features around the coupling location offer further insight into coupling selectivity of thiophene-based monomers.

It was demonstrated for the first time that the oxidative addition substrate impacts the energy of the concerted metalation-deprotonation transition state. From model systems with electron-donating and withdrawing groups, it was shown that an electron-poor oxidative addition substrate renders both the $\alpha$ and $\beta \mathrm{C}-\mathrm{H}$ bonds of the CMD substrate more kinetically accessible. This may explain the success of DHAP in the copolymerization of some pairs of electron-poor thiophene co-monomers. ${ }^{135,151,152}$

From distortion-interaction analysis, the activating effect of bromine on the activation energy of the adjacent $\mathrm{C}_{\beta}-\mathrm{H}$ bond was found to be due to the halide's inductive withdrawing effect, which lowers the distortion energy of the $\mathrm{C}_{\beta}-\mathrm{H}$ bond, and its resonance-donating effect, which maintains or even increases the energy of interaction between the substrate and the catalyst complex. This suggests that the risk of $\beta$-defects in copolymers prepared by DHAP originates from brominated thiophene-based monomers, regardless of their electron-withdrawing or -donating nature.

The high success of copolymerizations between a bromoarene (such as dibromocarbazole, dibromofluorene or dibromoisoindigo) and a thiophene derivative can be understood in light of these results. ${ }^{10,12,90,108,167}$ As the $\mathrm{C}-\mathrm{H}$ bonds of six-membered arenes are considered not reactive enough for polymerization conditions, there is no available " $\beta$ " position on these arenes. In such cases, the high polymer regioregularity originates from the good intrinsic selectivity of non-brominated thiophenes.

While these results represent small molecule model systems with strongly activating groups, the results explain the experimental observation that if a substrate with a bromothiophene fragment is used in DHAP, highly regioregular materials (and selective couplings) are most likely either if (a) there is no $\mathrm{C}_{\beta}-\mathrm{H}$ bond on that substrate, or (b) the co-monomer is particularly electron-rich or electron-deficient. These results therefore open the door to the design of monomers amenable to DHAP protocols with high coupling selectivity.

### 2.6 Computational Methods

Geometry optimizations and frequency calculations were performed using the Gaussian-09 suite of programs ${ }^{205}$ at the M06/6-31+G(d,p) level of theory ${ }^{206}$ using the IEFPCM solvation model (THF) and a superfine integration grid. ${ }^{191-193}$ Normal mode analysis confirmed that stationary points with all real frequencies were in fact minima, while those with one imaginary frequency were transition structures. A full conformational search was undertaken to find the global minima and lowest-energy TSs. Free energy corrections were extracted from the optimization and the electronic energies were calculated using DLPNO-CCSD (T) ${ }^{207}$ from the ORCA electronic structure package (version 3.0.3), ${ }^{208}$ using the DefBas4 basis set ${ }^{209}$ and the COSMO solvation model ( $\varepsilon=7.25$ for THF). ${ }^{210}$ Distortion and interaction calculations were performed as previously reported ${ }^{203}$ and energies were obtained from single point calculations using DLPNO-CCSD(T). To limit computational cost, the complex phosphine ligands used experimentally (such as tris(o-methoxyphenyl)phosphine) were simplified to phosphine $\left(\mathrm{PH}_{3}\right)$. Similarly, the bulky carboxylate base (i.e. pivalate) was replaced with acetate (see Annex 2 for results pertaining to test calculations of transition states using pivalate, $\mathrm{PMe}_{3}$ and $\mathrm{PCy}_{3}$ ). Similar truncation of palladium catalysts has been used previously with the computation of the direct arylation mechanism. ${ }^{53,}$ 132 These features were kept constant throughout the project and, as such, variations in transition state energies depended solely on the electronic and steric features of the thiophene units undergoing coupling.

## CONLUSIONS AND PERSPECTIVES

In this thesis, density functional theory and coupled cluster techniques were used to explore the selectivity of $\mathrm{C}-\mathrm{H}$ bond activation and coupling for a range of model thiophene pairs in palladium-catalyzed direct (hetero)arylation polymerization. By introducing simple functional groups which coarsely mimic the steric and electronic effects of thiophene-based monomers, it was possible to ascertain that, for most (electron-rich and electron-poor) coupling pairs with available $\mathrm{C}_{\alpha}-\mathrm{H}$ and $\mathrm{C}_{\beta}-\mathrm{H}$ bonds, there is an intrinsic preference for the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond. However, due to the activating effect of adjacent bromine, the $\mathrm{C}_{\beta}-\mathrm{H}$ bond on the $\alpha$-brominated monomer exhibits reactivities comparable to the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond on the co-monomer. This observation may explain numerous results pertaining to the divergence in the efficacy of DHAP for the polymerization of certain classes of co-monomers. In particular, the highly regioregular and high molecular weight materials prepared from brominated arene-based monomers (such as carbazole, fluorene and isoindigo) and brominated thiophene-based monomers without $\mathrm{C}_{\beta}-\mathrm{H}$ bonds can be rationalized from these results.

Despite the unambiguous results from the present computational study, due to the lack of concrete experimental evidence for $\beta$-defect formation, it is uncertain how prevalent this defect is. Also unclear is the degree to which $\beta$-defects are responsible for the divergence in the results of polymerization via DHAP compared to traditional techniques, such as Migita-Stille and Miyaura-Suzuki polymerization. A possible avenue to correlate the computational results with possible side-reactions during polymerization would be a series of small molecule coupling experiments with the same thiophene coupling pairs used in this study (e.g. thiophene-2carbonitrile, 5-bromothiophene-2-carbonitrile, 2-methoxythiophene, 5-bromo-2methoxythiophene, etc.). By examining the ratio of coupling products under polymerization conditions, the statistical likelihood of coupling in the $\beta$-position could be correlated with the difference in calculated $\mathrm{C}-\mathrm{H}$ bond activation energies for the model thiophenes. A proposed example of this is given in Figure 40, in which the $\mathrm{C}-\mathrm{H}$ bonds adjacent to the strongly withdrawing and donating groups are replaced by methyl groups, due to their expected high reactivity under DHAP conditions.
Free energies calculated in this study



-VS-


Figure 40 : Proposed comparison of computed activation energies and ratio of small molecule coupling products in an experimental study.

Electrospray vacuum deposition and high-resolution scanning tunneling microscopy have recently been used to observe individual homocoupling defects in the backbone of conjugated polymers. ${ }^{211}$ Using such an approach, it may also be possible to locate occasional $\beta$-defects, to confirm (or dismiss) the hypothesis that this defect limits the molecular weight, yield and/or solubility of polymers prepared via DHAP.

The poor results obtained using DHAP in certain instances and the importance of the choice of co-monomers are certainly not restricted to one factor, and it is possible that $\beta$-defects pose a smaller risk to DHAP than previously thought. If this is the case, computational tools similar to those used in this study may be employed to probe the causes of other defects. The present computational study did not cover the widely-studied defect of homocoupling. As discussed in the Introduction, this defect is widespread in DHAP and other palladium-catalyzed crosscoupling polymerization reactions, and a number of mechanisms have been proposed to explain
its origin. Due to the high dependence of homocoupling on the monomers and ligands used, possible computational approaches to study this defect might involve:

- the calculation of carbon-halogen bond stability on electron-rich and electron-poor monomers;
- potential mechanistic pathways involving phosphine ligands with secondary chelating abilities $\left(\mathrm{P}\left(o-\mathrm{NMe}_{2} \mathrm{C}_{6} \mathrm{H}_{4}\right)_{3}\right.$ and $\left.\mathrm{P}\left(o-\mathrm{OMeC}_{6} \mathrm{H}_{4}\right)_{3}\right)$ and their ability to prevent the formation of intermediate catalyst complexes which lead to homocoupling;
- possible in situ formation of bi-metallic complexes, i.e. two palladium catalysts bridged by carboxylate or carbonate ligands.

In short, a detailed computational exploration of homocoupling would be in order so as to paint a more complete picture of the possible side-reactions which occur during DHAP. The present study could therefore be seen as the first step towards using computational tools to screen monomers and even to design catalyst/ligand pairs for high selectivity DHAP protocols. Unlike traditional polymerization techniques, which were historically assumed to yield structurally perfect polymers in every instance, the search for a better understanding of the causes of structural defects in conjugated polymers and the impact of these on polymer performance in organic electronic devices has been at the center of attention in DHAP research since the advent of this reaction. This study suggests that computational chemistry will serve as a powerful tool to this end.

## ANNEX 1: UNPUBLISHED RESULTS FOR C-H ACTIVATION OF OTHER MODEL THIOPHENES

The $\mathrm{C}-\mathrm{H}$ activation of 2 -iodothiophene (ITh), the iodo- analog to $\mathbf{B r T h}$ was computed. The $\Delta E_{d-s u b}^{\ddagger}$ for all three CMD events on ITh were found to be higher than on the corresponding C H bonds of BrTh due to the poorer electron-withdrawing character of iodine (Figure 40 and Tables 4 and 5). Due to the slight resonance donating character of iodine, the interaction energies in the same three coupling positions are not only all higher on ITh than on $\mathbf{B r T h}$ (which would be expected with a less electron-withdrawing substituent), but also higher than the $\Delta E_{i}^{\ddagger}$ of non-substituted thiophene (Th). Once again, the variations in catalyst distortion energy between these two substrates are small, with virtually no difference between BrTh and ITh, indicating that the activating effect of the halogen is entirely electronic.


Figure 41 : The activation energies, substrate distortion energies and interaction energies of other model thiophene substrates. Calculated using DLPNO-CCSD(T)/DefBas4$\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})-L A N L 2 D Z-\operatorname{IEFPCM}(\varepsilon=7.25)$. Full results are detailed in Tables 4 and 5.

Finally, the effect of fused heterocycles on thiophene $\mathrm{C}-\mathrm{H}$ activation was explored by calculating the $\Delta G^{\ddagger}$ for the CMD TS of thieno[3,2-b]thiophene (Thth) using catalyst Int-4 (Figure 40). The $1.4 \mathrm{kcal} \mathrm{mol}^{-1}$ difference in $\Delta G^{\ddagger}$ between $\alpha$ and $\beta \mathrm{C}-\mathrm{H}$ bonds ( 25.6 and 27.0 $\mathrm{kcal} \mathrm{mol}{ }^{-1}$, respectively) is much smaller than that of $\mathbf{T h}$ with the same catalyst ( $3.0 \mathrm{kcal} \mathrm{mol}^{-1}$ ). The good selectivity for the $\alpha$-position of $\mathbf{T h}$ is due to the substantially higher $\Delta E_{i}^{\ddagger}$ for the activation of the $\mathrm{C}_{\alpha}-\mathrm{H}$ bond. While $\mathbf{T h t h}$ has a similar difference in $\Delta E_{i}^{\ddagger}$ to $\mathbf{T h}$, the $\Delta E_{d-s u b}^{\ddagger}$ of Thth is higher by $1.8 \mathrm{kcal} \mathrm{mol}^{-1}$ at the $\alpha$-position than at the $\beta$-position, while the difference is only $0.4 \mathrm{kcal} \mathrm{mol}^{-1}$ for $\mathbf{T h}$. This uneven increase in $\Delta E_{d-s u b}^{\ddagger}$ and consequent increase in reactivity at the $\beta$-position of $\mathbf{T h}$ th relative to $\mathbf{T h}$ may in part explain the poor quality of some polymers prepared by the DHAP of non-brominated fused thiophene units. ${ }^{96}$

## ANNEX 2: SYNTHESIS OF COMPUTATIONAL DATA




Figure 42 : Comparison of acetate and pivalate bases
A comparison of the Gibbs free energies of activation $\left(\Delta \mathrm{G}^{*}\right)$ for the concerted metalation of the $\alpha, \beta$ and $\gamma \mathrm{C}-\mathrm{H}$ bonds of bromothiophene ( $\mathbf{B r T h}$ ) with catalyst complexes containing acetate (Int-4) and pivalate (Int-4-Piv). Calculated using DLPNO$\operatorname{CCSD}(\mathrm{T}) / \mathrm{DefBas} 4-\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})$-LANL2DZ-IEFPCM $(\varepsilon=7.25)$.

Table 2 : Data for cross-coupling of thiophene with various ligands.
A comparison of the Gibbs free energies of activation $\left(\Delta G^{\ddagger}\right)$ and Gibbs free energies relative to the activation of the $\mathrm{C}-\mathrm{H}$ bond ( $\Delta \Delta G^{\ddagger}$ ) substrate for the concerted metalation of the $\alpha, \beta$ and $\gamma \mathrm{C}-\mathrm{H}$ bonds of bromothiophene ( $\mathbf{B r} \mathbf{T h}$ ) with catalyst complexes containing phosphine (Int-4), trimethylphosphine (Int-4-PMe $\mathbf{3}_{3}$ ), tricyclohexylphosphine (Int-4-PCy $\mathbf{3}^{\text {) }}$. Calculated using M06/6-31+G(d,p)-LANL2DZ-IEFPCM( $\varepsilon=7.25)$.

| Ligand (Catalyst) | Concerted metalationdeprotonation substrate | C-H bond | $\begin{gathered} \Delta G^{\ddagger} \\ \left(\text { kcal } \mathrm{mol}^{-1}\right) \end{gathered}$ | $\Delta \Delta G^{\ddagger}$ relative to $\mathrm{C}_{a}-\mathbf{H}\left(\mathrm{kcal} \mathrm{mol}^{-1}\right)$ |
| :---: | :---: | :---: | :---: | :---: |
| Phosphine (Int-4) | BrTh | $\alpha$ | 17.0 | 0.0 |
|  |  | $\beta$ | 21.1 | 4.1 |
|  |  | $\gamma$ | 19.2 | 2.2 |
| Trimethylphosphine (Int-4-PMe3) |  | $\alpha$ | 19.0 | 0.0 |
|  |  | $\beta$ | 23.7 | 4.7 |
|  |  | $\gamma$ | 20.0 | 1.0 |
| Tricyclohexylphosphine (Int-4-PCy ${ }_{3}$ ) |  | $\alpha$ | 20.6 | 0.0 |
|  |  | $\beta$ | 23.7 | 3.1 |
|  |  | $\gamma$ | 21.5 | 0.9 |

Table 3 : Data for cross-coupling of model thiophenes with electronic substituents.
Gibbs free energies of activation $\left(\Delta G^{\ddagger}\right)$; substrate ( $\Delta \boldsymbol{E}_{\boldsymbol{d}-\text { sub }}^{\ddagger}$ ), catalyst ( $\Delta \boldsymbol{E}_{\boldsymbol{d}-\boldsymbol{c a t}}^{\ddagger}$ ) and total ( $\Delta \boldsymbol{E}_{\boldsymbol{d}}^{\ddagger}$ ) distortion energies; interaction energies ( $\Delta \boldsymbol{E}_{\boldsymbol{i}}^{\ddagger}$ ); difference in activation energies for $\alpha$ and $\beta$ protons ( $\Delta \Delta \boldsymbol{G}_{\boldsymbol{\alpha} / \boldsymbol{\beta}}^{\ddagger}$ ); $\mathrm{C}-\mathrm{H}$ bond lengths in the transition state and change in $\mathrm{C}-\mathrm{H}$ bond lengths from ground state to transition state and $\mathrm{Pd}-\mathrm{C}$ bond length for CMD substrate in the transition state for the crosscoupling of electron-rich, electron-neutral and electron-poor thiophene derivatives. Calculated using DLPNO-CCSD(T)/DefBas4$\operatorname{COSMO}(\varepsilon=7.25) / / \mathrm{M} 06 / 6-31+\mathrm{G}(\mathrm{d}, \mathrm{p})-$ LANL2DZ-IEFPCM $(\varepsilon=7.25)$.

| Catalyst | Concerted metalationdeprotonation substrate | $\begin{gathered} \mathrm{C}-\mathrm{H} \\ \text { bond } \end{gathered}$ | $\begin{gathered} \Delta G^{\ddagger} \\ (\mathbf{k c a l} \\ \left.\mathbf{m o l}^{-1}\right) \end{gathered}$ | $\begin{gathered} \Delta E_{d-s u b}^{\ddagger} / \Delta E_{d-c a t}^{\ddagger} \\ {\left[\Delta E_{d}^{\ddagger}\right]} \\ \left(\mathrm{kcal}_{\mathrm{mol}}{ }^{-1}\right) \end{gathered}$ | $\begin{gathered} \Delta E_{i}^{\ddagger} \\ \left(\mathrm{kcal}^{\prime}\right. \\ \left.\mathrm{mol}^{-1}\right) \end{gathered}$ | $\begin{gathered} \Delta \Delta G_{\alpha / \beta}^{\ddagger} \\ (\mathbf{k c a l} \\ \left.\mathbf{m o l}^{-1}\right) \end{gathered}$ | C-H <br> bond length in TS (Å) | Change in $\mathbf{C}-\mathrm{H}$ bond length in TS (A) | Pd-C <br> bond length in TS (Å) | Pd-O-O- <br> C dihedral angle in TS ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $\begin{gathered} \text { Poor } \\ \text { (Int-11) } \end{gathered}$ | Poor(CNTh) | $\alpha$ | 24.6 | 24.2/17.0 [41.2] | -26.1 | 2.4 | 1.31 | 0.23 | 2.22 | 15.0 |
|  |  | $\beta$ | 27.0 | 27.5/16.7 [44.2] | -26.7 |  | 1.35 | 0.27 | 2.22 | 21.5 |
|  | Neutral (Th) | $\alpha$ | 25.3 | 29.1/18.7 [47.8] | -32.0 | 2.5 | 1.33 | 0.25 | 2.17 | 11.1 |
|  |  | $\beta$ | 27.8 | 29.2/18.1 [47.3] | -28.4 |  | 1.34 | 0.25 | 2.19 | -15.6 |
|  | $\begin{gathered} \text { Rich } \\ \text { (MeOTh) } \end{gathered}$ | $\alpha$ | 22.9 | 33.0/20.1 [53.1] | -39.6 | 4.8 | 1.35 | 0.27 | 2.14 | 9.2 |
|  |  | $\beta$ | 27.7 | 31.0/17.6 [48.6] | -30.9 |  | 1.37 | 0.28 | 2.19 | 23.5 |
|  | OA substrate (BrCNTh) | $\beta$ | 24.0 | 24.0/16.7 [40.7] | -26.8 |  | 1.32 | 0.23 | 2.24 | 9.8 |
| $\begin{aligned} & \text { Neutral } \\ & \text { (Int-4) } \end{aligned}$ | Poor(CNTh) | $\alpha$ | 25.7 | 24.8/16.3 [41.1] | -25.4 | 2.0 | 1.33 | 0.24 | 2.23 | 10.7 |
|  |  | $\beta$ | 27.7 | 27.7/16.3 [44.0] | -25.5 |  | 1.35 | 0.26 | 2.22 | -13.6 |
|  | Neutral (Th) | $\alpha$ | 26.8 | 29.8/17.8 [47.6] | -30.4 | 3.0 | 1.34 | 0.26 | 2.18 | 10.2 |
|  |  | $\beta$ | 29.8 | 30.2/17.1 [47.3] | -26.8 |  | 1.35 | 0.26 | 2.19 | -14.0 |
|  | $\begin{gathered} \text { Rich } \\ (\text { MeOTh }) \end{gathered}$ | $\alpha$ | 25.1 | 33.7/19.0 [52.7] | -37.1 | 4.3 | 1.36 | 0.28 | 2.15 | 10.4 |
|  |  | $\beta$ | 29.4 | 32.3/16.6 [48.9] | -29.4 |  | 1.38 | 0.30 | 2.19 | 24.2 |
|  | $\begin{gathered} \hline \text { OA substrate } \\ (\mathrm{BrTh}) \end{gathered}$ | $\beta$ | 26.3 | 27.0/16.5 [43.5] | -27.4 |  | 1.33 | 0.24 | 2.22 | 9.4 |
| $\begin{aligned} & \text { Rich } \\ & \text { (Int-16) } \end{aligned}$ | Poor(CNTh) | $\alpha$ | 25.1 | 25.1/16.2 [41.3] | -25.7 | 3.3 | 1.33 | 0.25 | 2.23 | 8.2 |
|  |  | $\beta$ | 28.4 | 27.8/16.2 [44.0] | -25.2 |  | 1.35 | 0.27 | 2.22 | 11.4 |
|  | Neutral (Th) | $\alpha$ | 27.0 | 30.0/17.4 [47.4] | -30.1 | 2.7 | 1.35 | 0.26 | 2.18 | 11.1 |
|  |  | $\beta$ | 29.7 | 31.4/16.3 [47.7] | -27.4 |  | 1.37 | 0.28 | 2.19 | 23.0 |
|  | $\begin{gathered} \text { Rich } \\ \text { (MeOTh) } \end{gathered}$ | $\alpha$ | 25.8 | 33.8/18.8 [52.6] | -36.9 | 4.1 | 1.37 | 0.28 | 2.15 | 9.7 |
|  |  | $\beta$ | 29.9 | 33.2/16.2 [49.4] | -30.1 |  | 1.39 | 0.31 | 2.19 | 24.5 |
|  | OA substrate (BrMeOTh) | $\beta$ | 25.6 | 27.3/16.0 [43.3] | -27.9 |  | 1.34 | 0.25 | 2.22 | 11.8 |

Table 4 : Data for cross-coupling of model thiophenes with steric substituents
Gibbs free energies of activation $\left(\Delta G^{\ddagger}\right)$; substrate ( $\Delta \boldsymbol{E}_{\boldsymbol{d}-\text { sub }}^{\ddagger}$ ), catalyst ( $\Delta \boldsymbol{E}_{\boldsymbol{d}-\boldsymbol{c a t}}^{\ddagger}$ ) and total ( $\Delta \boldsymbol{E}_{\boldsymbol{d}}^{\ddagger}$ ) distortion energies; interaction energies $\left(\Delta \boldsymbol{E}_{\boldsymbol{i}}^{\ddagger}\right)$; difference in activation energies for $\alpha$ and $\beta$ protons ( $\Delta \Delta \boldsymbol{G}_{\boldsymbol{\alpha} / \boldsymbol{\beta}}^{\ddagger}$ ); $\mathrm{C}-\mathrm{H}$ bond lengths in the transition state; change in $\mathrm{C}-$ H bond lengths from ground state to transition state and $\mathrm{Pd}-\mathrm{C}$ bond length for CMD substrate in the transition state for the crosscoupling of thiophene derivatives with various degrees of steric hindrance. Calculated using M06/6-31+G(d,p)-LANL2DZ$\operatorname{IEFPCM}(\varepsilon=7.25) / / \mathrm{DLPNO}-\operatorname{CCSD}(\mathrm{T}) /$ DefBas4-COSMO$(\varepsilon=7.25)$.

| Catalyst | Concerted metalationdeprotonation substrate | $\begin{gathered} \mathrm{C}-\mathrm{H} \\ \text { bond } \end{gathered}$ | $\Delta \boldsymbol{G}^{\ddagger}$ <br> (kcal <br> $\mathrm{mol}^{-1}$ ) | $\begin{gathered} \Delta E_{d-s u b}^{\ddagger} / \Delta E_{d-c a t}^{\ddagger} \\ {\left[\Delta E_{d}^{\ddagger}\right]} \\ \left(\mathbf{k c a l} \text { mol }^{-1}\right) \end{gathered}$ | $\Delta E_{i}^{\ddagger}$ (kcal $\mathrm{mol}^{-1}$ ) | $\begin{gathered} \Delta \Delta G_{\alpha / \beta}^{\ddagger} \\ (\mathbf{k c a l} \\ \left.\mathbf{m o l}^{-1}\right) \end{gathered}$ | C-H <br> bond length in TS <br> (A) | Change in C-H bond length in TS (Å) | Pd-C bond length in TS <br> (A) | $\begin{gathered} \hline \text { Pd-O-O- } \\ \mathrm{C} \\ \text { dihedral } \\ \text { angle in } \\ \mathrm{TS}\left(^{\circ}\right) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| No steric group <br> ( Int-4) | Unhindered (Th) | $\alpha$ | 26.8 | 29.8/17.8 [47.6] | -30.4 | 3.0 | 1.34 | 0.26 | 2.18 | 10.2 |
|  |  | $\beta$ | 29.8 | 30.2/17.1 [47.3] | -26.8 |  | 1.35 | 0.26 | 2.19 | -14.0 |
|  | $\beta$-methyl <br> (MeTh) | $\beta$ | 25.0 | 31.0/17.6 [48.6] | -34.0 |  | 1.33 | 0.25 | 2.16 | 15.0 |
|  | $\begin{aligned} & \beta \text {-ethyl } \\ & \text { (EtTh) } \end{aligned}$ | $\beta$ | 25.9 | 32.9/18.5 [51.4] | -36.5 |  | 1.35 | 0.27 | 2.17 | 6.9 |
| $\begin{gathered} \boldsymbol{\beta} \text {-methyl } \\ \text { ( Int-17) } \end{gathered}$ | Unhindered (Th) | $\alpha$ | 26.5 | 29.9/17.3 [47.2] | -30.5 | 2.4 | 1.34 | 0.26 | 2.17 | 15.7 |
|  |  | $\beta$ | 28.9 | 31.3/16.3 [47.6] | -28.3 |  | 1.36 | 0.28 | 2.19 | 24.7 |
|  | $\begin{gathered} \hline \boldsymbol{\beta} \text {-methyl } \\ (\text { MeTh) } \end{gathered}$ | $\beta$ | 24.8 | 31.5/17.9 [49.4] | -34.6 |  | 1.34 | 0.25 | 2.17 | -6.3 |
|  | $\begin{aligned} & \beta \text {-ethyl } \\ & \text { (EtTh) } \end{aligned}$ | $\beta$ | 26.3 | 33.5/18.2 [51.7] | -36.9 |  | 1.36 | 0.28 | 2.18 | 0.83 |
| $\beta$-ethyl <br> (Int-18) | Unhindered (Th) | $\alpha$ | 28.1 | 30.1/18.5 [48.6] | -30.7 | 1.6 | 1.35 | 0.26 | 2.18 | 9.7 |
|  |  | $\beta$ | 29.7 | 30.9/18.0 [48.9] | -28.6 |  | 1.35 | 0.26 | 2.20 | 30.4 |
|  | $\begin{gathered} \hline \boldsymbol{\beta} \text {-methyl } \\ (\text { MeTh }) \end{gathered}$ | $\beta$ | 25.1 | 31.5/19.1 [50.6] | -35.1 |  | 1.34 | 0.26 | 2.17 | -2.20 |
|  | $\begin{aligned} & \hline \beta \text {-ethyl } \\ & \text { (EtTh) } \end{aligned}$ | $\beta$ | 26.0 | 31.4/18.4 [49.8] | -34.7 |  | 1.33 | 0.24 | 2.16 | 24.1 |

Table 5 : Data for cross-coupling of other model thiophenes
Gibbs free energies of activation $\left(\Delta G^{\ddagger}\right)$; substrate $\left(\Delta \boldsymbol{E}_{\boldsymbol{d} \text {-sub }}^{\ddagger}\right)$, catalyst ( $\Delta \boldsymbol{E}_{\boldsymbol{d}-\boldsymbol{c a t}}^{\ddagger}$ ) and total ( $\Delta \boldsymbol{E}_{\boldsymbol{d}}^{\ddagger}$ ) distortion energies; interaction energies $\left(\Delta \boldsymbol{E}_{\boldsymbol{i}}^{\ddagger}\right)$; difference in activation energies for $\alpha$ and $\beta$ protons ( $\Delta \Delta \boldsymbol{G}_{\boldsymbol{\alpha} / \boldsymbol{\beta}}^{\ddagger}$ ); $\mathrm{C}-\mathrm{H}$ bond lengths in the transition state; change in $\mathrm{C}-$ $H$ bond lengths from ground state to transition state and $\mathrm{Pd}-\mathrm{C}$ bond length for CMD substrate in the transition state for the crosscoupling of a thienyl fragment with other thiophene-based substrates. Calculated using M06/6-31+G(d,p)-LANL2DZ$\operatorname{IEFPCM}(\varepsilon=7.25) / /$ DLPNO-CCSD(T)/DefBas4-COSMO( $\varepsilon=7.25)$.

| Catalyst | Concerted metalationdeprotonation substrate | $\begin{gathered} \text { C-H } \\ \text { bond } \end{gathered}$ | $\begin{gathered} \Delta G^{\ddagger} \\ \left(\mathbf{k c a l}^{-1}\right. \\ \text { mol } \left.^{-1}\right) \end{gathered}$ | $\begin{gathered} \Delta E_{d-s u b}^{\ddagger} / \Delta E_{d-c a t}^{\ddagger} \\ {\left[\Delta E_{d}^{\ddagger}\right]} \\ \left(\text { kcal mol }{ }^{-1}\right) \end{gathered}$ | $\Delta E_{i}^{\ddagger}$ (kcal $\mathrm{mol}^{-1}$ ) | $\begin{gathered} \Delta \Delta G_{\alpha / \beta}^{\ddagger} \\ \left(\mathbf{k c a l}^{\prime}\right. \\ \left.\mathbf{m o l}^{-1}\right) \end{gathered}$ | C-H <br> bond <br> length <br> in TS <br> (A) | Change in $\mathrm{C}-\mathrm{H}$ bond length in TS (Å) | Pd-C <br> bond length in TS (A) | Pd-O-O- <br> C dihedral angle in TS $\left(^{\circ}\right.$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Int-4 | BrTh | $\alpha$ | 25.7 | 28.3/17.0 [45.3] | -29.9 |  | 1.34 | 0.26 | 2.19 | 14.3 |
|  |  | $\beta$ | 28.3 | 30.2/16.2 [46.4] | -27.8 |  | 1.37 | 0.29 | 2.21 | 20.9 |
|  |  | $\gamma$ | 26.3 | 27.0/16.5 [43.5] | -27.4 |  | 1.33 | 0.24 | 2.22 | 9.4 |
| Int-4-Piv | BrTh with pivalate | $\alpha$ | 25.2 | 27.7/17.7 [45.4] | -29.9 |  | 1.34 | 0.24 | 2.19 | 13.2 |
|  |  | $\beta$ | 28.1 | 29.8/16.2 [46.0] | -27.8 |  | 1.37 | 0.28 | 2.21 | 28.0 |
|  |  | $\gamma$ | 26.0 | 26.8/16.9 [43.7] | -27.5 |  | 1.33 | 0.24 | 2.22 | 12.2 |
| $\beta$-ethyl <br> (Int-18) | 2-bromo-3ethylthiophene (2Br3EtTh) | $\alpha$ | 25.7 | 29.4/18.6 [48.0] | -33.1 | 3.0 | 1.36 | 0.27 | 2.18 | 12.1 |
|  |  | $\beta$ | 28.7 | 29.9/16.8 [46.7] | -29.2 |  | 1.35 | 0.26 | 2.23 | -23.9 |

Table 6: Data for cross-coupling of model thiophenes in Annex 1
Gibbs free energies of activation $\left(\Delta G^{\ddagger}\right)$; substrate $\left(\Delta E_{d-s u b}^{\ddagger}\right)$, catalyst $\left(\Delta E_{d-c a t}^{\ddagger}\right)$ and total $\left(\Delta E_{d}^{\ddagger}\right)$ distortion energies; interaction energies $\left(\Delta E_{i}^{\ddagger}\right)$; difference in activation energies for $\alpha$ and $\beta$ protons ( $\Delta \Delta G_{\alpha / \beta}^{\ddagger}$ ); $\mathrm{C}-\mathrm{H}$ bond lengths in the transition state; change in $\mathrm{C}-$ $H$ bond lengths from ground state to transition state and $\mathrm{Pd}-\mathrm{C}$ bond length for CMD substrate in the transition state for the crosscoupling of a thienyl fragment with thienothiophene. Calculated using M06/6-31+G(d,p)-LANL2DZ-IEFPCM( $\varepsilon=7.25$ )//DLPNO$\operatorname{CCSD}(\mathrm{T}) / \mathrm{DefBas} 4-\operatorname{COSMO}(\varepsilon=7.25)$.

| Catalyst | Concerted metalationdeprotonation substrate | $\begin{gathered} \text { C-H } \\ \text { bond } \end{gathered}$ | $\Delta \boldsymbol{G}^{\ddagger}$ (kcal $\mathrm{mol}^{-1}$ ) | $\begin{gathered} \Delta E_{d-s u b}^{\ddagger} / \Delta E_{d-c a t}^{\ddagger} \\ {\left[\Delta E_{d}^{\ddagger}\right]} \\ \left(\mathbf{k c a l} \mathrm{mol}^{-1}\right) \end{gathered}$ | $\Delta E_{i}^{\ddagger}$ <br> (keal <br> $\mathrm{mol}^{-1}$ ) | $\Delta \Delta \boldsymbol{G}_{\alpha / \beta}^{\ddagger}$ <br> (kcal $\mathrm{mol}^{-1}$ ) | C-H <br> bond <br> length <br> in TS <br> (A) | Change in C-H bond length in TS ( A ) | Pd-C bond length in TS (Å) | Pd-O-O-C <br> dihedral angle ( ${ }^{\circ}$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Thienyl fragment (Int-4) | $\begin{gathered} \text { Thieno[3,2-b] } \\ \text { thiophene (Thth) } \end{gathered}$ | $\alpha$ | 25.6 | 31.7/17.9 [49.6] | -33.6 | 1.4 | 1.37 | 0.29 | 2.18 | 15.7 |
|  |  | $\beta$ | 27.0 | 29.9/17.0 [46.9] | -30.3 |  | 1.36 | 0.27 | 2.20 | 27.0 |
|  | 2-iodo-thiophene (ITh) | $\alpha$ | 25.9 | 29.0/17.3 [46.3] | -30.7 |  | 1.35 | 0.27 | 2.19 | 12.9 |
|  |  | $\beta$ | 28.1 | 31.1/16.3 [47.4] | -29.2 |  | 1.38 | 0.30 | 2.20 | 21.8 |
|  |  | $\gamma$ | 25.0 | 27.6/16.5 [44.1] | -29.2 |  | 1.33 | 0.24 | 2.22 | 9.6 |

Table 7 : Data for model thiophenes in the ground state
Properties of model thiophenes in the ground state: C-H bond lengths, energy of C-H sigma orbitals and $\mathrm{C}-\mathrm{H}$ out-of-plane bending wave numbers (natural bond order analysis). Calculated using M06/6-31+G(d,p)-LANL2DZ-IEFPCM( $\varepsilon=7.25$ ).

| Model thiophene | $\begin{gathered} \mathrm{C}-\mathrm{H} \\ \text { bond } \end{gathered}$ | C-H bond length in ground state (A) | C-H $\sigma$ <br> orbital energy (eV) | C-H bond out-ofplane bending wave number $\left(\mathrm{cm}^{-1}\right)$ |
| :---: | :---: | :---: | :---: | :---: |
| CNTh | $\alpha$ | 1.08 | -11.9 | 718 |
|  | $\beta$ | 1.08 | -10.8 | 924 |
| BrCN | $\beta$ | 1.08 | -11.9 | 808 |
| Th | $\alpha$ | 1.08 | -11.5/-11.0 | 682 |
|  | $\beta$ | 1.09 | -10.8/-10.7 | 914 |
| BrTh | $\beta$ | 1.09 | -11.4 | 828 |
| MeOTh | $\alpha$ | 1.08 | -13.1 | 667 |
|  | $\beta$ | 1.09 | -10.8 | 893 |
| BrMeOTh | $\beta$ | 1.09 | -11.6 | 859 |
| BrTh | $\alpha$ | 1.08 | -11.5 | 690 |
|  | $\beta$ | 1.09 | -11.1 | 908 |
|  | $\gamma$ | 1.09 | -11.4 | 828 |

Idem for previously unpublished results reported in Annex 1

| Model <br> thiophene | C-H <br> bond | C-H bond <br> length in <br> ground state <br> $(\AA)$ | C-H $\sigma$ <br> orbital <br> energy <br> $(\mathbf{e V})$ | C-H bond out-of- <br> plane bending <br> wave number <br> $\left(\mathbf{c m}^{-1}\right)$ |
| :---: | :---: | :---: | :---: | :---: |
|  | $\alpha$ | 1.08 | -11.5 | 692 |
|  | $\beta$ | 1.09 | -10.4 | 911 |
|  | $\gamma$ | 1.09 | -11.2 | 830 |
| Thth | $\alpha$ | 1.08 | $-11.6 /-10.8$ | 667 |
|  | $\beta$ | 1.08 | $-10.7 /-10.2$ | 881 |

## ANNEX 3: OPTIMIZED GEOMETRIES

Table 8 : Labels, coordinates and energies of stationary points
Obtained with M06/6-31+G(d,p)-LANL2DZ-IEFPCM( $\varepsilon=7.25$ ) using a superfine integration grid. The reported free energies (G) were obtained from the sum of the DLPNO-CCSD(T) single point energy ( $\mathrm{E}_{\mathrm{CCSD}}$ ) and the DFT thermal energy correction ( $\mathrm{G}_{\mathrm{CORR} \text { DFT }}$ ) in Hartrees. In the columns, the atomic number is followed by its three cartesian ( $\mathrm{x}, \mathrm{y}, \mathrm{z}$ ) coordinates. Transition state labels correspond to those presented in the tables directly below.

Electronic substituents (Annex 3.4):

| Calculation label "x-CMD(oxidative addition substrate/C-H activation substrate)" | Bond activated | Catalyst | CMD substrate |
| :---: | :---: | :---: | :---: |
| $\alpha-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{CNTh})$ | $\alpha$ | $\begin{gathered} \text { Poor } \\ \text { (Int-11) } \end{gathered}$ | CNTh |
| $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{CNTh})$ | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{Th})$ | $\alpha$ |  | Th |
| $\beta$-CMD (CNTh/Th) | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{MeOTh})$ | $\alpha$ |  | MeOTh |
| $\beta$-CMD(CNTh/MeOTh) | $\beta$ |  |  |
| $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{BrCNTh})$ | $\beta$ |  | OA substrate BrCNTh |
| $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{CNTh})$ | $\alpha$ | $\begin{gathered} \text { Neutral } \\ \text { (Int-4) } \end{gathered}$ | CNTh |
| $\beta$-CMD(Th/CNTh) | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$ | $\alpha$ |  | Th |
| $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$ | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{MeOTh})$ | $\alpha$ |  | MeOTh |
| $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{MeOTh})$ | $\beta$ |  |  |
| $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{BrTh})$ | $\beta$ |  | OA substrate BrTh |
| $\alpha-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{CNTh})$ | $\alpha$ | $\begin{gathered} \text { Rich } \\ \text { (Int-16) } \end{gathered}$ | CNTh |
| $\beta$-CMD(MeOTh/CNTh) | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{Th})$ | $\alpha$ |  | Th |
| $\beta-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{Th})$ | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{MeOTh})$ | $\alpha$ |  | MeOTh |
| $\beta-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{MeOTh})$ | $\beta$ |  |  |
| $\beta-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{BrMeOTh})$ | $\beta$ |  | OA substrate BrMeOTh |

Steric substituents (Annex 3.5):

| Calculation label " x -CMD(oxidative addition substrate/C-H activation substrate)" | Bond activated | Catalyst | CMD substrate |
| :---: | :---: | :---: | :---: |
| $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$ | $\alpha$ | Unhindered ( Int-4) | Th |
| $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$ | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{MeTh})$ | $\alpha$ |  | MeTh |
| $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{EtTh})$ | $\alpha$ |  | EtTh |
| $\alpha-\mathrm{CMD}(\mathrm{MeTh} / \mathrm{Th})$ | $\alpha$ | $\begin{aligned} & \beta \text {-methyl } \\ & \text { ( Int-17) } \end{aligned}$ | Th |
| $\beta$-CMD (MeTh/Th) | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{MeTh} / \mathrm{MeTh})$ | $\alpha$ |  | MeTh |
| $\alpha-\mathrm{CMD}(\mathrm{MeTh} / \mathrm{EtTh})$ | $\alpha$ |  | EtTh |
| $\alpha-\mathrm{CMD}(\mathrm{EtTh} / \mathrm{Th})$ | $\alpha$ | $\beta$-ethyl (Int-18) | Th |
| $\beta-\mathrm{CMD}(\mathrm{EtTh} / \mathrm{Th})$ | $\beta$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{EtTh} / \mathrm{MeTh})$ | $\alpha$ |  | MeTh |
| $\alpha-\mathrm{CMD}(\mathrm{EtTh} / \mathrm{EtTh})$ | $\alpha$ |  | EtTh |

Coupling of bromothiophene (Annex 3.1), study of pivalate base (Annex 3.3) and model for P3HT (Annex 3.6):

| Calculation label | Bond activated | Catalyst | CMD substrate |
| :---: | :---: | :---: | :---: |
| $\alpha$-CMD | $\alpha$ | Thienyl fragment (Int-4) | BrTh |
| $\beta$-CMD | $\beta$ |  |  |
| $\gamma$-CMD | $\gamma$ |  |  |
| $\alpha$-CMD-Piv | $\alpha$ | $\begin{aligned} & \text { Int-4 with } \\ & \text { pivalate } \\ & \text { (Int-4-Piv) } \end{aligned}$ |  |
| $\beta$-CMD-Piv | $\beta$ |  |  |
| $\gamma$-CMD-Piv | $\gamma$ |  |  |
| $\alpha-\mathrm{CMD}(\mathrm{EtTh} / 2 \mathrm{Br} 3 \mathrm{EtTh})$ | $\alpha$ | $\beta$-ethyl <br> (Int-18) | 2-bromo-3- |
| $\beta-\mathrm{CMD}(\mathrm{EtTh} / 2 \mathrm{Br} 3 \mathrm{EtTh})$ | $\beta$ |  | ethylthiophene (2Br3EtTh) |

Unpublished results from Annex 1 (Annex 3.7):

| Calculation label | Bond <br> activated | Catalyst | CMD substrate |
| :---: | :---: | :---: | :---: |
| $\alpha$-CMD-I | $\alpha$ |  |  |
| $\beta$-CMD-I | $\beta$ |  | (Int-4) | | thieno[3,2- $b$ ] thiophene |
| :---: |
| (Thth) |

Study of ligand effect (Annex 3.2)

| Calculation label | Bond activated | Catalyst | CMD substrate |
| :---: | :---: | :---: | :---: |
| $\alpha$-CMD-PMe ${ }_{3}$ | $\alpha$ | Int-4 with | BrTh |
| $\beta$-CMD-PMe ${ }_{3}$ | $\beta$ | trimethylphosphine |  |
| $\gamma$-CMD-PMe ${ }^{\text {den }}$ | $\gamma$ | (Int-4-PMe ${ }^{\text {a }}$ ) |  |
| $\alpha$-CMD-PCy ${ }_{3}$ | $\alpha$ | Int-4 with tricyclohexylphosphine (Int-4-PCy3) |  |
| $\beta$-CMD-PCy ${ }_{3}$ | $\beta$ |  |  |
| $\gamma$-CMD-PCy ${ }_{3}$ | $\gamma$ |  |  |

## Annex 3.1 Catalytic cycle for the cross-coupling of 2-bromothiophene

## 2BrTh (2-bromothiophene)

$\mathrm{G}_{\mathrm{DFT}}=-565.334766$
$\mathrm{G}_{\mathrm{CORRDFT}}=0.025628$
$\mathrm{E}_{\text {CCSD }}=-3124.086145$
$\mathrm{G}=-3124.060517$

| C | -0.150351000 | 0.200219000 | 0.000000000 |
| :--- | :---: | :---: | :---: |
| C | -0.859243000 | 1.368423000 | 0.000000000 |
| C | -2.262689000 | 1.126603000 | 0.000000000 |
| C | -2.577608000 | -0.203436000 | 0.000000000 |
| S | -1.166033000 | -1.204416000 | 0.000000000 |
| H | -0.397193000 | 2.350284000 | 0.000000000 |
| H | -3.008787000 | 1.914982000 | 0.000000000 |
| H | -3.558478000 | -0.663959000 | 0.000000000 |
| Br | 1.734866000 | 0.020528000 | 0.000000000 |

## $\mathrm{CH}_{3} \mathrm{COO}^{-}$(acetate ion)

$\mathrm{G}_{\mathrm{DFT}}=-228.487248$
$\mathrm{G}_{\mathrm{CORR} \text { DFT }}=0.020982$
$\mathrm{E}_{\mathrm{CCSD}}=-228.1700306$
$G=-228.1490486$

| C | 0.189152000 | -0.000165000 | -0.006561000 |
| :--- | ---: | ---: | ---: |
| O | 0.805251000 | -1.098442000 | 0.001249000 |
| C | -1.341625000 | -0.047363000 | -0.002732000 |
| H | -1.707233000 | 0.284038000 | 0.977179000 |
| H | -1.725743000 | -1.054024000 | -0.195349000 |
| H | -1.746173000 | 0.649414000 | -0.745551000 |
| O | 0.706498000 | 1.149160000 | 0.001186000 |

## $\mathrm{Br}^{-}$(bromide ion)

$G_{\text {DFT }}=-13.303408$
$G_{\text {CORR DFT }}=-0.016176$
$\mathrm{E}_{\text {CCSD }}=-2572.721755$
$\mathrm{G}=-2572.737931$

```
\(\mathrm{Br} \quad 0.000000000 \quad 0.000000000 \quad 0.000000000\)
```


## $\mathbf{P H}_{3}$ (phosphine)

$G_{\text {DFT }}=-343.102299$
$\mathrm{G}_{\mathrm{CORRDFT}}=0.004119$
$\mathrm{E}_{\text {CCSD }}=-342.6545833$
$G=-342.6504643$
-----------------------

| P | 0.000000000 | 0.000000000 | 0.126790000 |
| :--- | :---: | :---: | :--- |
| H | 0.000000000 | 1.200764000 | -0.633949000 |
| H | -1.039892000 | -0.600382000 | -0.633949000 |
| H | 1.039892000 | -0.600382000 | -0.633949000 |

## $\mathrm{CH}_{3} \mathrm{COOH}$ (acetic acid)

$\mathrm{G}_{\mathrm{DFT}}=-228.952027$
$\mathrm{G}_{\text {CORR DFT }}=0.034407$
$\mathrm{E}_{\text {CCSD }}=-228.6600072$
$\mathrm{G}=-228.6256002$


| C | 0.088008000 | 0.120321000 | -0.000001000 |
| :--- | ---: | ---: | ---: |
| O | 0.772915000 | -1.036985000 | 0.000006000 |
| H | 1.720620000 | -0.823764000 | 0.000005000 |
| O | 0.642355000 | 1.199002000 | -0.000007000 |
| C | -1.386149000 | -0.108997000 | 0.000000000 |
| H | -1.670563000 | -0.692823000 | -0.880822000 |
| H | -1.670563000 | -0.692813000 | 0.880829000 |
| H | -1.912811000 | 0.845317000 | -0.000005000 |

## Int-1

$\mathrm{G}_{\mathrm{DFT}}=-813.002919$
$\mathrm{G}_{\text {CORR DFT }}=0.019717$
$\mathrm{E}_{\text {CCSD }}=-5623.556623$
$\mathrm{G}=-5623.536906$

| Pd | 2.177183000 | 2.732702000 | 0.148470000 |
| :--- | :---: | :---: | :---: |
| P | 4.492920000 | 2.733504000 | 0.149931000 |
| H | 5.211122000 | 2.774880000 | 1.368586000 |


| H | 5.214326000 | 1.659061000 | -0.422608000 |
| :---: | :---: | :---: | :---: |
| H | 5.212654000 | 3.768175000 | -0.493547000 |
| P | -0.138554000 | 2.734382000 | 0.150207000 |
| H | -0.856600000 | 2.776802000 | 1.368919000 |
| H | -0.857957000 | 3.768930000 | -0.493837000 |
| H | -0.860447000 | 1.659862000 | -0.421573000 |

## Int-2

$G_{\text {DFT }}=-1378.361525$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.068123$
$\mathrm{E}_{\mathrm{CCSD}}=-8747.688742$
$G=-8747.620619$
----------------------

| Pd | -0.566651000 | 0.438512000 | 0.033420000 |
| :--- | :---: | :---: | :---: |
| C | 1.435620000 | 0.091619000 | 0.189350000 |
| C | 2.278213000 | 0.240745000 | 1.262189000 |
| S | 2.308655000 | -0.504885000 | -1.189293000 |
| C | 3.626555000 | -0.145010000 | 0.982599000 |
| H | 1.948299000 | 0.607819000 | 2.231797000 |
| C | 3.803718000 | -0.564279000 | -0.305136000 |
| H | 4.428775000 | -0.109619000 | 1.714786000 |
| H | 4.711075000 | -0.913823000 | -0.784436000 |
| Br | -1.082463000 | -2.059385000 | 0.144818000 |
| P | 0.182726000 | 2.603511000 | -0.030865000 |
| H | -0.724743000 | 3.662921000 | -0.236559000 |
| H | 0.845715000 | 3.039829000 | 1.129717000 |
| H | 1.151106000 | 2.884382000 | -1.010274000 |
| P | -2.942298000 | 0.773528000 | -0.154084000 |
| H | -3.555381000 | 0.126501000 | -1.244193000 |
| H | -3.720222000 | 0.246349000 | 0.894512000 |
| H | -3.542012000 | 2.046678000 | -0.272370000 |

## Int-3

$\mathrm{G}_{\mathrm{DFT}}=-1593.541051$
$G_{\text {CORR DFT }}=0.113438$
$\mathrm{E}_{\text {CCSD }}=-6403.149012$
$G=-6403.035574$

Pd $\quad-0.568603000 \quad-0.542847000 \quad-0.153016000$
C $\quad 1.440347000 \quad-0.235631000 \quad-0.218399000$

| C | 2.405038000 | -0.771645000 | -1.036702000 |
| :--- | :---: | :---: | :---: |
| S | 2.137195000 | 0.964977000 | 0.828851000 |
| C | 3.702187000 | -0.206109000 | -0.835427000 |
| H | 2.198844000 | -1.541520000 | -1.777754000 |
| C | 3.718901000 | 0.743558000 | 0.146583000 |
| H | 4.582930000 | -0.497474000 | -1.401531000 |
| H | 4.558546000 | 1.327748000 | 0.506115000 |
| P | 0.080241000 | -2.600347000 | 0.556919000 |
| H | -0.898147000 | -3.551671000 | 0.909382000 |
| H | 0.870235000 | -3.346938000 | -0.334992000 |
| H | 0.891657000 | -2.613210000 | 1.703872000 |
| P | -2.961514000 | -0.780585000 | -0.155755000 |
| H | -3.651680000 | 0.217898000 | 0.558824000 |
| H | -3.584440000 | -0.636577000 | -1.411392000 |
| H | -3.651181000 | -1.920319000 | 0.307958000 |
| O | -0.917488000 | 1.435976000 | -0.871192000 |
| C | -1.093122000 | 2.279968000 | 0.087756000 |
| O | -1.162460000 | 1.982556000 | 1.289551000 |
| C | -1.172745000 | 3.723717000 | -0.353862000 |
| H | -0.150106000 | 4.111545000 | -0.437715000 |
| H | -1.644335000 | 3.819071000 | -1.335678000 |
| H | -1.706654000 | 4.325337000 | 0.385994000 |

## Int-4

$\mathrm{G}_{\mathrm{DFT}}=-1250.436876$
$\mathrm{G}_{\text {CORR DFT }}=0.090706$
$\mathrm{E}_{\text {CCSD }}=-6060.479804$
$\mathrm{G}=-6060.389098$

| Pd | -0.543546000 | 0.391847000 | 0.038181000 |
| :--- | :---: | :---: | :---: |
| C | 1.347922000 | -0.187440000 | 0.217213000 |
| C | 2.242911000 | -0.050577000 | 1.248197000 |
| S | 2.014785000 | -1.160360000 | -1.062161000 |
| C | 3.460207000 | -0.764780000 | 1.025647000 |
| H | 2.038672000 | 0.528157000 | 2.145893000 |
| C | 3.488674000 | -1.410548000 | -0.177640000 |
| H | 4.279688000 | -0.795148000 | 1.738254000 |
| H | 4.277054000 | -2.025176000 | -0.596844000 |
| O | -1.712524000 | -1.453188000 | 0.266788000 |
| O | -2.763072000 | 0.453683000 | -0.066816000 |
| C | -2.795789000 | -0.804029000 | 0.109991000 |
| C | -4.104344000 | -1.528473000 | 0.102386000 |
| H | -4.372391000 | -1.759899000 | -0.934761000 |


| H | -4.032681000 | -2.468316000 | 0.654660000 |
| :---: | :---: | :---: | :---: |
| H | -4.894191000 | -0.898472000 | 0.519321000 |
| P | 0.476301000 | 2.376286000 | -0.266471000 |
| H | 1.218992000 | 2.868236000 | 0.820343000 |
| H | 1.426523000 | 2.444594000 | -1.298793000 |
| H | -0.352332000 | 3.473627000 | -0.567316000 |

## $\alpha-$ CMD

$\mathrm{G}_{\mathrm{DFT}}=-1815.744609$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.132665$
$\mathrm{E}_{\mathrm{CCSD}}=-9184.541396$
$\mathrm{G}=-9184.408731$

| ---------------- |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| Pd | 1.605185000 | 0.216097000 | -0.055386000 |
| O | 2.989933000 | -1.447785000 | -0.399837000 |
| C | 2.826526000 | -2.563982000 | 0.157475000 |
| P | 3.131878000 | 1.779007000 | -0.822414000 |
| O | 1.819645000 | -2.865351000 | 0.880094000 |
| C | 3.863661000 | -3.631959000 | -0.033704000 |
| H | 4.735347000 | -3.244593000 | -0.563810000 |
| H | 4.161724000 | -4.035350000 | 0.938566000 |
| H | 3.425755000 | -4.456913000 | -0.605413000 |
| H | 0.954787000 | -1.940338000 | 0.824849000 |
| C | -0.030029000 | -1.040836000 | 0.679960000 |
| C | -0.778158000 | -0.593037000 | 1.766224000 |
| S | -1.132741000 | -1.401984000 | -0.640416000 |
| C | -2.171254000 | -0.530739000 | 1.564111000 |
| C | -2.501312000 | -0.939336000 | 0.291533000 |
| H | -2.902021000 | -0.206460000 | 2.298341000 |
| H | -0.304590000 | -0.303625000 | 2.701923000 |
| Br | -4.249478000 | -0.985771000 | -0.430469000 |
| H | 3.576267000 | 2.721477000 | 0.123827000 |
| H | 4.358853000 | 1.345142000 | -1.364409000 |
| H | 2.681838000 | 2.645058000 | -1.835848000 |
| C | 0.448571000 | 1.820636000 | 0.255361000 |
| C | 0.492086000 | 2.727086000 | 1.285503000 |
| S | -0.836719000 | 2.216770000 | -0.848249000 |
| C | -0.522425000 | 3.730292000 | 1.200304000 |
| H | 1.217422000 | 2.671555000 | 2.094717000 |
| C | -1.319881000 | 3.591335000 | 0.099621000 |
| H | -0.649640000 | 4.523262000 | 1.932537000 |
| H | -2.152639000 | 4.208948000 | -0.216665000 |

## $\beta$-CMD

```
G
G
E}\mp@subsup{\textrm{ECCSD}}{=-9184.536345}{
G=-9184.404574
```

| Pd | -1.618850000 | 0.315569000 | 0.101338000 |
| :--- | :---: | :---: | :---: |
| O | -3.278127000 | -1.111821000 | 0.081444000 |
| C | -3.127288000 | -2.219055000 | -0.495904000 |
| P | -3.013215000 | 2.144941000 | 0.337066000 |
| O | -2.014979000 | -2.633830000 | -0.966418000 |
| C | -4.308206000 | -3.129346000 | -0.655790000 |
| H | -4.474373000 | -3.322179000 | -1.720430000 |
| H | -4.092492000 | -4.092871000 | -0.183826000 |
| H | -5.205119000 | -2.690976000 | -0.215430000 |
| H | -1.097346000 | -1.881503000 | -0.582742000 |
| H | -2.910241000 | 3.154822000 | -0.637453000 |
| H | -4.407841000 | 1.943270000 | 0.366725000 |
| H | -2.830394000 | 2.911321000 | 1.502739000 |
| C | -0.144772000 | 1.664871000 | 0.153764000 |
| C | 0.623294000 | 2.057372000 | 1.219479000 |
| S | 0.409295000 | 2.425374000 | -1.310998000 |
| C | 1.674581000 | 2.956221000 | 0.857155000 |
| H | 0.461909000 | 1.696325000 | 2.232808000 |
| C | 1.692968000 | 3.249816000 | -0.476551000 |
| H | 2.388419000 | 3.366055000 | 1.566784000 |
| H | 2.369006000 | 3.900912000 | -1.018677000 |
| C | 2.290998000 | -1.128201000 | 0.037805000 |
| C | 1.180290000 | -0.967144000 | -0.730025000 |
| C | -0.039080000 | -1.219766000 | -0.009931000 |
| C | 0.235255000 | -1.576738000 | 1.297444000 |
| S | 1.920992000 | -1.603978000 | 1.672974000 |
| H | 1.225005000 | -0.663357000 | -1.772482000 |
| H | -0.477544000 | -1.843644000 | 2.073426000 |
| Br | 4.094525000 | -0.870679000 | -0.492157000 |

## $\gamma$-CMD

$G_{\text {DFT }}=-1815.741028$
$\mathrm{G}_{\text {CORR DFT }}=0.132657$
$\mathrm{E}_{\text {CCSD }}=-9184.540316$
$G=-9184.407659$

| Pd | -0.102985000 | -1.112923000 | 0.015860000 |
| :--- | :---: | :---: | :---: |
| O | -2.167737000 | -1.816738000 | 0.162769000 |
| C | -2.996279000 | -1.210661000 | 0.893080000 |
| P | 0.524589000 | -3.011638000 | -1.134605000 |
| O | -2.729078000 | -0.158628000 | 1.557636000 |
| C | -4.396530000 | -1.742172000 | 0.996078000 |
| H | -5.091656000 | -1.002060000 | 0.586459000 |
| H | -4.501866000 | -2.683103000 | 0.453533000 |
| H | -4.659155000 | -1.883978000 | 2.048752000 |
| H | -1.532801000 | 0.247254000 | 1.280932000 |
| H | 1.540368000 | -3.800595000 | -0.563877000 |
| H | -0.457614000 | -3.985319000 | -1.403513000 |
| H | 1.062782000 | -2.805544000 | -2.417591000 |
| C | 1.808559000 | -0.562690000 | -0.202368000 |
| C | 2.361361000 | 0.293390000 | -1.119581000 |
| S | 3.021081000 | -1.125496000 | 0.913832000 |
| C | 3.759298000 | 0.513836000 | -0.915858000 |
| H | 1.784671000 | 0.771766000 | -1.908767000 |
| C | 4.263428000 | -0.182381000 | 0.145804000 |
| H | 4.363253000 | 1.167196000 | -1.540023000 |
| H | 5.280090000 | -0.205420000 | 0.521021000 |
| C | 1.062837000 | 2.478618000 | 1.921354000 |
| C | 0.515668000 | 1.239783000 | 2.060876000 |
| C | -0.385718000 | 0.853896000 | 1.005071000 |
| C | -0.469735000 | 1.889958000 | 0.097692000 |
| S | 0.499218000 | 3.267331000 | 0.477767000 |
| H | 0.749317000 | 0.589247000 | 2.900325000 |
| H | 1.763568000 | 2.992090000 | 2.570109000 |
| Br | -1.534859000 | 1.916331000 | -1.473129000 |

## Int-5

---------------------
$G_{\text {DFT }}=-1815.756311$
$\mathrm{G}_{\text {CORR DFT }}=0.135703$
$\mathrm{E}_{\text {CCSD }}=-9184.559657$
$\mathrm{G}=-9184.423954$

| Pd | -1.484510000 | 0.526061000 | -0.101649000 |
| :--- | :---: | :---: | :---: |
| C | -1.982607000 | -1.382232000 | 0.191050000 |
| C | -2.799740000 | -1.922841000 | 1.154266000 |
| S | -1.398188000 | -2.628155000 | -0.871452000 |
| C | -2.963319000 | -3.338385000 | 1.031375000 |


| H | -3.275014000 | -1.330589000 | 1.933467000 |
| :--- | :---: | :---: | :---: |
| C | -2.273514000 | -3.866883000 | -0.022331000 |
| H | -3.576621000 | -3.934207000 | 1.702292000 |
| H | -2.226355000 | -4.898383000 | -0.352026000 |
| O | 0.541486000 | 2.835370000 | 1.262498000 |
| O | -0.941487000 | 2.689067000 | -0.417786000 |
| C | -0.174945000 | 3.351005000 | 0.281821000 |
| C | 0.034202000 | 4.812950000 | 0.099154000 |
| H | -0.124268000 | 5.331187000 | 1.049528000 |
| H | 1.071901000 | 4.993564000 | -0.199263000 |
| H | -0.642677000 | 5.200712000 | -0.661950000 |
| H | 0.430293000 | 1.853196000 | 1.273762000 |
| C | 0.413876000 | -0.049320000 | 0.392323000 |
| C | 0.962069000 | -0.574772000 | 1.542182000 |
| S | 1.653134000 | 0.103478000 | -0.828607000 |
| C | 2.364288000 | -0.833137000 | 1.473113000 |
| H | 0.365459000 | -0.785027000 | 2.427565000 |
| C | 2.872917000 | -0.515099000 | 0.246114000 |
| H | 2.962923000 | -1.233142000 | 2.286177000 |
| Br | 4.679192000 | -0.692717000 | -0.309523000 |
| P | -3.783464000 | 0.932642000 | -0.634625000 |
| H | -4.330671000 | 0.127381000 | -1.653592000 |
| H | -4.718809000 | 0.651416000 | 0.382553000 |
| H | -4.266942000 | 2.192151000 | -1.051109000 |

## Int-6

```
G
G
E}\mp@subsup{\textrm{ECSD}}{\mathrm{ C -9298.563015}}{
G=-9298.45876
----------------------
```

| Pd | -1.566596000 | -0.728357000 | 0.047564000 |
| :--- | :---: | :---: | :---: |
| C | -1.502080000 | 1.299259000 | 0.339284000 |
| C | -1.176682000 | 2.025167000 | 1.458621000 |
| S | -1.843723000 | 2.388106000 | -0.979225000 |
| C | -1.213892000 | 3.441247000 | 1.265935000 |
| H | -0.895182000 | 1.557773000 | 2.399891000 |
| C | -1.555551000 | 3.800286000 | -0.007221000 |
| H | -0.986302000 | 4.163121000 | 2.046279000 |
| H | -1.652059000 | 4.793716000 | -0.430150000 |
| C | 0.455730000 | -0.711460000 | 0.382547000 |
| C | 1.204143000 | -1.336521000 | 1.354473000 |
| C | 2.611616000 | -1.106389000 | 1.261728000 |


| H | 0.763397000 | -1.951181000 | 2.137235000 |
| :--- | :---: | :---: | :---: |
| C | 2.919803000 | -0.302454000 | 0.202506000 |
| H | 3.353215000 | -1.517636000 | 1.940735000 |
| Br | 4.655921000 | 0.255570000 | -0.330554000 |
| S | 1.500626000 | 0.192372000 | -0.674392000 |
| P | -3.919996000 | -0.508869000 | -0.300257000 |
| H | -4.794893000 | -1.613754000 | -0.388457000 |
| H | -4.612556000 | 0.256869000 | 0.658387000 |
| H | -4.317910000 | 0.184616000 | -1.461865000 |
| P | -1.350193000 | -3.091528000 | -0.217879000 |
| H | -0.443863000 | -3.511910000 | -1.211454000 |
| H | -0.798635000 | -3.778369000 | 0.883158000 |
| H | -2.425174000 | -3.960295000 | -0.509665000 |

## Int-7

$G_{\text {DFT }}=-1815.752992$
$\mathrm{G}_{\text {CORR DFT }}=0.132991$
$\mathrm{E}_{\text {CCSD }}=-9184.55455$
$\mathrm{G}=-9184.421559$

| Pd | 1.615130000 | -0.094228000 | 0.040657000 |
| :--- | :---: | :---: | :---: |
| C | 1.086028000 | 1.821083000 | -0.128715000 |
| C | 1.106378000 | 2.629616000 | -1.239607000 |
| S | 0.534569000 | 2.718387000 | 1.255175000 |
| C | 0.681648000 | 3.970017000 | -0.977459000 |
| H | 1.413463000 | 2.280093000 | -2.223313000 |
| C | 0.344445000 | 4.178120000 | 0.329685000 |
| H | 0.634961000 | 4.746572000 | -1.736549000 |
| H | 0.001694000 | 5.090705000 | 0.803689000 |
| O | 0.520562000 | -3.110853000 | -0.922489000 |
| O | 2.256217000 | -2.247491000 | 0.205885000 |
| C | 1.696441000 | -3.203386000 | -0.329664000 |
| C | 2.278186000 | -4.572186000 | -0.370042000 |
| H | 1.623231000 | -5.261249000 | 0.172502000 |
| H | 2.327186000 | -4.921061000 | -1.405939000 |
| H | 3.272456000 | -4.574543000 | 0.076292000 |
| H | 0.153663000 | -2.209749000 | -0.758494000 |
| P | 3.884721000 | 0.632988000 | -0.274313000 |
| H | 4.165643000 | 1.288314000 | -1.491734000 |
| H | 4.325979000 | 1.641387000 | 0.607213000 |
| H | 5.007376000 | -0.222695000 | -0.216000000 |
| C | -0.388697000 | -0.455932000 | 0.333678000 |
| C | -1.492931000 | 0.039987000 | -0.435336000 |


| C | -0.818900000 | -1.203847000 | 1.401469000 |
| :--- | :---: | :---: | :---: |
| C | -2.699599000 | -0.362022000 | 0.063562000 |
| H | -1.394420000 | 0.672559000 | -1.313916000 |
| S | -2.556873000 | -1.336425000 | 1.489814000 |
| H | -0.226375000 | -1.706826000 | 2.160332000 |
| Br | -4.413914000 | 0.049224000 | -0.642915000 |

## Int-8

| $\mathrm{G}_{\text {DFT }}=-1929.916451$ |  |  |  |
| :--- | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.104699$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-9298.559857$ |  |  |  |
| $\mathrm{G}=-9298.455158$ |  |  |  |
| $---\cdots--------$ |  |  |  |
|  |  |  |  |
| Pd | 1.628842000 | -0.638757000 | -0.113412000 |
| C | 1.419726000 | 1.403517000 | -0.031334000 |
| C | 1.726306000 | 2.358583000 | -0.975076000 |
| S | 0.772360000 | 2.184184000 | 1.383323000 |
| C | 1.449863000 | 3.700238000 | -0.564392000 |
| H | 2.134869000 | 2.114771000 | -1.954560000 |
| C | 0.936977000 | 3.772772000 | 0.700000000 |
| H | 1.629534000 | 4.572581000 | -1.187904000 |
| H | 0.647313000 | 4.653195000 | 1.262502000 |
| P | 3.946939000 | -0.252918000 | -0.551219000 |
| H | 4.904746000 | -1.277592000 | -0.724168000 |
| H | 4.243145000 | 0.518144000 | -1.694572000 |
| H | 4.626566000 | 0.523298000 | 0.408948000 |
| P | 1.579697000 | -3.017403000 | -0.175872000 |
| H | 1.136620000 | -3.651045000 | 1.003918000 |
| H | 0.665758000 | -3.592542000 | -1.081498000 |
| H | 2.704225000 | -3.826027000 | -0.453951000 |
| C | -0.385012000 | -0.719421000 | 0.294872000 |
| C | -1.398994000 | -0.177781000 | -0.559111000 |
| C | -0.914665000 | -1.237321000 | 1.445585000 |
| C | -2.650255000 | -0.306248000 | -0.025840000 |
| H | -1.208934000 | 0.299851000 | -1.516720000 |
| S | -2.655263000 | -1.072616000 | 1.527628000 |
| H | -0.406590000 | -1.694815000 | 2.289110000 |
| Br | -4.282307000 | 0.264192000 | -0.814607000 |

## Int-9

$G_{\text {DFT }}=-1815.755243$
$\mathrm{G}_{\text {CORR DFT }}=0.135362$
$\mathrm{E}_{\text {CCSD }}=-9184.558546$
$\mathrm{G}=-9184.423184$

| Pd | 0.433945000 | 1.041080000 | 0.161440000 |
| :--- | :---: | :---: | :---: |
| C | 2.153996000 | 0.030622000 | 0.182480000 |
| C | 3.264903000 | 0.231191000 | 0.966279000 |
| S | 2.431563000 | -1.280719000 | -0.926455000 |
| C | 4.341165000 | -0.662432000 | 0.669037000 |
| H | 3.317911000 | 0.995630000 | 1.738825000 |
| C | 4.047168000 | -1.536489000 | -0.338546000 |
| H | 5.296968000 | -0.647380000 | 1.186341000 |
| H | 4.674307000 | -2.308159000 | -0.770084000 |
| O | -2.869806000 | 0.914363000 | 1.205742000 |
| O | -1.457064000 | 2.273044000 | 0.113222000 |
| C | -2.564992000 | 2.042679000 | 0.594936000 |
| C | -3.692638000 | 3.012840000 | 0.541448000 |
| H | -4.517974000 | 2.577846000 | -0.031060000 |
| H | -4.064495000 | 3.202630000 | 1.552791000 |
| H | -3.369039000 | 3.944289000 | 0.077208000 |
| H | -2.098137000 | 0.298970000 | 1.162646000 |
| P | 1.681060000 | 2.944584000 | -0.591625000 |
| H | 2.689774000 | 3.419677000 | 0.272587000 |
| H | 2.470981000 | 2.748125000 | -1.742526000 |
| H | 1.077967000 | 4.174631000 | -0.935350000 |
| C | -0.367658000 | -0.743984000 | 0.799002000 |
| C | -0.127186000 | -1.380732000 | 2.064611000 |
| C | -1.145283000 | -1.563648000 | 0.025411000 |
| C | -0.715752000 | -2.606312000 | 2.206416000 |
| H | 0.479960000 | -0.928493000 | 2.845527000 |
| S | -1.594537000 | -3.068509000 | 0.787675000 |
| H | -0.688569000 | -3.273944000 | 3.060649000 |
| Br | -1.725337000 | -1.231894000 | -1.759060000 |

## Int-10

-------------------------
$\mathrm{G}_{\mathrm{DFT}}=-1929.921441$
$\mathrm{G}_{\text {CORR DFT }}=0.104269$
$\mathrm{E}_{\text {CCSD }}=-9298.563876$
$\mathrm{G}=-9298.459607$
$\qquad$

Pd $\quad-0.826282000 \quad-0.886286000 \quad 0.286398000$
C $\quad-1.713907000 \quad 0.949551000 \quad 0.034148000$

| C | -2.902440000 | 1.421253000 | 0.546596000 |
| :---: | :---: | :---: | :---: |
| S | -0.969100000 | 2.197529000 | -0.924188000 |
| C | -3.214060000 | 2.764065000 | 0.167542000 |
| H | -3.546799000 | 0.828416000 | 1.193826000 |
| C | -2.263478000 | 3.319974000 | -0.641584000 |
| H | -4.111609000 | 3.289124000 | 0.484938000 |
| H | -2.246761000 | 4.310172000 | -1.082874000 |
| P | -2.865083000 | -1.854792000 | -0.480456000 |
| H | -3.068367000 | -3.245850000 | -0.619244000 |
| H | -4.030085000 | -1.533759000 | 0.246821000 |
| H | -3.289139000 | -1.439569000 | -1.758328000 |
| P | 0.427837000 | -2.855706000 | 0.766025000 |
| H | 1.700757000 | -2.940715000 | 0.165214000 |
| H | 0.813224000 | -3.002473000 | 2.114228000 |
| H | -0.026620000 | -4.171058000 | 0.523672000 |
| C | 0.836904000 | 0.158699000 | 0.883617000 |
| C | 0.971888000 | 0.836367000 | 2.139739000 |
| C | 1.956416000 | 0.363357000 | 0.130912000 |
| C | 2.148308000 | 1.516984000 | 2.292154000 |
| H | 0.197804000 | 0.825803000 | 2.903837000 |
| S | 3.162314000 | 1.371574000 | 0.896524000 |
| H | 2.485077000 | 2.101630000 | 3.141282000 |
| Br | 2.276599000 | -0.248064000 | -1.647066000 |

## $\alpha-$ RE

$G_{\text {DFT }}=-1929.905518$
$\mathrm{G}_{\text {CORR DFT }}=0.1026$
$\mathrm{E}_{\text {CCSD }}=-9298.541209$
$\mathrm{G}=-9298.438609$

| Pd | -1.487068000 | -0.822039000 | -0.025319000 |
| :--- | :---: | :---: | :---: |
| P | -3.896214000 | -0.873457000 | -0.423782000 |
| P | -0.875726000 | -3.170763000 | 0.208548000 |
| H | -0.892700000 | -4.049271000 | -0.899590000 |
| H | 0.462086000 | -3.402543000 | 0.605853000 |
| H | -1.497519000 | -4.043234000 | 1.131651000 |
| H | -4.350714000 | 0.204683000 | -1.219011000 |
| H | -4.708378000 | -1.884464000 | -0.991081000 |
| H | -4.702990000 | -0.609893000 | 0.707478000 |
| C | 0.322429000 | 0.074346000 | 0.349474000 |
| C | 0.913605000 | 0.364523000 | 1.563133000 |
| S | 1.560968000 | -0.191953000 | -0.864099000 |
| C | 2.336924000 | 0.392124000 | 1.534639000 |


| H | 0.334682000 | 0.596635000 | 2.453908000 |
| :--- | :---: | :---: | :---: |
| C | 2.830255000 | 0.121938000 | 0.290496000 |
| H | 2.965226000 | 0.619878000 | 2.390898000 |
| C | -1.259821000 | 1.217754000 | -0.145646000 |
| C | -1.109200000 | 1.997347000 | -1.273531000 |
| S | -2.039169000 | 2.153141000 | 1.114770000 |
| C | -1.601553000 | 3.326463000 | -1.125616000 |
| H | -0.619799000 | 1.635893000 | -2.175045000 |
| C | -2.124552000 | 3.573295000 | 0.112342000 |
| H | -1.549383000 | 4.077548000 | -1.909296000 |
| H | -2.548066000 | 4.492940000 | 0.499330000 |
| Br | 4.654128000 | 0.087233000 | -0.229839000 |

## $\beta$-RE

------------------------1
$\mathrm{G}_{\text {CORR DFT }}=0.101422$
$\mathrm{E}_{\mathrm{CCSD}}=-9298.538712$
$\mathrm{G}=-9298.43729$

| ----------------- |  |  |  |
| :--- | :---: | :---: | :---: |
| Pd | -1.455890000 | -0.843464000 | -0.082558000 |
| P | -3.838337000 | -0.932570000 | -0.616917000 |
| P | -0.747246000 | -3.161333000 | 0.173476000 |
| H | 0.635167000 | -3.321061000 | 0.434553000 |
| H | -1.221496000 | -3.956932000 | 1.242684000 |
| H | -0.856850000 | -4.149768000 | -0.833143000 |
| H | -4.257738000 | 0.136186000 | -1.444594000 |
| H | -4.620107000 | -1.948965000 | -1.218633000 |
| H | -4.709948000 | -0.662417000 | 0.464463000 |
| C | 0.770403000 | 0.210419000 | 1.689592000 |
| C | 0.334921000 | 0.079741000 | 0.394195000 |
| S | 2.509330000 | 0.275372000 | 1.812880000 |
| C | 1.429483000 | 0.022348000 | -0.533709000 |
| C | 2.637757000 | 0.105800000 | 0.091698000 |
| H | 1.320847000 | -0.075956000 | -1.610775000 |
| C | -1.252186000 | 1.200301000 | -0.169597000 |
| C | -1.057654000 | 1.982212000 | -1.289258000 |
| S | -2.083401000 | 2.134163000 | 1.056665000 |
| C | -1.560837000 | 3.310797000 | -1.162648000 |
| H | -0.538814000 | 1.621733000 | -2.174677000 |
| C | -2.137097000 | 3.554943000 | 0.051376000 |
| H | -1.481819000 | 4.061068000 | -1.945011000 |
| H | -2.584876000 | 4.471244000 | 0.418466000 |
| H | 0.179611000 | 0.303976000 | 2.594782000 |

$\begin{array}{llll}\mathrm{Br} & 4.345346000 & 0.067910000 & -0.737755000\end{array}$
$\gamma$-RE
$\mathrm{G}_{\mathrm{DFT}}=-1929.905056$
$\mathrm{G}_{\mathrm{CORRDFT}}=0.103403$
$\mathrm{E}_{\text {CCSD }}=-9298.542479$
$G=-9298.439076$


| Pd | 0.925043000 | -0.921983000 | 0.275649000 |
| :--- | :---: | :---: | :---: |
| P | 3.208044000 | -1.220829000 | -0.532982000 |
| P | -0.129885000 | -3.104945000 | 0.375398000 |
| H | 0.427682000 | -4.393053000 | 0.558707000 |
| H | -1.144853000 | -3.201124000 | 1.356894000 |
| H | -0.939786000 | -3.420097000 | -0.740498000 |
| H | 4.116122000 | -2.288735000 | -0.333296000 |
| H | 3.387250000 | -1.100059000 | -1.931011000 |
| H | 4.075036000 | -0.167078000 | -0.156529000 |
| C | -1.843768000 | 0.287501000 | 0.029177000 |
| C | -0.740778000 | 0.164923000 | 0.839350000 |
| S | -3.334123000 | 0.580482000 | 0.891131000 |
| C | -1.142277000 | 0.293103000 | 2.215519000 |
| C | -2.475374000 | 0.508968000 | 2.395330000 |
| H | -0.439878000 | 0.231697000 | 3.043492000 |
| C | 0.969555000 | 1.132540000 | 0.425533000 |
| C | 1.525917000 | 1.859876000 | 1.459373000 |
| S | 1.078343000 | 2.056423000 | -1.059866000 |
| C | 2.024067000 | 3.135192000 | 1.068573000 |
| H | 1.559301000 | 1.495115000 | 2.483373000 |
| C | 1.853575000 | 3.392580000 | -0.263182000 |
| H | 2.480836000 | 3.840322000 | 1.758048000 |
| H | 2.117881000 | 4.284126000 | -0.820313000 |
| H | -3.013647000 | 0.643135000 | 3.327021000 |
| Br | -1.893808000 | 0.129572000 | -1.862293000 |

## $\alpha$-product

$G_{\text {DFT }}=-1116.966913$
$\mathrm{G}_{\text {CORR DFT }}=0.065185$
$\mathrm{E}_{\text {CCSD }}=-3675.033368$
$\mathrm{G}=-3674.968183$

| C | -2.121050000 | -0.116086000 | -0.068312000 |
| :--- | :---: | :--- | :--- |
| C | -2.672373000 | -1.362414000 | -0.258379000 |
| C | -4.088833000 | -1.367245000 | -0.163479000 |
| C | -4.605197000 | -0.128069000 | 0.095570000 |
| S | -3.365831000 | 1.067149000 | 0.243099000 |
| H | -2.077438000 | -2.244946000 | -0.479913000 |
| H | -4.701599000 | -2.253959000 | -0.291152000 |
| H | -5.643069000 | 0.160442000 | 0.211094000 |
| C | -0.727620000 | 0.273607000 | -0.096337000 |
| C | -0.181116000 | 1.522608000 | -0.278200000 |
| S | 0.524291000 | -0.926556000 | 0.130507000 |
| C | 1.238055000 | 1.536378000 | -0.248736000 |
| H | -0.784526000 | 2.410541000 | -0.448098000 |
| C | 1.751236000 | 0.287064000 | -0.043918000 |
| H | 1.850400000 | 2.422234000 | -0.381981000 |
| Br | 3.578921000 | -0.189110000 | 0.050946000 |

## $\beta$-product

$\mathrm{G}_{\mathrm{DFT}}=-1116.965784$
$\mathrm{G}_{\text {CORR DFT }}=0.065304$
$\mathrm{E}_{\mathrm{CCSD}}=-3675.033159$
$\mathrm{G}=-3674.967855$

|  | -0.719420000 | 0.528026000 | -0.019374000 |
| :--- | :---: | :---: | :---: |
| C | -0.329244000 | -0.440798000 | 0.091859000 |
| C | -0.227650000 | 1.799928000 | -0.197960000 |
| C | 1.563742000 | 0.130641000 | -0.001412000 |
| H | 0.172686000 | -1.504068000 | 0.251593000 |
| S | 1.497085000 | 1.847521000 | -0.222431000 |
| C | -2.140805000 | 0.212389000 | 0.057766000 |
| C | -3.180923000 | 1.040652000 | 0.405362000 |
| S | -2.730380000 | -1.381134000 | -0.333742000 |
| C | -4.447578000 | 0.399798000 | 0.358038000 |
| H | -3.034510000 | 2.073967000 | 0.708416000 |
| C | -4.363149000 | -0.911658000 | -0.020190000 |
| H | -5.384424000 | 0.888934000 | 0.606172000 |
| H | -5.161238000 | -1.635634000 | -0.132632000 |
| Br | 3.229974000 | -0.758726000 | 0.107451000 |
| H | -0.789659000 | 2.716136000 | -0.340112000 |

## $\gamma$-product

$$
G_{D F T}=-1116.965027
$$

$\mathrm{G}_{\text {CORR DFT }}=0.065727$
$\mathrm{E}_{\text {CCSD }}=-3675.031841$
$G=-3674.966114$

----------------------

| C | 0.056238000 | 0.967538000 | -0.028974000 |
| :--- | :---: | :---: | :---: |
| C | 0.469705000 | 2.340037000 | -0.126090000 |
| C | 1.163901000 | 0.146877000 | -0.001908000 |
| C | 1.819172000 | 2.513764000 | -0.159997000 |
| H | -0.236241000 | 3.162597000 | -0.192327000 |
| S | 2.664802000 | 1.009453000 | -0.085135000 |
| H | 2.373668000 | 3.440464000 | -0.247011000 |
| Br | 1.236647000 | -1.738374000 | 0.162590000 |
| C | -1.354101000 | 0.605806000 | 0.042330000 |
| C | -2.373918000 | 1.424590000 | 0.474470000 |
| S | -1.995588000 | -0.927941000 | -0.491588000 |
| C | -3.657358000 | 0.828291000 | 0.381957000 |
| H | -2.201281000 | 2.424206000 | 0.863332000 |
| C | -3.610415000 | -0.439785000 | -0.127268000 |
| H | -4.577059000 | 1.317807000 | 0.686444000 |
| H | -4.428503000 | -1.128874000 | -0.300624000 |

## Annex 3.2 C-H activation of 2-bromothiophene with various ligands

## Int-4-PMe ${ }_{3}$

$G_{\text {DFT }}=-1368.244629$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.172326$

| ------------------- |  |  |  |
| :--- | :--- | :--- | :--- |
| Pd | -0.6163990 | -0.0992250 | 0.0848930 |
| C | 1.2357430 | -0.8037470 | 0.2507670 |
| C | 2.1034230 | -0.8494560 | 1.3144250 |
| S | 1.9256210 | -1.6153230 | -1.1277370 |
| C | 3.3142770 | -1.5530300 | 1.0295090 |
| H | 1.8820060 | -0.4070720 | 2.2832030 |
| C | 3.3708390 | -2.0221380 | -0.2525120 |
| H | 4.1084150 | -1.7052860 | 1.7555270 |
| H | 4.1575920 | -2.5962040 | -0.7285190 |
| O | -2.0595170 | -1.8185610 | 0.1955870 |
| O | -2.8020740 | 0.2440820 | -0.0493250 |
| C | -3.0229150 | -1.0041720 | 0.0617760 |
| C | -4.4277810 | -1.5221130 | 0.0072010 |
| H | -4.6188450 | -1.9225720 | -0.9948340 |
| H | -4.5596800 | -2.3412720 | 0.7193320 |
| H | -5.1483550 | -0.7255610 | 0.2061530 |
| P | 0.4172910 | 1.8900530 | -0.0800700 |
| C | -0.7841720 | 3.1047620 | -0.7133560 |
| H | -1.6522290 | 3.1399740 | -0.0479160 |
| H | -0.3185990 | 4.0965430 | -0.7664760 |
| H | -1.1208930 | 2.8043430 | -1.7102990 |
| C | 0.9741750 | 2.5832550 | 1.5082530 |
| H | 1.7812600 | 1.9691910 | 1.9185100 |
| H | 1.3407040 | 3.6051660 | 1.3524620 |
| H | 0.1401630 | 2.5993680 | 2.2162050 |
| C | 1.8589830 | 2.0487640 | -1.1781900 |
| H | 2.6915500 | 1.4546210 | -0.7873050 |
| H | 1.6071720 | 1.6866110 | -2.1796480 |
| H | 2.1521130 | 3.1039570 | -1.2339730 |
|  |  |  |  |

## $\alpha$-CMD-PMe 3

| $\mathrm{G}_{\text {DFT }}=-1933.549141$ |  |  |  |
| :---: | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.213602$ |  |  |  |
| Pd | -1.2024850 | 0.2092800 | 0.1963590 |
| O | -2.3712690 | 2.0369310 | -0.1918110 |
| C | -1.9638240 | 3.1650610 | 0.1785590 |
| P | -3.0530770 | -1.0159210 | -0.4526030 |


|  |  |  |  |
| :--- | :--- | :--- | :--- |
| O | -0.8377620 | 3.3705260 | 0.7490270 |
| C | -2.8224690 | 4.3720400 | -0.0564300 |
| H | -3.8028780 | 4.0876300 | -0.4422430 |
| H | -2.9319800 | 4.9353650 | 0.8749780 |
| H | -2.3240420 | 5.0306380 | -0.7754520 |
| H | -0.1666390 | 2.3468450 | 0.7575470 |
| C | 0.6887160 | 1.2611540 | 0.6857890 |
| C | 1.4184890 | 0.8061760 | 1.7771990 |
| S | 1.7440330 | 1.2655130 | -0.7168640 |
| C | 2.7626600 | 0.4571800 | 1.5171880 |
| C | 3.0724220 | 0.6540700 | 0.1924650 |
| H | 3.4705570 | 0.0816990 | 2.2498080 |
| H | 0.9670730 | 0.7070290 | 2.7625660 |
| Br | 4.7511630 | 0.3047510 | -0.6145810 |
| C | -0.2715300 | -1.5295520 | 0.5082080 |
| C | -0.2251280 | -2.3122460 | 1.6339840 |
| S | 0.6400000 | -2.2724480 | -0.7760690 |
| C | 0.5445880 | -3.5053840 | 1.4696330 |
| H | -0.7269550 | -2.0448470 | 2.5618430 |
| C | 1.0738490 | -3.6343520 | 0.2161320 |
| H | 0.6997830 | -4.2365130 | 2.2590580 |
| H | 1.6992030 | -4.4265540 | -0.1791520 |
| C | -4.6280030 | -0.2915280 | 0.1174480 |
| H | -5.4733580 | -0.8282830 | -0.3303100 |
| H | -4.6919020 | -0.3594750 | 1.2079350 |
| H | -4.6602330 | 0.7630880 | -0.1719510 |
| C | -3.1844030 | -0.9833680 | -2.2729380 |
| H | -3.2006220 | 0.0580600 | -2.6113020 |
| H | -2.3132630 | -1.4821890 | -2.7107010 |
| H | -4.0996990 | -1.4901140 | -2.6024150 |
| C | -3.2004400 | -2.7808150 | -0.0250700 |
| H | -4.1264040 | -3.1829390 | -0.4537920 |
| H | -2.3409140 | -3.3352980 | -0.4163090 |
| H | -3.2198100 | -2.8977830 | 1.0629540 |
|  |  |  |  |

## $\beta$-CMD-PMe 3

------------------------
$\mathrm{G}_{\text {CORR DFT }}=0.213920$

| Pd | -1.2382180 | -0.2305680 | -0.0098500 |
| :--- | :--- | :--- | :--- |
| O | -2.5070500 | -2.0261320 | -0.0145140 |
| C | -2.0673450 | -3.0805740 | -0.5339320 |
| P | -3.0748810 | 1.1543870 | 0.2144340 |
| O | -0.8668710 | -3.2231010 | -0.9554080 |
| C | -2.9711770 | -4.2671830 | -0.6806180 |


| H | -3.9852000 | -4.0311640 | -0.3540870 |
| :--- | :--- | :--- | :--- |
| H | -2.9802490 | -4.5940030 | -1.7249030 |
| H | -2.5756230 | -5.0974740 | -0.0867350 |
| H | -0.1959690 | -2.2801510 | -0.5882770 |
| C | -0.1565690 | 1.4469450 | 0.0188810 |
| C | 0.3456660 | 2.1483560 | 1.0860580 |
| S | 0.3471370 | 2.1849180 | -1.4755130 |
| C | 1.1410440 | 3.2752950 | 0.7057960 |
| H | 0.1705010 | 1.8592480 | 2.1207510 |
| C | 1.2355380 | 3.4315340 | -0.6478900 |
| H | 1.6245840 | 3.9397920 | 1.4171570 |
| H | 1.7719610 | 4.1891040 | -1.2076260 |
| C | 2.9424990 | -0.7587050 | 0.1168450 |
| C | 1.8502120 | -0.8693140 | -0.6878880 |
| C | 0.6883140 | -1.3570980 | 0.0038130 |
| C | 0.9871540 | -1.6054380 | 1.3281350 |
| S | 2.6275850 | -1.2488890 | 1.7573500 |
| H | 1.8683000 | -0.5961950 | -1.7398410 |
| H | 0.3236670 | -1.9931300 | 2.0971520 |
| Br | 4.6668080 | -0.1339440 | -0.3771830 |
| C | -4.6512800 | 0.3492790 | -0.2301440 |
| H | -4.7565930 | -0.5789730 | 0.3388350 |
| H | -5.4906540 | 1.0200260 | -0.0101010 |
| H | -4.6505020 | 0.1024850 | -1.2964430 |
| C | -3.3145940 | 1.6549850 | 1.9531730 |
| H | -2.4455090 | 2.2297780 | 2.2894560 |
| H | -4.2171900 | 2.2708710 | 2.0484780 |
| H | -3.4145640 | 0.7639450 | 2.5808210 |
| C | -3.1180400 | 2.7355220 | -0.6931710 |
| H | -2.2830240 | 3.3685790 | -0.3743640 |
| H | -3.0274940 | 2.5541570 | -1.7687260 |
| H | -4.0661720 | 3.2472110 | -0.4879240 |
|  |  |  |  |

## $\gamma$-CMD-PMe ${ }_{3}$

$G_{D F T}=-1933.547474$
$\mathrm{G}_{\text {CORR DFT }}=0.213000$

| Pd | -0.5961300 | -0.3760400 | -0.2373220 |
| :--- | :--- | :--- | :--- |
| O | -0.5688870 | -2.5605580 | -0.4832240 |
| C | 0.3694810 | -3.1109650 | -1.1143060 |
| P | -2.7441610 | -0.5539790 | 0.5770600 |
| O | 1.3664960 | -2.4847370 | -1.6045680 |
| C | 0.3432650 | -4.5975310 | -1.3167880 |
| H | 0.4068190 | -4.8222380 | -2.3859880 |
| H | 1.2232760 | -5.0420310 | -0.8410260 |


| H | -0.5635260 | -5.0362940 | -0.8971570 |
| :--- | :--- | :--- | :--- |
| H | 1.3162640 | -1.2664560 | -1.2948740 |
| C | -0.7691490 | 1.5969800 | -0.0025640 |
| C | -0.3172520 | 2.4056140 | 1.0081080 |
| S | -1.5835930 | 2.5472800 | -1.2146230 |
| C | -0.6171160 | 3.7898650 | 0.8085630 |
| H | 0.2217980 | 2.0258520 | 1.8741400 |
| C | -1.3037550 | 4.0308980 | -0.3476750 |
| H | -0.3280090 | 4.5749620 | 1.5026840 |
| H | -1.6463310 | 4.9774860 | -0.7495810 |
| C | 2.6614980 | 1.9702750 | -1.6566450 |
| C | 1.7072450 | 1.0465010 | -1.9620750 |
| C | 1.4926330 | 0.0370240 | -0.9574340 |
| C | 2.3564850 | 0.2735850 | 0.0864360 |
| S | 3.3765720 | 1.6590640 | -0.1034650 |
| H | 1.1424970 | 1.0797720 | -2.8912060 |
| H | 2.9994190 | 2.8200240 | -2.2394050 |
| Br | 2.5027180 | -0.7667900 | 1.6719270 |
| C | -3.4270040 | 0.7716630 | 1.6240700 |
| H | -4.4495870 | 0.5106610 | 1.9225310 |
| H | -2.8039580 | 0.8913560 | 2.5160960 |
| H | -3.4334900 | 1.7198380 | 1.0763540 |
| C | -2.9709770 | -2.0641160 | 1.5741710 |
| H | -2.3561100 | -2.0037540 | 2.4775180 |
| H | -4.0252280 | -2.1718090 | 1.8567920 |
| H | -2.6489120 | -2.9302550 | 0.9889130 |
| C | -3.9520570 | -0.7339220 | -0.7786530 |
| H | -3.6641260 | -1.5872730 | -1.4017340 |
| H | -4.9580980 | -0.8991350 | -0.3737460 |
| H | -3.9517700 | 0.1700770 | -1.3963540 |

## Int-4-PCy ${ }_{3}$

$G_{\text {DFT }}=-1953.543462$
$G_{\text {CORR DFT }}=0.524515$

| Pd | -1.2294250 | 1.1501080 | 0.1874440 |
| :--- | :--- | :--- | :--- |
| C | -2.2690230 | -0.4526370 | 0.7392970 |
| C | -2.3092870 | -1.2562200 | 1.8526120 |
| S | -3.5095720 | -0.9371150 | -0.3898810 |
| C | -3.3344010 | -2.2508810 | 1.8046910 |
| H | -1.6330930 | -1.1461860 | 2.6976370 |
| C | -4.0655140 | -2.2123510 | 0.6514720 |
| H | -3.5186530 | -2.9633030 | 2.6045410 |
| H | -4.9036120 | -2.8350360 | 0.3598270 |
| O | -2.7021010 | 2.8371640 | 0.1611400 |


| O | -0.6162780 | 3.1981920 | -0.4597760 |
| :---: | :---: | :---: | :---: |
| C | -1.7984670 | 3.6215770 | -0.2634210 |
| C | -2.1426560 | 5.0527630 | -0.5452490 |
| H | -2.8112390 | 5.0978360 | -1.4118510 |
| H | -2.6836730 | 5.4807540 | 0.3040590 |
| H | -1.2466540 | 5.6414440 | -0.7536870 |
| P | 0.5441520 | -0.2683420 | -0.0457260 |
| C | 1.8258850 | 0.7683840 | -0.9059580 |
| C | 2.3308340 | 1.8938130 | 0.0072740 |
| C | 2.9989410 | 0.0421150 | -1.5755400 |
| H | 1.2289060 | 1.2456230 | -1.7050230 |
| C | 3.1871580 | 2.8783190 | -0.7826750 |
| H | 2.9395910 | 1.4638670 | 0.8190060 |
| H | 1.4857790 | 2.4177710 | 0.4717950 |
| C | 3.8552820 | 1.0380680 | -2.3562330 |
| H | 3.6199320 | -0.4545050 | -0.8147850 |
| H | 2.6412040 | -0.7421960 | -2.2542850 |
| C | 4.3517730 | 2.1711990 | -1.4661710 |
| H | 3.5518940 | 3.6707520 | -0.1164230 |
| H | 2.5561700 | 3.3703970 | -1.5405870 |
| H | 4.6989120 | 0.5124400 | -2.8222250 |
| H | 3.2534650 | 1.4578530 | -3.1787530 |
| H | 4.9464110 | 2.8844680 | -2.0515010 |
| H | 5.0248640 | 1.7575960 | -0.6968540 |
| C | 1.1734400 | -0.9417780 | 1.5641810 |
| C | 2.6286740 | -1.4288690 | 1.5711450 |
| C | 0.9427240 | 0.0243700 | 2.7335520 |
| H | 0.5180730 | -1.8187940 | 1.7217430 |
| C | 2.9437860 | -2.1202260 | 2.8959700 |
| H | 3.3029630 | -0.5666450 | 1.4501210 |
| H | 2.8333110 | -2.1074620 | 0.7345710 |
| C | 1.2638270 | -0.6558770 | 4.0608720 |
| H | 1.5896420 | 0.9072600 | 2.6107990 |
| H | -0.0900310 | 0.3994180 | 2.7254010 |
| C | 2.6908930 | -1.1926890 | 4.0788680 |
| H | 3.9848160 | -2.4682260 | 2.8932940 |
| H | 2.3118660 | -3.0187560 | 2.9902640 |
| H | 1.1045430 | 0.0474230 | 4.8882220 |
| H | 0.5592170 | -1.4898080 | 4.2176490 |
| H | 2.8938250 | -1.7123420 | 5.0240840 |
| H | 3.3948730 | -0.3459680 | 4.0280330 |
| C | 0.0928760 | -1.7234760 | -1.1053440 |
| C | -0.2850340 | -1.2565210 | -2.5155570 |
| C | 1.0538530 | -2.9165970 | -1.1345950 |
| H | -0.8329640 | -2.0751310 | -0.6169690 |
| C | -0.8606600 | -2.4086220 | -3.3327680 |


| H | 0.6052070 | -0.8619800 | -3.0317050 |
| :--- | :--- | :--- | :--- |
| H | -1.0073940 | -0.4285020 | -2.4566440 |
| C | 0.4547240 | -4.0503070 | -1.9655230 |
| H | 2.0254830 | -2.6292450 | -1.5640810 |
| H | 1.2480080 | -3.2765870 | -0.1152020 |
| C | 0.1049870 | -3.5870980 | -3.3745550 |
| H | -1.0979500 | -2.0632190 | -4.3471880 |
| H | -1.8113070 | -2.7313180 | -2.8777040 |
| H | 1.1554040 | -4.8947170 | -1.9958190 |
| H | -0.4581310 | -4.4155480 | -1.4671430 |
| H | -0.3236480 | -4.4147790 | -3.9541940 |
| H | 1.0277840 | -3.2822290 | -3.8958400 |

## $\alpha$-CMD-PCy 3

$G_{\text {DFT }}=-2518.845459$
$G_{\text {CORR DFT }}=0.565768$

|  |  |  |  |
| :--- | :--- | :--- | :--- |
| Pd | -0.2704470 | -0.4977870 | 0.6097090 |
| O | 0.0826670 | -2.6371430 | 0.2207860 |
| C | -0.4094040 | -3.4919740 | 0.9999960 |
| P | 1.8462440 | 0.1752540 | -0.2175470 |
| O | -1.3013640 | -3.2282410 | 1.8756070 |
| C | 0.0933700 | -4.9035510 | 0.9343500 |
| H | 0.7775770 | -5.0650140 | 1.7764140 |
| H | -0.7302980 | -5.6143410 | 1.0398340 |
| H | 0.6372920 | -5.0784750 | 0.0028320 |
| H | -1.7480380 | -2.0799270 | 1.6287870 |
| C | -2.3532700 | -0.9430990 | 1.1971320 |
| C | -3.1122620 | -0.1552820 | 2.0529040 |
| S | -3.2465230 | -1.1465730 | -0.3044620 |
| C | -4.3559050 | 0.2789370 | 1.5456300 |
| C | -4.5561270 | -0.1846910 | 0.2662520 |
| H | -5.0731220 | 0.8954590 | 2.0788710 |
| H | -2.7575740 | 0.1108530 | 3.0462680 |
| Br | -6.0793030 | 0.1580770 | -0.8070470 |
| C | -0.6774330 | 1.4275350 | 0.9430670 |
| C | -0.6012250 | 2.1678500 | 2.0955910 |
| S | -1.3143090 | 2.4055440 | -0.3508530 |
| C | -1.0353230 | 3.5206480 | 1.9392900 |
| H | -0.2446130 | 1.7609810 | 3.0399710 |
| C | -1.4488120 | 3.8094230 | 0.6691150 |
| H | -1.0381790 | 4.2490540 | 2.7466450 |
| H | -1.8272590 | 4.7446690 | 0.2729060 |
| C | 2.4929690 | 1.7240420 | 0.6018270 |
| C | 2.8227410 | 1.5171210 | 2.0823260 |


|  |  |  |  |
| :--- | :--- | :--- | :--- |
| C | 3.6310350 | 2.4766350 | -0.0924060 |
| H | 1.6011850 | 2.3723520 | 0.5573460 |
| C | 3.0617240 | 2.8523990 | 2.7796150 |
| H | 3.7426500 | 0.9165840 | 2.1681470 |
| H | 2.0212500 | 0.9542390 | 2.5818210 |
| C | 3.9020460 | 3.8035720 | 0.6186330 |
| H | 4.5485520 | 1.8638320 | -0.0982490 |
| H | 3.3772560 | 2.6914930 | -1.1372960 |
| C | 4.1932490 | 3.6153450 | 2.1015910 |
| H | 3.2880540 | 2.6845370 | 3.8408160 |
| H | 2.136630 | 3.4509380 | 2.7419590 |
| H | 4.7315520 | 4.3242670 | 0.1223380 |
| H | 3.0139480 | 4.4473690 | 0.5050410 |
| H | 4.3509910 | 4.5875340 | 2.5865050 |
| H | 5.1318480 | 3.0489280 | 2.2193600 |
| C | 3.1596720 | -1.1473510 | -0.1007510 |
| C | 3.1972100 | -1.7803220 | 1.2997480 |
| C | 2.9876470 | -2.2660810 | -1.1392420 |
| H | 4.1220390 | -0.6330380 | -0.2854150 |
| C | 4.3276640 | -2.7995130 | 1.4132990 |
| H | 2.2319740 | -2.2812440 | 1.4760830 |
| H | 3.3039250 | -1.0238330 | 2.0832610 |
| C | 4.1209430 | -3.2841910 | -1.0348520 |
| H | 2.0246230 | -2.7645860 | -0.9578070 |
| H | 2.9519210 | -1.8685790 | -2.1580900 |
| C | 4.1980610 | -3.8916450 | 0.3598490 |
| H | 4.3337060 | -3.2322640 | 2.4224400 |
| H | 5.2941830 | -2.2840210 | 1.2874870 |
| H | 3.9815490 | -4.0681630 | -1.7910220 |
| H | 5.0779390 | -2.7889790 | -1.2694930 |
| H | 5.0361360 | -4.5976480 | 0.4288910 |
| H | 3.2799830 | -4.4713520 | 0.5522260 |
| C | 1.6277870 | 0.6901110 | -1.9993370 |
| C | 2.8702220 | 0.7250540 | -2.9017820 |
| C | 0.4978640 | -0.0712830 | -2.7043030 |
| H | 1.2772010 | 1.7326670 | -1.8736840 |
| C | 2.5341710 | 1.4214660 | -4.2187880 |
| H | 3.1956310 | -0.2989210 | -3.1302560 |
| H | 3.7212590 | 1.2133870 | -2.4153700 |
| C | 0.1667550 | 0.5839110 | -4.0425640 |
| H | 0.7998610 | -1.1196540 | -2.8629660 |
| H | -0.3983730 | -0.1016900 | -2.0668850 |
| C | 1.3964710 | 0.7029230 | -4.9365180 |
| H | 3.4266580 | 1.4629810 | -4.8568710 |
| H | 2.2434680 | 2.4653340 | -4.0139840 |
| H | -0.6255880 | 0.0184140 | -4.5499610 |
|  |  |  |  |


| H | -0.2411420 | 1.5900940 | -3.8493230 |
| :--- | :--- | :--- | :--- |
| H | 1.1415520 | 1.2208690 | -5.8702940 |
| H | 1.7361280 | -0.3068310 | -5.2202140 |

## $\beta$-CMD-PCy ${ }_{3}$

| $\mathrm{G}_{\text {DFT }}=-2518.840500$ |  |  |  |
| :---: | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.566210$ |  |  |  |
| Pd | 0.210146000 | -0.679337000 | -0. |
| O | -0.611022000 | -2.714207000 | 0.094844000 |
| C | -0.090485000 | -3.613851000 | -0.610372000 |
| O | 1.021965000 | -3.478793000 | -1.227156000 |
| C | -0.818318000 | -4.917169000 | -0.749574000 |
| H | -1.774888000 | -4.735223000 | -1.253932000 |
| H | -0.237946000 | -5.644766000 | -1.319011000 |
| H | -1.048946000 | -5.313911000 | 0.243917000 |
| H | 1.555236000 | -2.470258000 | -0.804500000 |
| C | 1.073036000 | 1.133113000 | -0.196318000 |
| C | 1.770185000 | 1.811330000 | 0.774327000 |
| S | 1.298816000 | 1.928334000 | -1.733421000 |
| C | 2.473132000 | 2.957640000 | 0.294027000 |
| H | 1.813746000 | 1.487761000 | 1.812471000 |
| C | 2.320961000 | 3.155005000 | -1.049224000 |
| H | 3.070349000 | 3.606878000 | 0.929467000 |
| H | 2.725998000 | 3.944666000 | -1.671651000 |
| C | 4.449469000 | -0.618117000 | 0.083034000 |
| C | 3.390634000 | -0.803901000 | -0.750702000 |
| C | 2.290436000 | -1.481233000 | -0.119310000 |
| C | 2.597514000 | -1.778981000 | 1.192862000 |
| S | 4.173968000 | -1.250021000 | 1.681914000 |
| H | 3.385541000 | -0.452490000 | -1.779622000 |
| H | 1.976474000 | -2.298985000 | 1.918276000 |
| Br | 6.084757000 | 0.258404000 | -0.322741000 |
| P | -1.874372000 | 0.404077000 | 0.102865000 |
| H | -0.719420000 | 0.345782000 | -2.579434000 |
| C | -1.759198000 | 0.676203000 | -2.706899000 |
| H | -1.632733000 | 2.290415000 | -1.307343000 |
| C | -1.888815000 | 1.582778000 | -3.925867000 |
| H | -1.533097000 | 1.056364000 | -4.821207000 |
| H | -1.232425000 | 2.458683000 | -3.793137000 |
| H | -3.260938000 | 3.661714000 | -2.681576000 |
| C | -3.327475000 | 2.050882000 | -4.111770000 |
| H | -3.406164000 | 2.723663000 | -4.975652000 |
| H | -3.965853000 | 1.179294000 | -4.332287000 |
| C | -3.839353000 | 2.739379000 | -2.852681000 |


| H | -4.886726000 | 3.044638000 | -2.976256000 |
| :--- | ---: | ---: | ---: |
| C | -3.709336000 | 1.836633000 | -1.626668000 |
| C | -2.255109000 | 1.386585000 | -1.438764000 |
| H | -4.358626000 | 0.956928000 | -1.761799000 |
| H | -4.082592000 | 2.365677000 | -0.742493000 |
| H | -2.335420000 | 4.181237000 | 2.501086000 |
| H | -3.687128000 | 2.672367000 | 1.105700000 |
| C | -2.884650000 | 3.356927000 | 2.984190000 |
| H | -3.845562000 | 3.772603000 | 3.314820000 |
| H | -2.347537000 | -0.238439000 | -2.876876000 |
| H | -0.086658000 | 0.641142000 | 2.384923000 |
| C | -1.027860000 | 1.104956000 | 2.708217000 |
| H | -1.607635000 | 0.310681000 | 3.201232000 |
| H | -0.134072000 | 2.989229000 | 3.250480000 |
| C | -0.770177000 | 2.218745000 | 3.717327000 |
| H | -0.209403000 | 1.824583000 | 4.575142000 |
| H | -2.673423000 | 2.094166000 | 4.717128000 |
| C | -2.080680000 | 2.849525000 | 4.175093000 |
| H | -1.890663000 | 3.666257000 | 4.883628000 |
| C | -3.128298000 | 2.256151000 | 1.951793000 |
| H | -3.765746000 | 1.475464000 | 2.398409000 |
| H | -3.165861000 | -0.741883000 | 2.570353000 |
| H | -2.317758000 | -2.047770000 | 1.730949000 |
| C | -1.801305000 | 1.641962000 | 1.495564000 |
| H | -1.183210000 | 2.443419000 | 1.050708000 |
| C | -3.241075000 | -1.448253000 | 1.734892000 |
| C | -4.444113000 | -2.359256000 | 1.963111000 |
| C | -4.632469000 | -3.334315000 | 0.809410000 |
| H | -5.504822000 | -3.977400000 | 0.985026000 |
| H | -5.701614000 | -1.967408000 | -0.464792000 |
| C | -4.782094000 | -2.575305000 | -0.501918000 |
| H | -4.900503000 | -3.270073000 | -1.344317000 |
| H | -3.751253000 | -1.112319000 | -1.693980000 |
| H | -2.680861000 | -2.272471000 | -0.900737000 |
| H | -3.754917000 | -3.999202000 | 0.748511000 |
| C | -3.586273000 | -1.663079000 | -0.760057000 |
| C | -3.351437000 | -0.692501000 | 0.405144000 |
| H | -4.218908000 | -0.009431000 | 0.467591000 |
| H | -5.351934000 | -1.741431000 | 2.065427000 |
| H | -4.322914000 | -2.896071000 | 2.913099000 |
|  |  |  |  |

$\gamma$-CMD-PCy 3
$G_{\text {DFT }}=-2518.844030$
$G_{\text {CORR DFT }}=0.567240$
$\qquad$

|  |  |  |  |
| :--- | ---: | ---: | ---: |
| Pd | 0.591981000 | -0.187861000 | -0.566688000 |
| O | 0.280779000 | -2.332758000 | -0.893643000 |
| C | 1.049518000 | -3.000393000 | -1.631139000 |
| O | 2.109841000 | -2.536680000 | -2.163098000 |
| C | 0.698953000 | -4.437950000 | -1.886793000 |
| H | 1.320361000 | -4.868770000 | -2.673782000 |
| H | 0.845021000 | -5.006329000 | -0.961505000 |
| H | -0.360319000 | -4.516490000 | -2.153157000 |
| H | 2.313634000 | -1.374992000 | -1.696546000 |
| C | 0.917648000 | 1.773345000 | -0.248555000 |
| C | 1.643421000 | 2.367588000 | 0.755454000 |
| S | 0.458147000 | 2.982262000 | -1.421328000 |
| C | 1.820008000 | 3.775341000 | 0.594323000 |
| H | 2.067189000 | 1.814962000 | 1.592081000 |
| C | 1.236856000 | 4.261602000 | -0.541596000 |
| H | 2.363613000 | 4.397964000 | 1.300700000 |
| H | 1.207333000 | 5.280808000 | -0.909601000 |
| C | 4.431826000 | 1.392830000 | -1.632639000 |
| C | 3.286907000 | 0.793173000 | -2.062064000 |
| C | 2.758148000 | -0.215237000 | -1.178919000 |
| C | 3.593216000 | -0.319888000 | -0.089638000 |
| S | 4.948605000 | 0.756806000 | -0.099367000 |
| H | 2.804614000 | 1.062141000 | -2.999283000 |
| H | 5.014301000 | 2.172689000 | -2.110584000 |
| Br | 3.374328000 | -1.505318000 | 1.382125000 |
| P | -1.604122000 | 0.128596000 | 0.229987000 |
| C | -2.578944000 | 1.222621000 | -0.928489000 |
| H | -2.226196000 | 2.234723000 | -0.660387000 |
| H | -1.095522000 | 1.002299000 | -2.505479000 |
| H | -4.431270000 | 3.242575000 | -1.396616000 |
| C | -2.188629000 | 0.979562000 | -2.394020000 |
| C | -4.750626000 | 2.233377000 | -1.703482000 |
| H | -2.501678000 | -0.030662000 | -2.700527000 |
| H | -4.752336000 | 1.026415000 | -3.487436000 |
| C | -4.357171000 | 2.001347000 | -3.156937000 |
| H | -4.814262000 | 2.760935000 | -3.804405000 |
| H | -2.557180000 | 1.806919000 | -4.354744000 |
| C | -2.841126000 | 2.006149000 | -3.313135000 |
| H | -2.451473000 | 3.007596000 | -3.065994000 |
| C | -4.105895000 | 1.202895000 | -0.777657000 |
| H | -1.942560000 | -2.428429000 | -1.292282000 |
| H | -2.627730000 | -1.408947000 | 0.480773000 |
| H | -3.408515000 | 1.400692000 | 0.256858000 |
| H | -4.497390000 | -1.492175000 | -1.548629000 |
|  | -2.902642000 | 0.205470000 | -1.031037000 |
| H |  |  |  |


| H | -3.593443000 | -1.047012000 | 0.880924000 |
| :--- | ---: | ---: | ---: |
| C | -3.746347000 | -3.398422000 | -0.607261000 |
| H | -3.909063000 | -3.910871000 | -1.564863000 |
| H | -4.742374000 | -3.104194000 | -0.235422000 |
| C | -3.092330000 | -4.332382000 | 0.402101000 |
| H | -3.712214000 | -5.224396000 | 0.562018000 |
| H | -3.825831000 | -3.315867000 | 2.151214000 |
| C | -2.853635000 | -3.603469000 | 1.716920000 |
| H | -2.368325000 | -4.263617000 | 2.447708000 |
| H | -2.127072000 | -4.684090000 | 0.001460000 |
| C | -2.004986000 | -2.350396000 | 1.518882000 |
| H | -3.668865000 | 1.522109000 | 2.019407000 |
| H | -5.841874000 | 2.200882000 | -1.587080000 |
| H | -0.670472000 | -0.478255000 | 3.148290000 |
| H | 0.510524000 | 0.422699000 | 2.209240000 |
| H | -0.993454000 | -2.631803000 | 1.186440000 |
| H | -1.898396000 | -1.839023000 | 2.482703000 |
| H | -1.258300000 | 2.052610000 | 1.535297000 |
| C | -1.545920000 | 1.034815000 | 1.858440000 |
| C | -0.424144000 | 0.526095000 | 2.773695000 |
| C | -0.243145000 | 1.458044000 | 3.966885000 |
| H | 0.569137000 | 1.091321000 | 4.608316000 |
| H | 0.064486000 | 2.453222000 | 3.604422000 |
| C | -1.540373000 | 1.581315000 | 4.758699000 |
| H | -1.415326000 | 2.271863000 | 5.602955000 |
| H | -1.792582000 | 0.598763000 | 5.190697000 |
| H | -2.478245000 | 3.067349000 | 3.512759000 |
| C | -2.683264000 | 2.042505000 | 3.862371000 |
| H | -3.624008000 | 2.086880000 | 4.426759000 |
| C | -2.856505000 | 1.134073000 | 2.644712000 |
| H | -3.165764000 | 0.130546000 | 2.980723000 |

## Annex 3.3 C-H activation of 2-bromothiophene with pivalate

## Int-4-Piv

$\begin{array}{llll} & \mathrm{G}_{\text {DFT }}=-1368.207765 \\ \mathrm{G}_{\text {CORR DFT }}=0.171137 \\ \mathrm{E}_{\text {CCSD }}=-6178.133051 \\ \mathrm{G}=-6177.961914 \\ ----\cdots--------------- & & \\ \\ \mathrm{Pd} & 0.266862000 & 0.608199000 & -0.001474000 \\ \mathrm{C} & 2.006853000 & -0.326403000 & 0.215980000\end{array}$

| C | 2.870268000 | -0.392229000 | 1.280561000 |
| :--- | :---: | :---: | :---: |
| S | 2.527550000 | -1.373194000 | -1.072720000 |
| C | 3.937556000 | -1.319650000 | 1.074946000 |
| H | 2.743930000 | 0.189813000 | 2.190399000 |
| C | 3.890630000 | -1.925404000 | -0.148488000 |
| H | 4.707334000 | -1.525919000 | 1.813323000 |
| H | 4.564058000 | -2.667472000 | -0.561862000 |
| O | -1.240313000 | -0.980753000 | 0.108496000 |
| O | -1.886499000 | 1.103323000 | -0.167644000 |
| C | -2.174661000 | -0.126653000 | -0.025478000 |
| C | -3.627219000 | -0.564752000 | 0.053810000 |
| P | 1.653158000 | 2.372247000 | -0.187793000 |
| H | 2.435183000 | 2.675363000 | 0.939667000 |
| H | 2.636634000 | 2.294731000 | -1.187787000 |
| H | 1.059335000 | 3.617288000 | -0.468184000 |
| C | -4.492366000 | 0.299336000 | -0.861138000 |
| H | -4.195366000 | 0.189190000 | -1.911748000 |
| H | -5.541793000 | -0.009832000 | -0.771787000 |
| H | -4.420232000 | 1.359203000 | -0.596220000 |
| C | -3.771172000 | -2.036731000 | -0.321525000 |
| H | -3.181627000 | -2.679414000 | 0.340548000 |
| H | -4.825302000 | -2.332435000 | -0.242250000 |
| H | -3.443208000 | -2.220457000 | -1.352104000 |
| C | -4.058517000 | -0.360894000 | 1.513499000 |
| H | -3.970866000 | 0.691672000 | 1.809077000 |
| H | -5.106758000 | -0.664505000 | 1.632097000 |
| H | -3.448869000 | -0.967267000 | 2.195257000 |

## $\alpha$-CMD-Piv

$\mathrm{G}_{\mathrm{DFT}}=-1933.516182$
$\mathrm{G}_{\mathrm{CORR} \text { DFT }}=0.212221$
$\mathrm{E}_{\text {CCSD }}=-9302.194419$
$\mathrm{G}=-9301.982198$

| Pd | 0.826832000 | 1.037776000 | -0.046401000 |
| :--- | :---: | :---: | :---: |
| O | 2.774486000 | 0.094168000 | -0.376794000 |
| C | 3.076310000 | -1.008536000 | 0.148435000 |
| P | 1.599571000 | 3.098535000 | -0.764949000 |
| O | 2.265714000 | -1.714696000 | 0.833827000 |
| H | 1.098693000 | -1.214021000 | 0.785195000 |
| C | -0.162062000 | -0.785683000 | 0.657980000 |
| C | -1.012140000 | -0.676863000 | 1.756103000 |
| S | -1.047805000 | -1.547784000 | -0.654974000 |


| C | -2.318760000 | -1.169682000 | 1.568035000 |
| :--- | :---: | :---: | :---: |
| C | -2.475726000 | -1.669618000 | 0.295013000 |
| H | -3.108949000 | -1.164610000 | 2.312257000 |
| H | -0.679596000 | -0.228564000 | 2.689961000 |
| Br | -4.071242000 | -2.402723000 | -0.409375000 |
| H | 1.606429000 | 4.123912000 | 0.199165000 |
| H | 2.906758000 | 3.208411000 | -1.281963000 |
| H | 0.855323000 | 3.725152000 | -1.781475000 |
| C | -0.889173000 | 2.028655000 | 0.248789000 |
| C | -1.232716000 | 2.869568000 | 1.278368000 |
| S | -2.208046000 | 1.877612000 | -0.875838000 |
| C | -2.565008000 | 3.376918000 | 1.175789000 |
| H | -0.559536000 | 3.108023000 | 2.099399000 |
| C | -3.220723000 | 2.933946000 | 0.061983000 |
| H | -3.013558000 | 4.046095000 | 1.905284000 |
| H | -4.227509000 | 3.162608000 | -0.268286000 |
| C | 4.497626000 | -1.548473000 | -0.004799000 |
| C | 5.314456000 | -0.688798000 | -0.962234000 |
| H | 5.391844000 | 0.345668000 | -0.609079000 |
| H | 6.328516000 | -1.100339000 | -1.045347000 |
| H | 4.870046000 | -0.670880000 | -1.964332000 |
| C | 5.145145000 | -1.531060000 | 1.385131000 |
| H | 4.591847000 | -2.161462000 | 2.089880000 |
| H | 6.172496000 | -1.910899000 | 1.314265000 |
| H | 5.189748000 | -0.511847000 | 1.790688000 |
| C | 4.432421000 | -2.986853000 | -0.523506000 |
| H | 3.952069000 | -3.033831000 | -1.509301000 |
| H | 5.450150000 | -3.384891000 | -0.625552000 |
| H | 3.874973000 | -3.633092000 | 0.162290000 |

## $\beta$-CMD-Piv

$G_{\text {DFT }}=-1933.509422$
$\mathrm{G}_{\text {CORR DFT }}=0.212466$
$\mathrm{E}_{\text {CCSD }}=-9302.190096$
$G=-9301.977630$

| ------------------- |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| Pd | -0.86742600 | 1.08157300 | 0.03400500 |
| S | -2.84660000 | 0.19311800 | 0.29189900 |
| C | -3.10318700 | -0.86682400 | -0.33762100 |
| P | -1.58517700 | 3.26992100 | 0.17608300 |
| S | -2.24123600 | -1.49596500 | -1.03775100 |
| C | -4.48635000 | -1.49390900 | -0.19729000 |
| H | -1.09295400 | -1.10006300 | -0.70123800 |


| H | -1.36375800 | 4.06406500 | -0.96428700 |
| :--- | ---: | ---: | ---: |
| H | -2.94450000 | 3.54175200 | 0.43143400 |
| H | -0.96559900 | 4.06848500 | 1.15483900 |
| C | 0.93248400 | 1.91677100 | -0.20193700 |
| C | 1.50632100 | 2.44774800 | -1.32972900 |
| S | 2.06477200 | 1.91550000 | 1.11732700 |
| C | 2.87088500 | 2.83089500 | -1.14088400 |
| H | 0.97901900 | 2.54370300 | -2.27654600 |
| C | 3.31812500 | 2.60620900 | 0.13034200 |
| H | 3.49080900 | 3.25991500 | -1.92359300 |
| H | 4.29591300 | 2.81197200 | 0.55055100 |
| C | 2.31585300 | -1.65552100 | -0.02303200 |
| C | 1.37118700 | -1.05132400 | -0.79243000 |
| C | 0.11752900 | -0.88685500 | -0.10702800 |
| C | 0.19478300 | -1.39157800 | 1.17803500 |
| S | 1.73907200 | -2.05864900 | 1.57125500 |
| H | 1.56390800 | -0.71311600 | -1.80700600 |
| H | -0.59944100 | -1.43177400 | 1.91989600 |
| Br | 4.11498800 | -2.02358600 | -0.49945900 |
| C | -5.52750700 | -0.44540500 | 0.18043100 |
| H | -6.50695700 | -0.92767600 | 0.29129000 |
| H | -5.27713900 | 0.04878000 | 1.12473400 |
| H | -5.61586600 | 0.32638000 | -0.59431600 |
| C | -4.89511300 | -2.19664400 | -1.49012300 |
| H | -4.18254600 | -2.98095900 | -1.76426900 |
| H | -5.88270800 | -2.65651900 | -1.35764300 |
| H | -4.96201400 | -1.48815800 | -2.32532500 |
| C | -4.35558400 | -2.52526400 | 0.93352800 |
| H | -4.05996100 | -2.04511200 | 1.87532900 |
| H | -5.32266800 | -3.01935800 | 1.09229600 |
| H | -3.61425000 | -3.29462000 | 0.68540900 |

## $\gamma$-CMD-Piv

$G_{D F T}=-1933.513414$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.212242$
$\mathrm{E}_{\text {CCSD }}=-9302.193313$
$\mathrm{G}=-9301.981071$

| Pd | 0.218662000 | -1.015414000 | -0.042683000 |
| :--- | :--- | :---: | :---: |
| O | -1.956087000 | -1.207111000 | -0.065558000 |
| C | -2.670910000 | -0.440327000 | 0.633784000 |
| P | 0.474709000 | -2.987700000 | -1.207983000 |
| O | -2.201919000 | 0.444333000 | 1.418514000 |


| C | -4.188218000 | -0.512067000 | 0.475922000 |
| :---: | :---: | :---: | :---: |
| H | -0.932378000 | 0.580817000 | 1.214773000 |
| H | 1.112481000 | -2.884826000 | -2.457321000 |
| H | 1.261630000 | -3.989481000 | -0.610254000 |
| H | -0.680859000 | -3.717400000 | -1.550752000 |
| C | 2.213657000 | -0.907787000 | -0.134307000 |
| C | 2.993843000 | -0.190255000 | -1.004049000 |
| S | 3.204578000 | -1.726010000 | 1.040390000 |
| C | 4.391331000 | -0.281397000 | -0.716443000 |
| H | 2.582621000 | 0.406068000 | -1.816294000 |
| C | 4.666643000 | -1.074318000 | 0.361368000 |
| H | 5.159813000 | 0.225755000 | -1.293896000 |
| H | 5.629426000 | -1.321094000 | 0.793921000 |
| C | 2.030924000 | 2.277852000 | 1.912541000 |
| C | 1.258393000 | 1.164038000 | 2.039144000 |
| C | 0.314756000 | 0.957983000 | 0.970219000 |
| C | 0.439060000 | 1.993290000 | 0.066868000 |
| S | 1.646025000 | 3.162506000 | 0.465579000 |
| H | 1.354431000 | 0.478861000 | 2.877957000 |
| H | 2.808024000 | 2.647387000 | 2.572182000 |
| Br | -0.595386000 | 2.229532000 | -1.508017000 |
| C | -4.535276000 | 0.513736000 | -0.613424000 |
| H | -5.620140000 | 0.517575000 | -0.780757000 |
| H | -4.229906000 | 1.525107000 | -0.317370000 |
| H | -4.043562000 | 0.265236000 | -1.562711000 |
| C | -4.889848000 | -0.135035000 | 1.778216000 |
| H | -5.976799000 | -0.178198000 | 1.632211000 |
| H | -4.629655000 | -0.829272000 | 2.587146000 |
| H | -4.624336000 | 0.877149000 | 2.099376000 |
| C | -4.626724000 | -1.903434000 | 0.029950000 |
| H | -4.165423000 | -2.184895000 | -0.922185000 |
| H | -4.360382000 | -2.663557000 | 0.775113000 |
| H | -5.716933000 | -1.919709000 | -0.095259000 |
|  |  |  |  |

## Annex 3.4 C-H activation of model thiophenes with electronic substituents

## Int-11

$G_{\text {DFT }}=-1342.632969$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.087403$
$\mathrm{E}_{\text {CCSD }}=-6152.537218$
$\mathrm{G}=-6152.449815$

| Pd | -1.055828000 | 0.350673000 | 0.010526000 |
| :--- | :---: | :---: | :---: |
| C | 0.895100000 | 0.206597000 | 0.344146000 |
| C | 1.638837000 | 0.560126000 | 1.448812000 |
| S | 1.861494000 | -0.586207000 | -0.849724000 |
| C | 2.994568000 | 0.163864000 | 1.355068000 |
| H | 1.223135000 | 1.078979000 | 2.308103000 |
| C | 3.284530000 | -0.470178000 | 0.166515000 |
| H | 3.738808000 | 0.333974000 | 2.127194000 |
| O | -1.833496000 | -1.662568000 | 0.335234000 |
| O | -3.210182000 | -0.039169000 | -0.221484000 |
| C | -3.011855000 | -1.261735000 | 0.066112000 |
| C | -4.147216000 | -2.232061000 | 0.058124000 |
| H | -4.258165000 | -2.635224000 | -0.954860000 |
| H | -3.948639000 | -3.065886000 | 0.735489000 |
| H | -5.081413000 | -1.733039000 | 0.326953000 |
| P | -0.502518000 | 2.504021000 | -0.389757000 |
| H | 0.028909000 | 3.213271000 | 0.700305000 |
| H | 0.476805000 | 2.727407000 | -1.371454000 |
| H | -1.543891000 | 3.348570000 | -0.813007000 |
| C | 4.531550000 | -0.983970000 | -0.244796000 |
| N | 5.560392000 | -1.408850000 | -0.596407000 |

## Int-16

$$
\mathrm{G}_{\mathrm{DFT}}=-1364.868926
$$

$\mathrm{G}_{\text {CORR DFT }}=0.119976$
$\mathrm{E}_{\text {CCSD }}=-6174.777189$
$\mathrm{G}=-6174.657213$

| Pd | -1.194720000 | 0.369075000 | 0.032305000 |
| :--- | :---: | :---: | :---: |
| C | 0.774627000 | 0.221670000 | 0.269424000 |
| C | 1.598014000 | 0.574641000 | 1.301065000 |
| S | 1.670189000 | -0.595257000 | -0.996619000 |
| C | 2.960025000 | 0.158800000 | 1.128230000 |


| H | 1.251826000 | 1.110996000 | 2.181825000 |
| :--- | :---: | :---: | :---: |
| C | 3.149614000 | -0.478834000 | -0.066431000 |
| H | 3.741075000 | 0.329439000 | 1.862208000 |
| O | -1.974057000 | -1.674143000 | 0.300127000 |
| O | -3.375482000 | -0.024919000 | -0.110527000 |
| C | -3.160747000 | -1.257756000 | 0.109192000 |
| C | -4.297557000 | -2.230301000 | 0.112592000 |
| H | -4.404183000 | -2.650657000 | -0.893911000 |
| H | -4.097468000 | -3.055329000 | 0.800749000 |
| H | -5.233742000 | -1.731612000 | 0.374523000 |
| P | -0.588642000 | 2.506126000 | -0.308783000 |
| H | -0.008570000 | 3.172012000 | 0.784087000 |
| H | 0.365916000 | 2.741535000 | -1.312019000 |
| H | -1.613736000 | 3.398808000 | -0.676409000 |
| O | 4.249617000 | -1.022944000 | -0.613444000 |
| C | 5.422429000 | -0.949949000 | 0.184289000 |
| H | 6.215599000 | -1.435200000 | -0.385454000 |
| H | 5.693144000 | 0.095840000 | 0.379567000 |
| H | 5.274785000 | -1.474676000 | 1.137028000 |

## CNTh (thiophene-2-carbonitrile)

$G_{\text {DFT }}=-645.019055$
$\mathrm{G}_{\text {CORR DFT }}=0.035152$
$\mathrm{E}_{\text {CCSD }}=-644.1869739$
$G=-644.1518219$


| C | 1.919474000 | -0.227015000 | 0.000000000 |
| :--- | :---: | :---: | :---: |
| C | 1.635702000 | 1.113245000 | 0.000000000 |
| S | 0.506609000 | -1.205164000 | 0.000000000 |
| C | 0.245834000 | 1.372570000 | 0.000000000 |
| C | -0.502462000 | 0.215876000 | 0.000000000 |
| H | -0.199790000 | 2.361591000 | 0.000000000 |
| H | 2.397372000 | 1.885059000 | 0.000000000 |
| C | -1.911675000 | 0.116004000 | 0.000000000 |
| N | -3.073920000 | 0.027844000 | 0.000000000 |
| H | 2.892868000 | -0.703018000 | 0.000000000 |

## Th (thiophene)

$G_{\text {DFT }}=-552.82203$
$\mathrm{G}_{\text {CORR DFT }}=0.038986$
$\mathrm{E}_{\text {CCSD }}=-552.1313618$

```
G=-552.0923758
```

| C | 0.009921000 | -1.238234000 | 0.000000000 |
| :--- | :---: | :---: | :---: |
| C | 1.271599000 | -0.712452000 | -0.000001000 |
| S | -1.196758000 | 0.000000000 | 0.000001000 |
| C | 1.271599000 | 0.712452000 | -0.000001000 |
| C | 0.009921000 | 1.238234000 | 0.000000000 |
| H | 2.170569000 | 1.320924000 | -0.000002000 |
| H | 2.170569000 | -1.320924000 | -0.000002000 |
| H | -0.285623000 | -2.280510000 | 0.000001000 |
| H | -0.285623000 | 2.280510000 | 0.000000000 |

## MeOTh (2-methoxythiophene)

$\mathrm{G}_{\mathrm{DFT}}=-667.25663$
$\mathrm{G}_{\text {CORR DFT }}=0.067734$
$\mathrm{E}_{\text {CCSD }}=-666.4287049$
$\mathrm{G}=-666.3609709$

| C | 2.066419000 | 0.197947000 | -0.000002000 |
| :--- | :---: | :---: | :---: |
| C | 1.395869000 | 1.383219000 | 0.000002000 |
| S | 0.973879000 | -1.158171000 | -0.000004000 |
| C | -0.025845000 | 1.238947000 | 0.000003000 |
| C | -0.396655000 | -0.078836000 | 0.000000000 |
| H | -0.723092000 | 2.069740000 | 0.000007000 |
| H | 1.897210000 | 2.346349000 | 0.000004000 |
| O | -1.610340000 | -0.653579000 | 0.000000000 |
| C | -2.709154000 | 0.247008000 | 0.000004000 |
| H | -2.690467000 | 0.879393000 | -0.896564000 |
| H | -3.610858000 | -0.365657000 | 0.000003000 |
| H | -2.690465000 | 0.879389000 | 0.896575000 |
| H | 3.134521000 | 0.020453000 | -0.000003000 |

## BrCNTh (5-bromothiophene-2-carbonitrile)

$G_{D F T}=-657.526527$
$\mathrm{G}_{\mathrm{CORR} \text { DFT }}=0.021815$
$\mathrm{E}_{\mathrm{CCSD}}=-3216.13996$
$\mathrm{G}=-3216.118145$
$\begin{array}{llll}\text { C } & 0.000000000 & 0.562235000 & 0.000000000\end{array}$

| C | 1.363542000 | 0.701942000 | 0.000000000 |
| :--- | ---: | ---: | :---: |
| S | -0.527676000 | -1.081290000 | 0.000000000 |
| C | 2.014872000 | -0.551920000 | 0.000000000 |
| C | 1.135103000 | -1.611927000 | 0.000000000 |
| H | 3.091980000 | -0.682080000 | 0.000000000 |
| H | 1.868435000 | 1.661614000 | 0.000000000 |
| C | 1.460130000 | -2.986667000 | 0.000000000 |
| N | 1.722549000 | -4.122664000 | 0.000000000 |
| Br | -1.269067000 | 1.957079000 | 0.000000000 |

## BrTh (2-bromothiophene)

$\mathrm{G}_{\mathrm{DFT}}=-565.334766$
$\mathrm{G}_{\mathrm{CORR} \text { DFT }}=0.025628$
$\mathrm{E}_{\text {CCSD }}=-3124.086145$
$G=-3124.060517$
$\qquad$

| C | -0.150351000 | 0.200219000 | 0.000000000 |
| :--- | :---: | :---: | :---: |
| C | -0.859243000 | 1.368423000 | 0.000000000 |
| C | -2.262689000 | 1.126603000 | 0.000000000 |
| C | -2.577608000 | -0.203436000 | 0.000000000 |
| S | -1.166033000 | -1.204416000 | 0.0000000000 |
| H | -0.397193000 | 2.350284000 | 0.000000000 |
| H | -3.008787000 | 1.914982000 | 0.000000000 |
| H | -3.558478000 | -0.663959000 | 0.000000000 |
| Br | 1.734866000 | 0.020528000 | 0.000000000 |

## BrMeOTh (2-bromo-5-methoxythiophene)

| $\mathrm{G}_{\text {DFT }}=-679.76759$ |  |  |  |
| :---: | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.054468$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-3238.383605$ |  |  |  |
| $\mathrm{G}=-3238.329137$ |  |  |  |
| C | 0.621158000 | 0.240655000 | 0.000002000 |
| C | -0.052255000 | 1.423052000 | 0.000009000 |
| S | -0.439303000 | -1.145388000 | -0.000007000 |
| C | -1.470231000 | 1.246757000 | 0.000006000 |
| C | -1.822989000 | -0.076184000 | -0.000002000 |
| H | -2.178664000 | 2.068093000 | 0.000010000 |
| H | 0.440272000 | 2.390380000 | 0.000015000 |
| Br | 2.498130000 | -0.009859000 | 0.000002000 |


| O | -3.023585000 | -0.668289000 | -0.000007000 |
| :--- | :--- | :--- | :--- |
| C | -4.140027000 | 0.213507000 | -0.000003000 |
| H | -4.131695000 | 0.844762000 | -0.897309000 |
| H | -5.029163000 | -0.417115000 | -0.000008000 |
| H | -4.131697000 | 0.844751000 | 0.897311000 |

## $\alpha-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{CNTh})$

$\mathrm{G}_{\mathrm{DFT}}=-1987.614156$
$\mathrm{G}_{\text {CORR DFT }}=0.13783$
$\mathrm{E}_{\text {CCSD }}=-6796.70029$
$G=-6796.56246$
$\qquad$

| Pd | -1.126933000 | -0.720707000 | -0.036380000 |
| :--- | :---: | :---: | :---: |
| O | -3.232244000 | -0.378773000 | -0.435055000 |
| C | -3.834017000 | 0.616420000 | 0.056158000 |
| P | -1.335128000 | -2.946993000 | -0.608337000 |
| O | -3.268024000 | 1.532293000 | 0.731833000 |
| C | -5.312104000 | 0.745505000 | -0.168528000 |
| H | -5.819502000 | 0.851527000 | 0.795135000 |
| H | -5.509949000 | 1.658344000 | -0.739493000 |
| H | -5.707349000 | -0.117694000 | -0.706282000 |
| H | -1.974645000 | 1.379992000 | 0.684740000 |
| C | -0.667625000 | 1.363673000 | 0.567242000 |
| C | 0.174894000 | 1.548878000 | 1.660156000 |
| S | -0.045540000 | 2.249903000 | -0.797439000 |
| C | 1.292069000 | 2.364652000 | 1.414213000 |
| C | 1.312261000 | 2.826494000 | 0.108988000 |
| H | 2.054808000 | 2.619002000 | 2.143297000 |
| H | -0.023487000 | 1.087402000 | 2.624196000 |
| H | -1.093406000 | -3.868166000 | 0.426153000 |
| H | -2.583849000 | -3.378051000 | -1.093184000 |
| H | -0.458567000 | -3.427859000 | -1.596562000 |
| C | 0.782066000 | -1.189915000 | 0.324559000 |
| C | 1.323651000 | -1.807704000 | 1.431915000 |
| S | 2.002184000 | -0.791978000 | -0.832158000 |
| C | 2.730628000 | -1.943249000 | 1.367697000 |
| H | 0.727155000 | -2.140805000 | 2.277378000 |
| C | 3.262717000 | -1.442242000 | 0.198786000 |
| H | 3.341332000 | -2.391785000 | 2.145710000 |
| C | 4.617609000 | -1.434321000 | -0.188827000 |
| N | 5.737640000 | -1.425292000 | -0.518802000 |
| C | 2.289148000 | 3.672142000 | -0.467629000 |
| N | 3.088267000 | 4.369372000 | -0.951425000 |

## $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{CNTh})$

| $\mathrm{G}_{\text {DFT }}=-1987.609022$ |  |  |  |
| :--- | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.137684$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-6796.69632$ |  |  |  |
| $\mathrm{G}=-6796.558636$ |  |  |  |
| --------------- |  |  |  |
|  |  |  |  |
| Pd | 1.173034000 | -0.678400000 | 0.150587000 |
| O | 3.317318000 | -0.402061000 | -0.009907000 |
| C | 3.764387000 | 0.532042000 | -0.730118000 |
| P | 1.425037000 | -2.925649000 | 0.634712000 |
| O | 3.034739000 | 1.419393000 | -1.279702000 |
| C | 5.242708000 | 0.624711000 | -0.962022000 |
| H | 5.769611000 | -0.204080000 | -0.486904000 |
| H | 5.442024000 | 0.626976000 | -2.038021000 |
| H | 5.611167000 | 1.575509000 | -0.564052000 |
| H | 1.855001000 | 1.343848000 | -0.810935000 |
| H | 0.781890000 | -3.837047000 | -0.221790000 |
| H | 2.734521000 | -3.440681000 | 0.663072000 |
| H | 0.928142000 | -3.349777000 | 1.879787000 |
| C | -0.786517000 | -1.001613000 | 0.349043000 |
| C | -1.584072000 | -0.786854000 | 1.451684000 |
| S | -1.719109000 | -1.534007000 | -1.006399000 |
| C | -2.957516000 | -1.027608000 | 1.207431000 |
| H | -1.196269000 | -0.445820000 | 2.407932000 |
| C | -3.207564000 | -1.440105000 | -0.083555000 |
| H | -3.743773000 | -0.906053000 | 1.946735000 |
| C | -1.355682000 | 2.646269000 | -0.166713000 |
| C | -0.529263000 | 1.812903000 | -0.878635000 |
| C | 0.666271000 | 1.452980000 | -0.182274000 |
| C | 0.688012000 | 2.059843000 | 1.063259000 |
| S | -0.687210000 | 3.028231000 | 1.405240000 |
| H | -0.782155000 | 1.465029000 | -1.876808000 |
| H | 1.473670000 | 1.994216000 | 1.811526000 |
| C | -4.452872000 | -1.779419000 | -0.649308000 |
| N | -5.478589000 | -2.065933000 | -1.128053000 |
| C | -2.606025000 | 3.163972000 | -0.576730000 |
| N | -3.637912000 | 3.591657000 | -0.911256000 |
|  |  |  |  |

## $\alpha-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{Th})$

$G_{\text {DFT }}=-1895.422815$
$\mathrm{G}_{\text {CORR DFT }}=0.141421$
$\mathrm{E}_{\text {CCSD }}=-6704.64335$
$G=-6704.501929$

| Pd | 0.776050000 | -0.653073000 | 0.115849000 |
| :--- | :---: | :---: | :---: |
| O | 2.916503000 | -1.013654000 | -0.047984000 |
| C | 3.694557000 | -0.169667000 | -0.568283000 |
| P | 0.434874000 | -2.895638000 | 0.656655000 |
| O | 3.335969000 | 0.982480000 | -0.973437000 |
| C | 5.143240000 | -0.526322000 | -0.731350000 |
| H | 5.410254000 | -0.475422000 | -1.791713000 |
| H | 5.760445000 | 0.210235000 | -0.207637000 |
| H | 5.349469000 | -1.526181000 | -0.346082000 |
| H | 2.112659000 | 1.192468000 | -0.665989000 |
| C | 0.873317000 | 1.482456000 | -0.273844000 |
| C | -0.016264000 | 2.053286000 | -1.183221000 |
| S | 0.800676000 | 2.413282000 | 1.214787000 |
| C | -0.718613000 | 3.179483000 | -0.708226000 |
| C | -0.374957000 | 3.491824000 | 0.588543000 |
| H | -1.438421000 | 3.747604000 | -1.289622000 |
| H | -0.145947000 | 1.649146000 | -2.185214000 |
| H | -0.451065000 | -3.629326000 | -0.154597000 |
| H | 1.550339000 | -3.755050000 | 0.684004000 |
| H | -0.129354000 | -3.147979000 | 1.920977000 |
| C | -1.196243000 | -0.418356000 | 0.315442000 |
| C | -1.910840000 | 0.011928000 | 1.413098000 |
| S | -2.248155000 | -0.764714000 | -1.013745000 |
| C | -3.306551000 | 0.078956000 | 1.189033000 |
| H | -1.442284000 | 0.285865000 | 2.354345000 |
| C | -3.664974000 | -0.309781000 | -0.084003000 |
| H | -4.032835000 | 0.398621000 | 1.930728000 |
| H | -0.748500000 | 4.314344000 | 1.189296000 |
| C | -4.962395000 | -0.368176000 | -0.628668000 |
| N | -6.033996000 | -0.421411000 | -1.090543000 |

## $\boldsymbol{\beta}-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{Th})$

$\mathrm{G}_{\mathrm{DFT}}=-1895.415862$
$\mathrm{G}_{\text {CORR DFT }}=0.140465$
$\mathrm{E}_{\text {CCSD }}=-6704.638419$
$\mathrm{G}=-6704.497954$
-----------------------

Pd $-0.878504000 \quad-0.662967000 \quad 0.140815000$

| O | -3.036581000 | -0.893360000 | -0.002486000 |
| :---: | :---: | :---: | :---: |
| C | -3.735213000 | 0.010941000 | -0.534865000 |
| P | -0.648026000 | -2.945408000 | 0.548304000 |
| O | -3.272393000 | 1.126737000 | -0.935070000 |
| C | -5.207399000 | -0.219225000 | -0.710475000 |
| H | -5.487854000 | -1.229361000 | -0.407978000 |
| H | -5.758944000 | 0.511556000 | -0.110186000 |
| H | -5.481757000 | -0.050537000 | -1.756176000 |
| H | -2.048746000 | 1.237524000 | -0.567764000 |
| H | -0.051992000 | -3.302457000 | 1.771902000 |
| H | -1.809193000 | -3.742027000 | 0.570896000 |
| H | 0.162983000 | -3.676977000 | -0.339787000 |
| C | 1.106434000 | -0.540967000 | 0.331507000 |
| C | 1.846766000 | -0.190162000 | 1.440103000 |
| S | 2.132684000 | -0.881126000 | -1.019039000 |
| C | 3.242790000 | -0.180256000 | 1.208336000 |
| H | 1.396089000 | 0.071311000 | 2.393593000 |
| C | 3.575210000 | -0.531639000 | -0.082594000 |
| H | 3.987792000 | 0.074506000 | 1.956604000 |
| C | 0.110785000 | 3.208738000 | 1.268055000 |
| C | -0.802524000 | 2.199568000 | 1.206582000 |
| C | -0.841034000 | 1.517644000 | -0.063199000 |
| C | 0.081106000 | 2.078334000 | -0.929206000 |
| S | 0.964774000 | 3.377971000 | -0.235085000 |
| H | -1.451679000 | 1.940655000 | 2.040497000 |
| H | 0.295674000 | 1.783098000 | -1.951699000 |
| H | 0.334253000 | 3.877465000 | 2.091557000 |
| C | 4.864828000 | -0.628043000 | -0.640028000 |
| N | 5.929559000 | -0.711895000 | -1.113193000 |

## $\alpha-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{MeOTh})$

```
G
```

$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.170042$
$\mathrm{E}_{\text {CCSD }}=-6818.944307$
$G=-6818.774265$

| ---------------------- |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| Pd | -1.121014000 | -0.764852000 | -0.146247000 |
| O | -3.287982000 | -0.535784000 | 0.005981000 |
| C | -3.828846000 | 0.459325000 | 0.553107000 |
| P | -1.395435000 | -2.992895000 | -0.841696000 |
| O | -3.189897000 | 1.460992000 | 1.018197000 |
| C | -5.323641000 | 0.498400000 | 0.678003000 |
| H | -5.708784000 | 1.370823000 | 0.140596000 |


| H | -5.776172000 | -0.410878000 | 00 |
| :---: | :---: | :---: | :---: |
| H | -5.598021000 | 0.620962000 | 1.730398000 |
| H | -1.970319000 | 1.348934000 | 0.765505000 |
| C | -0.666971000 | 1.256466000 | 0.408098000 |
| C | 0.293580000 | 1.498189000 | 1.392006000 |
| S | -0.275353000 | 2.276490000 | -0.988299000 |
| C | 1.283187000 | 2.446133000 | 1.084250000 |
| C | 1.104225000 | 2.955640000 | -0.192170000 |
| H | 2.075506000 | 2.753085000 | 1.758935000 |
| H | 0.262930000 | 0.975832000 | 2.346741000 |
| H | -0.809026000 | -3.994678000 | -0.043483000 |
| H | -2.695951000 | -3.514391000 | -0.993183000 |
| H | -0.835302000 | -3.333676000 | -2.087893000 |
| C | 0.849495000 | -1.032563000 | -0.312947000 |
| C | 1.691113000 | -0.701599000 | -1.354414000 |
| S | 1.729917000 | -1.774174000 | 0.979477000 |
| C | 3.046214000 | -1.032205000 | -1.117261000 |
| H | 1.344197000 | -0.219384000 | -2.264136000 |
| C | 3.247814000 | -1.625464000 | 0.111039000 |
| H | 3.854920000 | -0.847446000 | -1.818661000 |
| C | 4.464420000 | -2.081644000 | 0.653369000 |
| N | 5.468053000 | -2.464131000 | 1.113152000 |
| O | 1.807159000 | 3.875587000 | -0.846674000 |
| C | 2.928598000 | 4.427501000 | -0.158622000 |
| H | 3.653272000 | 3.641391000 | 0.082963000 |
| H | 3.378246000 | 5.149443000 | -0.840065000 |
| H | 2.603912000 | 4.933011000 | 0.758281000 |

## $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{MeOTh})$

$\mathrm{G}_{\mathrm{DFT}}=-2009.849283$
$\mathrm{G}_{\text {CORR DFT }}=0.170972$
$\mathrm{E}_{\text {CCSD }}=-6818.93765$
$\mathrm{G}=-6818.766678$

| Pd | 1.204938000 | -0.724124000 | 0.161192000 |
| :--- | :---: | :---: | :---: |
| O | 3.342420000 | -0.379127000 | -0.045260000 |
| C | 3.736187000 | 0.542075000 | -0.809140000 |
| P | 1.521134000 | -2.991194000 | 0.594173000 |
| O | 2.959609000 | 1.384549000 | -1.369117000 |
| C | 5.203170000 | 0.683496000 | -1.084099000 |
| H | 5.372718000 | 0.706940000 | -2.164717000 |
| H | 5.552409000 | 1.639979000 | -0.681771000 |
| H | 5.769164000 | -0.132937000 | -0.632996000 |


|  |  |  |  |
| :---: | :---: | :---: | :---: |
| H | 1.822449000 | 1.297047000 | -0.844326000 |
| H | 1.053428000 | -3.462746000 | 1.834782000 |
| H | 0.884592000 | -3.905195000 | -0.266614000 |
| H | 2.835221000 | -3.498379000 | 0.595241000 |
| C | -0.747179000 | -1.058415000 | 0.385897000 |
| C | -1.540069000 | -0.837673000 | 1.491653000 |
| S | -1.689577000 | -1.592566000 | -0.961394000 |
| C | -2.915173000 | -1.071432000 | 1.255280000 |
| H | -1.146606000 | -0.486231000 | 2.441681000 |
| C | -3.175574000 | -1.487210000 | -0.033693000 |
| H | -3.697079000 | -0.941027000 | 1.997946000 |
| C | -1.297124000 | 2.647444000 | 0.023587000 |
| C | -0.578497000 | 1.779463000 | -0.743851000 |
| C | 0.660048000 | 1.375412000 | -0.125854000 |
| C | 0.818098000 | 1.977346000 | 1.106839000 |
| S | -0.492985000 | 3.024230000 | 1.535904000 |
| H | -0.911528000 | 1.417763000 | -1.712255000 |
| H | 1.657796000 | 1.883753000 | 1.789938000 |
| C | -4.426096000 | -1.808427000 | -0.595843000 |
| N | -5.457730000 | -2.074055000 | -1.075351000 |
| O | -2.487493000 | 3.235528000 | -0.174502000 |
| C | -3.187778000 | 2.799892000 | -1.332644000 |
| H | -3.351691000 | 1.714022000 | -1.295187000 |
| H | -4.145925000 | 3.320339000 | -1.329259000 |
| H | -2.630323000 | 3.056637000 | -2.242317000 |

## $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{BrCNTh})$

## $G_{\text {DFT }}=-2000.131268$

$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.125362$
$\mathrm{E}_{\text {CCSD }}=-9368.655082$
$\mathrm{G}=-9368.52972$

| ------------------- |  |  |  |
| :--- | :---: | :---: | :---: |
| Pd | -0.776734000 | -1.153456000 | 0.133959000 |
| O | -2.870097000 | -1.4065555000 | 0.630255000 |
| C | -3.478609000 | -0.550368000 | 1.330438000 |
| P | -0.691511000 | -3.297666000 | -0.701343000 |
| O | -2.952927000 | 0.521722000 | 1.765509000 |
| C | -4.917992000 | -0.795789000 | 1.675342000 |
| H | -5.250408000 | -1.769909000 | 1.313378000 |
| H | -5.050194000 | -0.732650000 | 2.759599000 |
| H | -5.532275000 | -0.007402000 | 1.228537000 |
| H | -1.751233000 | 0.656937000 | 1.291080000 |
| H | 0.253847000 | -4.168278000 | -0.131669000 |


| H | -1.874423000 | -4.054177000 | -0.616606000 |
| :--- | :---: | :---: | :---: |
| H | -0.368684000 | -3.412343000 | -2.064213000 |
| C | 1.142897000 | -1.028506000 | -0.405956000 |
| C | 1.676238000 | -0.475846000 | -1.549508000 |
| S | 2.385243000 | -1.576761000 | 0.665710000 |
| C | 3.092151000 | -0.468229000 | -1.562054000 |
| H | 1.067749000 | -0.071329000 | -2.354782000 |
| C | 3.640493000 | -1.029575000 | -0.429316000 |
| H | 3.697148000 | -0.067838000 | -2.370232000 |
| C | 1.330121000 | 2.320676000 | 1.107062000 |
| C | 0.545951000 | 1.304478000 | 1.592648000 |
| C | -0.583849000 | 0.985173000 | 0.776820000 |
| C | -0.598486000 | 1.833328000 | -0.315670000 |
| S | 0.695794000 | 2.966015000 | -0.394116000 |
| H | 0.786277000 | 0.783682000 | 2.516162000 |
| Br | -1.894253000 | 1.840226000 | -1.691579000 |
| C | 5.008159000 | -1.194402000 | -0.130896000 |
| N | 6.138037000 | -1.339350000 | 0.124940000 |
| C | 2.518048000 | 2.83226000 | 1.677361000 |
| N | 3.499158000 | 3.255196000 | 2.144034000 |

## $\alpha-$ CMD (Th/CNTh)

$\mathrm{G}_{\mathrm{DFT}}=-1895.416762$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.141685$
$\mathrm{E}_{\mathrm{CCSD}}=-6704.6417$
$G=-6704.500015$

```
----------------------
```

| Pd | 0.998727000 | 0.478091000 | -0.128448000 |
| :--- | :---: | :--- | :---: |
| O | 2.973250000 | -0.452165000 | -0.253628000 |
| C | 3.203509000 | -1.576836000 | 0.265131000 |
| P | 1.809920000 | 2.487061000 | -0.903549000 |
| O | 2.321383000 | -2.298899000 | 0.832943000 |
| C | 4.600136000 | -2.124635000 | 0.218499000 |
| H | 5.288190000 | -1.412854000 | -0.240440000 |
| H | 4.932033000 | -2.365007000 | 1.233201000 |
| H | 4.601553000 | -3.059541000 | -0.351091000 |
| H | 1.158785000 | -1.772387000 | 0.694463000 |
| C | -0.089319000 | -1.353921000 | 0.522851000 |
| C | -0.980118000 | -1.210029000 | 1.582016000 |
| S | -0.929207000 | -2.024615000 | -0.845820000 |
| C | -2.301530000 | -1.600815000 | 1.304123000 |
| C | -2.435678000 | -2.070151000 | 0.008801000 |
| H | -3.129659000 | -1.552363000 | 2.004383000 |


|  |  |  |  |
| :---: | :---: | :---: | :---: |
| H | -0.670009000 | -0.812731000 | 2.545262000 |
| H | 1.603625000 | 3.614859000 | -0.089273000 |
| H | 3.189531000 | 2.581375000 | -1.171516000 |
| H | 1.257994000 | 2.940738000 | -2.114436000 |
| C | -0.746342000 | 1.459467000 | -0.069125000 |
| C | -1.728086000 | 1.534201000 | -1.023050000 |
| S | -1.215631000 | 2.333550000 | 1.362032000 |
| C | -2.873875000 | 2.275836000 | -0.596043000 |
| H | -1.646214000 | 1.062037000 | -1.999405000 |
| C | -2.748900000 | 2.772739000 | 0.669712000 |
| H | -3.754087000 | 2.432710000 | -1.213649000 |
| C | -3.622635000 | -2.548293000 | -0.593504000 |
| N | -4.595639000 | -2.943101000 | -1.100593000 |
| H | -3.455120000 | 3.366932000 | 1.238105000 |

## $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{CNTh})$

$G_{\text {DFT }}=-1895.411832$
$\mathrm{G}_{\text {CORR DFT }}=0.140561$
$\mathrm{E}_{\text {CCSD }}=-6704.637346$
$G=-6704.496785$

| Pd | 1.046209000 | 0.432498000 | 0.167202000 |
| :--- | :---: | :---: | :---: |
| O | 2.971969000 | -0.592910000 | 0.301013000 |
| C | 3.140450000 | -1.698782000 | -0.276649000 |
| P | 1.953460000 | 2.390700000 | 0.979906000 |
| O | 2.219063000 | -2.331700000 | -0.889106000 |
| C | 4.499858000 | -2.333062000 | -0.256186000 |
| H | 5.218907000 | -1.707473000 | 0.274982000 |
| H | 4.434684000 | -3.314326000 | 0.224309000 |
| H | 4.838564000 | -2.499332000 | -1.283574000 |
| H | 1.102941000 | -1.752547000 | -0.710903000 |
| H | 1.407730000 | 2.862817000 | 2.186952000 |
| H | 3.331551000 | 2.418568000 | 1.271074000 |
| H | 1.817432000 | 3.537670000 | 0.176817000 |
| C | -0.657355000 | 1.484504000 | 0.103891000 |
| C | -1.662868000 | 1.561040000 | 1.032535000 |
| S | -1.051430000 | 2.435377000 | -1.301388000 |
| C | -2.761371000 | 2.374213000 | 0.610630000 |
| H | -1.631169000 | 1.040960000 | 1.987395000 |
| C | -2.581370000 | 2.917116000 | -0.629193000 |
| H | -3.649345000 | 2.546015000 | 1.213073000 |
| C | -2.207452000 | -2.082884000 | 0.393928000 |
| C | -0.867619000 | -1.891838000 | 0.636774000 |


| C | -0.152675000 | -1.328619000 | -0.465016000 |
| :--- | :---: | :---: | :---: |
| C | -1.013601000 | -1.131167000 | -1.530673000 |
| S | -2.638359000 | -1.584594000 | -1.225804000 |
| H | -0.410337000 | -2.152012000 | 1.588604000 |
| H | -0.773667000 | -0.711978000 | -2.503410000 |
| C | -3.170359000 | -2.613753000 | 1.281006000 |
| N | -3.965149000 | -3.049660000 | 2.015197000 |
| H | -3.244220000 | 3.567593000 | -1.188066000 |

## $\alpha-\mathrm{CMD}(\mathbf{T h} / \mathbf{T h})$

$\mathrm{G}_{\mathrm{DFT}}=-1803.224002$
$\mathrm{G}_{\text {CORR DFT }}=0.145026$
$\mathrm{E}_{\text {CCSD }}=-6612.583806$
$\mathrm{G}=-6612.43878$

| Pd | -0.454173000 | -0.650522000 | -0.086814000 |
| :--- | :---: | :---: | :---: |
| O | -2.636868000 | -0.861704000 | -0.085668000 |
| C | -3.388139000 | 0.057052000 | 0.331846000 |
| P | -0.180139000 | -2.907268000 | -0.569909000 |
| O | -2.976772000 | 1.196542000 | 0.729068000 |
| C | -4.871090000 | -0.174298000 | 0.367097000 |
| H | -5.359623000 | 0.524308000 | -0.320047000 |
| H | -5.117053000 | -1.198987000 | 0.083517000 |
| H | -5.252679000 | 0.039734000 | 1.370037000 |
| H | -1.726542000 | 1.300575000 | 0.535014000 |
| C | -0.430135000 | 1.499617000 | 0.255543000 |
| C | 0.416953000 | 2.027087000 | 1.227347000 |
| S | -0.159477000 | 2.385409000 | -1.236774000 |
| C | 1.242210000 | 3.086561000 | 0.794977000 |
| C | 1.036980000 | 3.391561000 | -0.531775000 |
| H | 1.951452000 | 3.612800000 | 1.426899000 |
| H | 0.430794000 | 1.638831000 | 2.243821000 |
| H | 0.575949000 | -3.670796000 | 0.340013000 |
| H | -1.316148000 | -3.728661000 | -0.720325000 |
| H | 0.513532000 | -3.200551000 | -1.758966000 |
| C | 1.544930000 | -0.572279000 | -0.106748000 |
| C | 2.398007000 | -0.226842000 | -1.123258000 |
| S | 2.445560000 | -0.956187000 | 1.334749000 |
| C | 3.776475000 | -0.256722000 | -0.742810000 |
| H | 2.054013000 | 0.057219000 | -2.115098000 |
| C | 3.966992000 | -0.632488000 | 0.556159000 |
| H | 4.592564000 | -0.008981000 | -1.416575000 |
| H | 4.897047000 | -0.741720000 | 1.102072000 |

```
H \(\quad 1.523444000 \quad 4.167526000 \quad-1.113333000\)
```


## $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$

$G_{\text {DFT }}=-1803.216627$
$\mathrm{G}_{\text {CORR DFT }}=0.144435$
$\mathrm{E}_{\mathrm{CCSD}}=-6612.578481$
$G=-6612.434046$


| Pd | -0.611740000 | -0.628421000 | 0.113997000 |
| :--- | :---: | :---: | :---: |
| O | -2.800623000 | -0.555112000 | 0.128025000 |
| C | -3.398050000 | 0.474183000 | -0.280816000 |
| P | -0.624362000 | -2.929735000 | 0.431306000 |
| O | -2.808784000 | 1.545465000 | -0.640535000 |
| C | -4.897082000 | 0.467082000 | -0.355188000 |
| H | -5.301411000 | -0.503600000 | -0.063454000 |
| H | -5.295553000 | 1.246645000 | 0.301953000 |
| H | -5.213108000 | 0.711662000 | -1.374010000 |
| H | -1.563026000 | 1.451666000 | -0.390556000 |
| H | 0.022624000 | -3.389086000 | 1.593827000 |
| H | -1.853795000 | -3.612892000 | 0.528601000 |
| H | 0.035974000 | -3.713658000 | -0.533962000 |
| C | 1.382108000 | -0.812262000 | 0.123991000 |
| C | 2.266566000 | -0.651231000 | 1.159158000 |
| S | 2.234266000 | -1.209578000 | -1.343091000 |
| C | 3.631902000 | -0.835209000 | 0.774378000 |
| H | 1.955790000 | -0.389921000 | 2.168182000 |
| C | 3.780276000 | -1.141189000 | -0.548122000 |
| H | 4.469045000 | -0.742089000 | 1.461322000 |
| H | 4.691602000 | -1.332872000 | -1.102793000 |
| C | 1.051396000 | 3.021611000 | 1.246648000 |
| C | -0.000314000 | 2.154961000 | 1.261223000 |
| C | -0.272720000 | 1.535761000 | -0.011536000 |
| C | 0.622393000 | 1.994695000 | -0.959681000 |
| S | 1.758275000 | 3.126285000 | -0.336276000 |
| H | -0.586860000 | 1.957768000 | 2.156241000 |
| H | 0.683797000 | 1.711634000 | -2.006019000 |
| H | 1.456106000 | 3.617591000 | 2.056820000 |

## $\alpha$-CMD(Th/MeOTh)

$G_{\text {DFT }}=-1917.661459$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.173757$

| $\mathrm{E}_{\text {CCSD }}=-6726.883784$ |  |  |  |
| :--- | :---: | :---: | :---: |
| $\mathrm{G}=-6726.710027$ |  |  |  |
| $--\cdots-\cdots------$ |  |  |  |
|  |  |  |  |
| Pd | 1.160735000 | 0.361771000 | -0.112999000 |
| O | 2.909798000 | -0.973416000 | -0.164979000 |
| C | 2.880959000 | -2.131677000 | 0.319422000 |
| P | 2.457649000 | 2.204054000 | -0.754848000 |
| O | 1.838731000 | -2.679418000 | 0.816357000 |
| C | 4.135487000 | -2.955587000 | 0.325203000 |
| H | 4.342888000 | -3.300662000 | 1.342768000 |
| H | 3.984719000 | -3.846411000 | -0.293217000 |
| H | 4.983367000 | -2.383776000 | -0.055603000 |
| H | 0.850367000 | -1.943940000 | 0.657032000 |
| C | -0.248090000 | -1.179122000 | 0.391412000 |
| C | -1.17150000 | -0.971871000 | 1.415054000 |
| S | -1.141765000 | -1.751373000 | -1.028706000 |
| C | -2.516217000 | -1.257924000 | 1.117939000 |
| C | -2.655323000 | -1.690153000 | -0.189939000 |
| H | -3.337106000 | -1.165581000 | 1.821463000 |
| H | -0.855083000 | -0.608725000 | 2.391404000 |
| H | 2.461915000 | 3.315646000 | 0.111131000 |
| H | 3.841730000 | 2.066356000 | -0.990845000 |
| H | 2.064691000 | 2.846605000 | -1.945014000 |
| C | -0.388016000 | 1.627498000 | -0.085025000 |
| C | -1.334818000 | 1.871500000 | -1.047024000 |
| S | -0.695978000 | 2.607632000 | 1.323085000 |
| C | -2.312873000 | 2.838080000 | -0.653068000 |
| H | -1.346118000 | 1.363235000 | -2.008477000 |
| C | -2.105988000 | 3.330115000 | 0.604033000 |
| H | -3.136800000 | 3.154120000 | -1.28783900 |
| H | -2.683368000 | 4.069006000 | 1.147808000 |
| O | -3.748015000 | -2.069616000 | -0.851335000 |
| C | -4.976101000 | -2.011310000 | -0.130241000 |
| H | -5.181884000 | -0.984117000 | 0.193322000 |
| H | -5.751261000 | -2.344553000 | -0.820357000 |
| H | -4.941943000 | -2.677333000 | 0.740104000 |
|  |  |  |  |

## $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{MeOTh})$

$G_{D F T}=-1917.650561$
$\mathrm{G}_{\text {CORR DFT }}=0.174208$
$\mathrm{E}_{\text {CCSD }}=-6726.877495$
$\mathrm{G}=-6726.703287$

| Pd | -1.131785000 | 0.483218000 | 0.142486000 |
| :--- | :---: | :---: | :---: |
| O | -3.029697000 | -0.614353000 | 0.119198000 |
| C | -3.107093000 | -1.655196000 | -0.582337000 |
| P | -2.153011000 | 2.537138000 | 0.496370000 |
| O | -2.109468000 | -2.196211000 | -1.169208000 |
| C | -4.435270000 | -2.331067000 | -0.749333000 |
| H | -4.637882000 | -2.486396000 | -1.813202000 |
| H | -4.395274000 | -3.319900000 | -0.280794000 |
| H | -5.235491000 | -1.743592000 | -0.296374000 |
| H | -1.061038000 | -1.685006000 | -0.732840000 |
| H | -1.907583000 | 3.544478000 | -0.456351000 |
| H | -3.557768000 | 2.610053000 | 0.593495000 |
| H | -1.777144000 | 3.222806000 | 1.666794000 |
| C | 0.581961000 | 1.509600000 | 0.175252000 |
| C | 1.473506000 | 1.680949000 | 1.202536000 |
| S | 1.193896000 | 2.228685000 | -1.287633000 |
| C | 2.661356000 | 2.374123000 | 0.811205000 |
| H | 1.303105000 | 1.296618000 | 2.205745000 |
| C | 2.663347000 | 2.735486000 | -0.506407000 |
| H | 3.48098600 | 2.595511000 | 1.489871000 |
| C | 2.380414000 | -1.829155000 | 0.005825000 |
| C | 1.375995000 | -1.309350000 | -0.755270000 |
| C | 0.100141000 | -1.313208000 | -0.084121000 |
| C | 0.209640000 | -1.852803000 | 1.180863000 |
| S | 1.820128000 | -2.358396000 | 1.580235000 |
| H | 1.525856000 | -0.911390000 | -1.754662000 |
| H | -0.581507000 | -2.010561000 | 1.908789000 |
| H | 3.421858000 | 3.276468000 | -1.060604000 |
| O | 3.692901000 | -1.985340000 | -0.238540000 |
| C | 4.146448000 | -1.412673000 | -1.457149000 |
| H | 3.923071000 | -0.337023000 | -1.481294000 |
| H | 5.225110000 | -1.569789000 | -1.491215000 |
| H | 3.674029000 | -1.905011000 | -2.316907000 |

## $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{BrTh})$

$\mathrm{G}_{\mathrm{DFT}}=-1815.741028$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.132657$
$\mathrm{E}_{\text {CCSD }}=-9184.540316$
$\mathrm{G}=-9184.407659$

| Pd | -0.102985000 | -1.112923000 | 0.015860000 |
| :--- | :--- | :--- | :--- |
| O | -2.167737000 | -1.816738000 | 0.162769000 |


| C | -2.996279000 | -1.210661000 | 0.893080000 |
| :--- | :---: | :---: | :---: |
| P | 0.524589000 | -3.011638000 | -1.134605000 |
| O | -2.729078000 | -0.158628000 | 1.557636000 |
| C | -4.396530000 | -1.742172000 | 0.996078000 |
| H | -5.091656000 | -1.002060000 | 0.586459000 |
| H | -4.501866000 | -2.683103000 | 0.453533000 |
| H | -4.659155000 | -1.883978000 | 2.048752000 |
| H | -1.532801000 | 0.247254000 | 1.280932000 |
| H | 1.540368000 | -3.800595000 | -0.563877000 |
| H | -0.457614000 | -3.985319000 | -1.403513000 |
| H | 1.062782000 | -2.805544000 | -2.417591000 |
| C | 1.808559000 | -0.562690000 | -0.202368000 |
| C | 2.361361000 | 0.293390000 | -1.119581000 |
| S | 3.021081000 | -1.125496000 | 0.913832000 |
| C | 3.759298000 | 0.513836000 | -0.915858000 |
| H | 1.784671000 | 0.771766000 | -1.908767000 |
| C | 4.263428000 | -0.182381000 | 0.145804000 |
| H | 4.363253000 | 1.167196000 | -1.540023000 |
| H | 5.280090000 | -0.205420000 | 0.521021000 |
| C | 1.062837000 | 2.478618000 | 1.921354000 |
| C | 0.515668000 | 1.239783000 | 2.060876000 |
| C | -0.385718000 | 0.853896000 | 1.005071000 |
| C | -0.469735000 | 1.889958000 | 0.097692000 |
| S | 0.499218000 | 3.267331000 | 0.477767000 |
| H | 0.749317000 | 0.589247000 | 2.900325000 |
| H | 1.763568000 | 2.992090000 | 2.570109000 |
| Br | -1.534859000 | 1.916331000 | -1.473129000 |

## $\alpha-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{CNTh})$

$\mathrm{G}_{\mathrm{DFT}}=-2009.849251$
$\mathrm{G}_{\mathrm{CORR} \text { DFT }}=0.170231$
$\mathrm{E}_{\text {CCSD }}=-6818.939306$
$\mathrm{G}=-6818.769075$

| Pd | -1.142527000 | -0.736027000 | -0.155830000 |
| :--- | :---: | :---: | :---: |
| O | -3.328299000 | -0.767983000 | -0.100294000 |
| C | -3.989971000 | 0.155849000 | 0.442128000 |
| P | -1.034257000 | -2.868404000 | -1.009054000 |
| O | -3.474933000 | 1.204340000 | 0.950811000 |
| C | -5.485461000 | 0.041576000 | 0.498056000 |
| H | -5.928961000 | 0.848887000 | -0.093906000 |
| H | -5.821982000 | -0.922197000 | 0.112534000 |
| H | -5.825628000 | 0.173641000 | 1.529564000 |


|  |  |  |  |
| :---: | :---: | :---: | :---: |
| H | -2.214222000 | 1.223685000 | 0.751976000 |
| C | -0.907543000 | 1.371729000 | 0.533295000 |
| C | 0.006647000 | 1.578355000 | 1.561643000 |
| S | -0.472050000 | 2.363612000 | -0.827953000 |
| C | 1.042041000 | 2.481976000 | 1.264220000 |
| C | 0.920220000 | 2.998011000 | -0.014146000 |
| H | 1.846627000 | 2.756953000 | 1.939187000 |
| H | -0.074050000 | 1.064147000 | 2.516138000 |
| H | -0.256850000 | -3.799250000 | -0.297365000 |
| H | -2.237576000 | -3.581016000 | -1.181425000 |
| H | -0.460326000 | -2.978229000 | -2.287790000 |
| C | 0.855557000 | -0.867379000 | -0.253522000 |
| C | 1.711132000 | -0.514567000 | -1.256077000 |
| S | 1.744348000 | -1.476272000 | 1.131160000 |
| C | 3.100680000 | -0.696026000 | -0.937953000 |
| H | 1.372661000 | -0.115374000 | -2.209922000 |
| C | 3.272542000 | -1.209369000 | 0.316345000 |
| H | 3.911978000 | -0.455338000 | -1.617829000 |
| O | 4.386397000 | -1.528904000 | 1.000319000 |
| C | 1.785817000 | 3.931702000 | -0.629556000 |
| N | 2.494594000 | 4.699058000 | -1.148013000 |
| C | 5.605659000 | -1.276944000 | 0.318166000 |
| H | 6.407593000 | -1.575061000 | 0.994562000 |
| H | 5.661684000 | -1.867234000 | -0.605864000 |
| H | 5.700969000 | -0.210250000 | 0.076642000 |

## $\beta-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{CNTh})$

## $G_{D F T}=-2009.84284$

$\mathrm{G}_{\text {CORR DFT }}=0.170526$
$\mathrm{E}_{\mathrm{CCSD}}=-6818.93434$
$\mathrm{G}=-6818.763814$

| Pd | -1.146800000 | -0.769615000 | 0.191793000 |
| :--- | :---: | :---: | :---: |
| O | -3.332585000 | -0.838189000 | 0.149300000 |
| C | -3.984695000 | 0.053484000 | -0.453848000 |
| P | -1.007016000 | -2.892597000 | 1.077846000 |
| O | -3.456172000 | 1.071364000 | -1.010180000 |
| C | -5.478691000 | -0.060666000 | -0.530633000 |
| H | -5.930677000 | 0.781265000 | 0.003813000 |
| H | -5.799242000 | 0.010524000 | -1.574346000 |
| H | -5.825041000 | -0.999359000 | -0.095316000 |
| H | -2.211939000 | 1.103435000 | -0.766729000 |
| H | -0.422705000 | -2.976001000 | 2.354294000 |


| H | -2.192855000 | -3.629410000 | 1.270581000 |
| :--- | :---: | :---: | :---: |
| H | -0.216357000 | -3.821381000 | 0.377204000 |
| C | 0.854785000 | -0.856170000 | 0.283259000 |
| C | 1.710322000 | -0.457644000 | 1.268434000 |
| S | 1.747541000 | -1.494177000 | -1.086221000 |
| C | 3.101387000 | -0.635217000 | 0.952182000 |
| H | 1.370379000 | -0.027582000 | 2.208467000 |
| C | 3.275688000 | -1.185273000 | -0.285792000 |
| H | 3.911839000 | -0.365128000 | 1.622001000 |
| C | 0.491638000 | 3.007792000 | 0.403202000 |
| C | -0.599796000 | 2.201073000 | 0.623266000 |
| C | -0.916803000 | 1.340846000 | -0.473099000 |
| C | -0.029359000 | 1.559901000 | -1.511874000 |
| S | 1.167347000 | 2.744881000 | -1.187981000 |
| H | -1.158411000 | 2.227966000 | 1.555983000 |
| H | -0.004083000 | 1.058434000 | -2.474915000 |
| O | 4.391202000 | -1.515948000 | -0.962604000 |
| C | 1.050630000 | 3.951987000 | 1.292989000 |
| N | 1.513533000 | 4.729110000 | 2.029673000 |
| C | 5.609025000 | -1.238065000 | -0.288476000 |
| H | 5.668192000 | -1.800908000 | 0.652410000 |
| H | 6.412597000 | -1.551415000 | -0.956033000 |
| H | 5.699051000 | -0.164343000 | -0.077834000 |

## $\alpha-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{Th})$

$G_{\text {DFT }}=-1917.655251$
$\mathrm{G}_{\text {CORR DFT }}=0.174452$
$\mathrm{E}_{\text {CCSD }}=-6726.880958$
$\mathrm{G}=-6726.706506$

| Pd | 0.897611000 | -0.657295000 | 0.109390000 |
| :--- | :---: | :---: | :---: |
| O | 3.062705000 | -1.001895000 | 0.000502000 |
| C | 3.839813000 | -0.143258000 | -0.490142000 |
| P | 0.486792000 | -2.877869000 | 0.648669000 |
| O | 3.473878000 | 1.010778000 | -0.891418000 |
| C | 5.299554000 | -0.469341000 | -0.618591000 |
| H | 5.880419000 | 0.228846000 | -0.007260000 |
| H | 5.503850000 | -1.493471000 | -0.301801000 |
| H | 5.615694000 | -0.328815000 | -1.656830000 |
| H | 2.252867000 | 1.199017000 | -0.617407000 |
| C | 0.989636000 | 1.487933000 | -0.256657000 |
| C | 0.118518000 | 2.064582000 | -1.177284000 |
| S | 0.864936000 | 2.390498000 | 1.244832000 |


| C | -0.614366000 | 3.172262000 | -0.700158000 |
| :---: | :---: | :---: | :---: |
| C | -0.311174000 | 3.465826000 | 0.610121000 |
| H | -1.328294000 | 3.739158000 | -1.290391000 |
| H | 0.018956000 | 1.677062000 | -2.189245000 |
| H | -0.084025000 | -3.094904000 | 1.916924000 |
| H | -0.442410000 | -3.569028000 | -0.151919000 |
| H | 1.547827000 | -3.806600000 | 0.679412000 |
| C | -1.090550000 | -0.456719000 | 0.249134000 |
| C | -1.863995000 | -0.081978000 | 1.309016000 |
| S | -2.091076000 | -0.760871000 | -1.160395000 |
| C | -3.271785000 | -0.016667000 | 1.023766000 |
| H | -1.449260000 | 0.162146000 | 2.284759000 |
| C | -3.545258000 | -0.357175000 | -0.270135000 |
| H | -4.023436000 | 0.265611000 | 1.754563000 |
| H | -0.714032000 | 4.269941000 | 1.216824000 |
| O | -4.710499000 | -0.431899000 | -0.942680000 |
| C | -5.861831000 | -0.087253000 | -0.189122000 |
| H | -6.715856000 | -0.189614000 | -0.859901000 |
| H | -5.981308000 | -0.763103000 | 0.668157000 |
| H | -5.794760000 | 0.948192000 | 0.170230000 |

## $\boldsymbol{\beta}$-CMD(MeOTh/Th)

$\mathrm{G}_{\mathrm{DFT}}=-1917.648303$
$\mathrm{G}_{\text {CORR DFT }}=0.174107$
$\mathrm{E}_{\text {CCSD }}=-6726.876337$
$G=-6726.70223$
-----------------------

| Pd | -0.921725000 | -0.688921000 | -0.197011000 |
| :--- | :---: | :---: | :---: |
| O | -3.101553000 | -0.924985000 | -0.158893000 |
| C | -3.766635000 | -0.206405000 | 0.631186000 |
| P | -0.541552000 | -2.872150000 | -0.875189000 |
| O | -3.270020000 | 0.751159000 | 1.313566000 |
| C | -5.235319000 | -0.463405000 | 0.795886000 |
| H | -5.463314000 | -0.613850000 | 1.855553000 |
| H | -5.794999000 | 0.418399000 | 0.467740000 |
| H | -5.549676000 | -1.334893000 | 0.219335000 |
| H | -2.108772000 | 0.991837000 | 0.889947000 |
| H | 0.336653000 | -3.638501000 | -0.085892000 |
| H | -1.620958000 | -3.769811000 | -1.010377000 |
| H | 0.076273000 | -3.020043000 | -2.131204000 |
| C | 1.070905000 | -0.528495000 | -0.272637000 |
| C | 1.872988000 | -0.061604000 | -1.272948000 |
| S | 2.026025000 | -0.937147000 | 1.140310000 |


| C | 3.268753000 | -0.004048000 | -0.934764000 |
| :--- | :---: | :---: | :---: |
| H | 1.485580000 | 0.265203000 | -2.235885000 |
| C | 3.502910000 | -0.443413000 | 0.337390000 |
| H | 4.041057000 | 0.344688000 | -1.613499000 |
| C | 0.582191000 | 3.209970000 | 0.536091000 |
| C | 0.058793000 | 2.088802000 | 1.105088000 |
| C | -0.956008000 | 1.445029000 | 0.312039000 |
| C | -1.148397000 | 2.142606000 | -0.866740000 |
| S | -0.134595000 | 3.530491000 | -1.014159000 |
| H | 0.384692000 | 1.717745000 | 2.073794000 |
| H | -1.858115000 | 1.920075000 | -1.659203000 |
| H | 1.347008000 | 3.874820000 | 0.921615000 |
| O | 4.646419000 | -0.563722000 | 1.039688000 |
| C | 5.818175000 | -0.150838000 | 0.354921000 |
| H | 6.651022000 | -0.302143000 | 1.042846000 |
| H | 5.971419000 | -0.753351000 | -0.550313000 |
| H | 5.752973000 | 0.910108000 | 0.079525000 |

## $\alpha-\mathrm{CMD}(\mathrm{MeOTh} / \mathrm{MeOTh})$

G----------------------- $_{\text {DFT }}=-2032.09199$
$\mathrm{G}_{\text {CORR DFT }}=0.203813$
$\mathrm{E}_{\text {CCSD }}=-6841.180845$
$\mathrm{G}=-6840.977032$

| Pd | -1.172168000 | -0.816849000 | -0.139013000 |
| :---: | :---: | :---: | :---: |
| O | -3.370575000 | -0.720865000 | -0.044628000 |
| C | -3.975966000 | 0.240639000 | 0.489548000 |
| P | -1.215107000 | -3.040717000 | -0.868701000 |
| O | -3.401762000 | 1.277699000 | 0.967867000 |
| C | -5.473593000 | 0.204578000 | 0.582288000 |
| H | -5.781587000 | 0.364229000 | 1.620129000 |
| H | -5.890730000 | 1.026788000 | -0.008325000 |
| H | -5.867196000 | -0.745486000 | 0.217107000 |
| H | -2.183808000 | 1.235834000 | 0.741341000 |
| C | -0.858420000 | 1.235937000 | 0.407412000 |
| C | 0.070553000 | 1.560326000 | 1.394330000 |
| S | -0.516771000 | 2.251217000 | -1.004812000 |
| C | 1.003702000 | 2.564056000 | 1.075819000 |
| C | 0.808295000 | 3.034091000 | -0.211346000 |
| H | 1.768603000 | 2.932752000 | 1.751463000 |
| H | 0.063744000 | 1.056708000 | 2.359532000 |
| H | -0.462023000 | -3.971489000 | -0.125915000 |
| H | -2.429749000 | -3.747757000 | -0.996752000 |


| H | -0.661338000 | -3.267998000 | -2.143770000 |
| :--- | :---: | :---: | :---: |
| C | 0.820830000 | -0.980926000 | -0.249232000 |
| C | 1.682505000 | -0.655220000 | -1.256398000 |
| S | 1.708263000 | -1.616496000 | 1.126302000 |
| C | 3.068465000 | -0.897695000 | -0.958236000 |
| H | 1.350138000 | -0.230749000 | -2.201422000 |
| C | 3.236803000 | -1.416167000 | 0.293808000 |
| H | 3.879431000 | -0.696353000 | -1.651605000 |
| O | 1.461472000 | 3.983271000 | -0.881485000 |
| O | 4.347908000 | -1.787898000 | 0.960956000 |
| C | 5.562805000 | -1.602495000 | 0.253297000 |
| H | 6.363209000 | -1.939768000 | 0.913234000 |
| H | 5.569196000 | -2.196903000 | -0.670122000 |
| H | 5.709463000 | -0.542935000 | 0.004429000 |
| C | 2.540301000 | 4.612481000 | -0.195114000 |
| H | 3.307082000 | 3.875293000 | 0.071080000 |
| H | 2.955892000 | 5.345724000 | -0.886410000 |
| H | 2.178110000 | 5.117100000 | 0.708519000 |

## $\beta$-CMD(MeOTh/MeOTh)

```
\(G_{D F T}=-2032.08134\)
```

$\mathrm{G}_{\text {CORR DFT }}=0.204440$
$\mathrm{E}_{\text {CCSD }}=-6841.174939$
$\mathrm{G}=-6840.970499$

| Pd | 1.301057000 | -0.736969000 | 0.179617000 |
| :--- | :---: | :---: | :---: |
| O | 3.462553000 | -0.405145000 | 0.017644000 |
| C | 3.867766000 | 0.489965000 | -0.766103000 |
| P | 1.495677000 | -2.997423000 | 0.655162000 |
| O | 3.098656000 | 1.322502000 | -1.358100000 |
| C | 5.336174000 | 0.620867000 | -1.039067000 |
| H | 5.512012000 | 0.585354000 | -2.118559000 |
| H | 5.682525000 | 1.598282000 | -0.688029000 |
| H | 5.900349000 | -0.170062000 | -0.542394000 |
| H | 1.973178000 | 1.255537000 | -0.855062000 |
| H | 0.784761000 | -3.885014000 | -0.174870000 |
| H | 2.764089000 | -3.614489000 | 0.664730000 |
| H | 1.004381000 | -3.403343000 | 1.910269000 |
| C | -0.666585000 | -1.061167000 | 0.338343000 |
| C | -1.512774000 | -0.810516000 | 1.378682000 |
| S | -1.570455000 | -1.536249000 | -1.087971000 |
| C | -2.905167000 | -0.971032000 | 1.061390000 |
| H | -1.165636000 | -0.473069000 | 2.353124000 |


| C | -3.090548000 | -1.352353000 | -0.237581000 |
| :---: | :---: | :---: | :---: |
| H | -3.709728000 | -0.806404000 | 1.771637000 |
| C | -1.161229000 | 2.655886000 | 0.022653000 |
| C | -0.452436000 | 1.778323000 | -0.741663000 |
| C | 0.788805000 | 1.371567000 | -0.132446000 |
| C | 0.964614000 | 1.990114000 | 1.087652000 |
| S | -0.340030000 | 3.050693000 | 1.520211000 |
| H | -0.806093000 | 1.394338000 | -1.694049000 |
| H | 1.811629000 | 1.904435000 | 1.762938000 |
| O | -2.364403000 | 3.227791000 | -0.164363000 |
| O | -4.214293000 | -1.609378000 | -0.936185000 |
| C | -5.423579000 | -1.389818000 | -0.227734000 |
| H | -6.236059000 | -1.619344000 | -0.918354000 |
| H | -5.486556000 | -2.048029000 | 0.648896000 |
| H | -5.496186000 | -0.342732000 | 0.097133000 |
| C | -3.108851000 | 2.712101000 | -1.259576000 |
| H | -3.253511000 | 1.627341000 | -1.147363000 |
| H | -4.073571000 | 3.220874000 | -1.245512000 |
| H | -2.598826000 | 2.917367000 | -2.209495000 |

## $\beta$-CMD(MeOTh/BrMeOTh)

```
G
G
E
G=-9412.945531
```

| Pd | -0.878765000 | -1.176930000 | 0.132577000 |
| :--- | :---: | :---: | :---: |
| O | -2.996075000 | -1.385674000 | 0.648794000 |
| C | -3.563197000 | -0.511668000 | 1.355332000 |
| P | -0.749860000 | -3.340372000 | -0.651649000 |
| O | -2.995175000 | 0.547905000 | 1.777434000 |
| C | -5.005155000 | -0.700531000 | 1.726926000 |
| H | -5.132381000 | -0.559142000 | 2.804150000 |
| H | -5.604063000 | 0.067707000 | 1.226421000 |
| H | -5.362006000 | -1.688499000 | 1.431160000 |
| H | -1.829684000 | 0.655979000 | 1.262638000 |
| H | 0.229392000 | -4.173580000 | -0.079932000 |
| H | -1.890181000 | -4.164239000 | -0.563601000 |
| H | -0.424684000 | -3.475490000 | -2.013261000 |
| C | 1.054035000 | -1.081791000 | -0.379726000 |
| C | 1.643609000 | -0.531284000 | -1.479602000 |
| S | 2.268815000 | -1.608092000 | 0.771985000 |
| C | 3.079451000 | -0.494847000 | -1.424839000 |


| H | 1.074216000 | -0.122024000 | -2.312316000 |
| :---: | :---: | :---: | :---: |
| C | 3.558846000 | -1.035301000 | -0.265193000 |
| H | 3.703715000 | -0.085665000 | -2.213224000 |
| C | 1.192738000 | 2.390463000 | 0.921810000 |
| C | 0.484118000 | 1.361958000 | 1.466751000 |
| C | -0.662555000 | 0.965683000 | 0.682762000 |
| C | -0.759818000 | 1.768673000 | -0.428008000 |
| S | 0.484915000 | 2.969578000 | -0.577200000 |
| H | 0.770377000 | 0.858959000 | 2.385966000 |
| Br | -2.099233000 | 1.689587000 | -1.773350000 |
| O | 4.818025000 | -1.203184000 | 0.183516000 |
| O | 2.313808000 | 3.012085000 | 1.317149000 |
| C | 5.834163000 | -0.727340000 | -0.685192000 |
| H | 5.723998000 | 0.351743000 | -0.856001000 |
| H | 6.785554000 | -0.926868000 | -0.190444000 |
| H | 5.799628000 | -1.254306000 | -1.647902000 |
| C | 2.941333000 | 2.449472000 | 2.463090000 |
| H | 3.848818000 | 3.029442000 | 2.633245000 |
| H | 2.284711000 | 2.523964000 | 3.339128000 |
| H | 3.197106000 | 1.397053000 | 2.281055000 |

## Energy profile of the coupling of two electron-poor substrates

## Int-11

$G_{\text {DFT }}=-1342.632969$
$\mathrm{G}_{\text {CORR DFT }}=0.087403$
$\mathrm{E}_{\text {CCSD }}=-6152.537218$
$G=-6152.449815$

| ------------------- |  |  |  |
| :--- | :---: | :---: | :---: |
| Pd | -1.055828000 | 0.350673000 | 0.010526000 |
| C | 0.895100000 | 0.206597000 | 0.344146000 |
| C | 1.638837000 | 0.560126000 | 1.448812000 |
| S | 1.861494000 | -0.586207000 | -0.849724000 |
| C | 2.994568000 | 0.163864000 | 1.355068000 |
| H | 1.223135000 | 1.078979000 | 2.308103000 |
| C | 3.284530000 | -0.470178000 | 0.166515000 |
| H | 3.738808000 | 0.333974000 | 2.127194000 |
| O | -1.833496000 | -1.662568000 | 0.335234000 |
| O | -3.210182000 | -0.039169000 | -0.221484000 |
| C | -3.011855000 | -1.261735000 | 0.066112000 |
| C | -4.147216000 | -2.232061000 | 0.058124000 |
| H | -4.258165000 | -2.635224000 | -0.954860000 |
| H | -3.948639000 | -3.065886000 | 0.735489000 |
| H | -5.081413000 | -1.733039000 | 0.326953000 |
| P | -0.502518000 | 2.504021000 | -0.389757000 |
| H | 0.028909000 | 3.213271000 | 0.700305000 |
| H | 0.476805000 | 2.727407000 | -1.371454000 |
| H | -1.543891000 | 3.348570000 | -0.813007000 |
| C | 4.531550000 | -0.983970000 | -0.244796000 |
| N | 5.560392000 | -1.408850000 | -0.596407000 |

## $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{CNTh})$

$G_{\text {DFT }}=-1987.609022$
$\mathrm{G}_{\text {CORR DFT }}=0.137684$
$\mathrm{E}_{\text {CCSD }}=-6796.69632$
$\mathrm{G}=-6796.558636$

| Pd | 1.173034000 | -0.678400000 | 0.150587000 |
| :--- | :---: | :---: | :--- |
| O | 3.317318000 | -0.402061000 | -0.009907000 |
| C | 3.764387000 | 0.532042000 | -0.730118000 |
| P | 1.425037000 | -2.925649000 | 0.634712000 |
| O | 3.034739000 | 1.419393000 | -1.279702000 |


| C | 5.242708000 | 0.624711000 | -0.962022000 |
| :---: | :---: | :---: | :---: |
| H | 5.769611000 | -0.204080000 | -0.486904000 |
| H | 5.442024000 | 0.626976000 | -2.038021000 |
| H | 5.611167000 | 1.575509000 | -0.564052000 |
| H | 1.855001000 | 1.343848000 | -0.810935000 |
| H | 0.781890000 | -3.837047000 | -0.221790000 |
| H | 2.734521000 | -3.440681000 | 0.663072000 |
| H | 0.928142000 | -3.349777000 | 1.879787000 |
| C | -0.786517000 | -1.001613000 | 0.349043000 |
| C | -1.584072000 | -0.786854000 | 1.451684000 |
| S | -1.719109000 | -1.534007000 | -1.006399000 |
| C | -2.957516000 | -1.027608000 | 1.207431000 |
| H | -1.196269000 | -0.445820000 | 2.407932000 |
| C | -3.207564000 | -1.440105000 | -0.083555000 |
| H | -3.743773000 | -0.906053000 | 1.946735000 |
| C | -1.355682000 | 2.646269000 | -0.166713000 |
| C | -0.529263000 | 1.812903000 | -0.878635000 |
| C | 0.666271000 | 1.452980000 | -0.182274000 |
| C | 0.688012000 | 2.059843000 | 1.063259000 |
| S | -0.687210000 | 3.028231000 | 1.405240000 |
| H | -0.782155000 | 1.465029000 | -1.876808000 |
| H | 1.473670000 | 1.994216000 | 1.811526000 |
| C | -4.452872000 | -1.779419000 | -0.649308000 |
| N | -5.478589000 | -2.065933000 | -1.128053000 |
| C | -2.606025000 | 3.163972000 | -0.576730000 |
| N | -3.637912000 | 3.591657000 | -0.911256000 |

## $\beta-\mathrm{CMD}(\mathrm{CNTh} / \mathrm{BrCNTh})$

| $\mathrm{G}_{\text {DFT }}=-2000.131268$ |  |  |  |
| :---: | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.125362$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-9368.655082$ |  |  |  |
| $\mathrm{G}=-9368.52972$ |  |  |  |
| Pd | -0.776734000 | -1.153456000 | 0.133959000 |
| O | -2.870097000 | -1.406555000 | 0.630255000 |
| C | -3.478609000 | -0.550368000 | 1.330438000 |
| P | -0.691511000 | -3.297666000 | -0.701343000 |
| O | -2.952927000 | 0.521722000 | 1.765509000 |
| C | -4.917992000 | -0.795789000 | 1.675342000 |
| H | -5.250408000 | -1.769909000 | 1.313378000 |
| H | -5.050194000 | -0.732650000 | 2.759599000 |
| H | -5.532275000 | -0.007402000 | 1.228537000 |
| H | -1.751233000 | 0.656937000 | 1.291080000 |


| H | 0.253847000 | -4.168278000 | -0.131669000 |
| :--- | :---: | :---: | :---: |
| H | -1.874423000 | -4.054177000 | -0.616606000 |
| H | -0.368684000 | -3.412343000 | -2.064213000 |
| C | 1.142897000 | -1.028506000 | -0.405956000 |
| C | 1.676238000 | -0.475846000 | -1.549508000 |
| S | 2.385243000 | -1.576761000 | 0.665710000 |
| C | 3.092151000 | -0.468229000 | -1.562054000 |
| H | 1.067749000 | -0.071329000 | -2.354782000 |
| C | 3.640493000 | -1.029575000 | -0.429316000 |
| H | 3.697148000 | -0.067838000 | -2.370232000 |
| C | 1.330121000 | 2.320676000 | 1.107062000 |
| C | 0.545951000 | 1.304478000 | 1.592648000 |
| C | -0.583849000 | 0.985173000 | 0.776820000 |
| C | -0.598486000 | 1.833328000 | -0.315670000 |
| S | 0.695794000 | 2.966015000 | -0.394116000 |
| H | 0.786277000 | 0.783682000 | 2.516162000 |
| Br | -1.894253000 | 1.840226000 | -1.691579000 |
| C | 5.008159000 | -1.194402000 | -0.130896000 |
| N | 6.138037000 | -1.339350000 | 0.124940000 |
| C | 2.518048000 | 2.83226000 | 1.677361000 |
| N | 3.499158000 | 3.255196000 | 2.144034000 |

## Int-12

$\mathrm{G}_{\mathrm{DFT}}=-1987.625110$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.140532$
$\mathrm{E}_{\mathrm{CCSD}}=-6796.716100$
$\mathrm{G}=-6796.575568$

|  |  |  |  |
| :--- | :---: | :--- | :---: |
| Pd | 0.577602000 | -1.087158000 | -0.055737000 |
| C | -1.363110000 | -0.839493000 | 0.301300000 |
| C | -2.059797000 | -1.020253000 | 1.479368000 |
| S | -2.423278000 | -0.375224000 | -0.980473000 |
| C | -3.450871000 | -0.789518000 | 1.355473000 |
| H | -1.583843000 | -1.312066000 | 2.412101000 |
| C | -3.822424000 | -0.434131000 | 0.076491000 |
| H | -4.163756000 | -0.882729000 | 2.169586000 |
| O | 3.428409000 | 0.145518000 | 1.059659000 |
| O | 2.755245000 | -1.369856000 | -0.450714000 |
| C | 3.655029000 | -0.805675000 | 0.171919000 |
| C | 5.095852000 | -1.124618000 | -0.006160000 |
| H | 5.611074000 | -0.248360000 | -0.412623000 |
| H | 5.548712000 | -1.344423000 | 0.965126000 |
| H | 5.215512000 | -1.971574000 | -0.681335000 |


| H | 2.471293000 | 0.369951000 | 1.048162000 |
| :--- | :---: | :---: | :---: |
| P | 0.211643000 | -3.461477000 | 0.121232000 |
| H | -0.276240000 | -3.924541000 | 1.360485000 |
| H | -0.789043000 | -3.996008000 | -0.715174000 |
| H | 1.231510000 | -4.411416000 | -0.098280000 |
| C | 0.670268000 | 0.961002000 | -0.190573000 |
| C | 0.072354000 | 1.933220000 | 0.659304000 |
| C | 1.342754000 | 1.567443000 | -1.226571000 |
| C | 0.318834000 | 3.233006000 | 0.266255000 |
| H | -0.526792000 | 1.697551000 | 1.535490000 |
| S | 1.279579000 | 3.297015000 | -1.183816000 |
| H | 1.895107000 | 1.098896000 | -2.035965000 |
| C | -0.126521000 | 4.411523000 | 0.904972000 |
| N | -0.492287000 | 5.384851000 | 1.434267000 |
| C | -5.121777000 | -0.152342000 | -0.388839000 |
| N | -6.195062000 | 0.081034000 | -0.786084000 |

## Int-13

$\mathrm{G}_{\mathrm{DFT}}=-2101.793480$
$\mathrm{G}_{\text {CORR DFT }}=0.108387$
$E_{C C S D}=-6910.722112$
$\mathrm{G}=-6910.613725$

| $-----\cdots----------$ |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| Pd | -0.086705000 | -1.411494000 | -0.021523000 |
| C | 1.282634000 | 0.051471000 | 0.412604000 |
| C | 1.492891000 | 0.743211000 | 1.589251000 |
| S | 2.393709000 | 0.585892000 | -0.799892000 |
| C | 2.545844000 | 1.686131000 | 1.528305000 |
| H | 0.890008000 | 0.583041000 | 2.479517000 |
| C | 3.150279000 | 1.734657000 | 0.289591000 |
| H | 2.854791000 | 2.318535000 | 2.355858000 |
| P | 1.708281000 | -2.990970000 | -0.221665000 |
| H | 1.501967000 | -4.383352000 | -0.323479000 |
| H | 2.573530000 | -2.811394000 | -1.320584000 |
| H | 2.664617000 | -2.974189000 | 0.813104000 |
| P | -1.918704000 | -2.867365000 | -0.442786000 |
| H | -2.896464000 | -2.906297000 | 0.571788000 |
| H | -2.743388000 | -2.522754000 | -1.531493000 |
| H | -1.779909000 | -4.250476000 | -0.686549000 |
| C | -1.468336000 | 0.094176000 | 0.176071000 |
| C | -1.590172000 | 1.190895000 | -0.719574000 |
| C | -2.372959000 | 0.194045000 | 1.202960000 |
| C | -2.580399000 | 2.083514000 | -0.361146000 |


| H | -0.970900000 | 1.337714000 | -1.601056000 |
| :--- | :---: | :--- | :---: |
| S | -3.382721000 | 1.603036000 | 1.106267000 |
| H | -2.520735000 | -0.477666000 | 2.043437000 |
| C | -2.946856000 | 3.262925000 | -1.045891000 |
| N | -3.251203000 | 4.236115000 | -1.613453000 |
| C | 4.219263000 | 2.557629000 | -0.112608000 |
| N | 5.108673000 | 3.231862000 | -0.458423000 |

## Int-14

G $_{\text {DFT }}=-----------------\quad 000.148124$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.127704$
$\mathrm{E}_{\text {CCSD }}=-9368.674391$
$G=-9368.546687$

| $-\cdots-\cdots-\cdots-\cdots-\cdots-\cdots---$ |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| Pd | -0.305382000 | -1.285638000 | -0.435245000 |
| C | 1.640799000 | -0.887375000 | -0.480699000 |
| C | 2.521124000 | -1.020837000 | -1.534398000 |
| S | 2.447366000 | -0.332635000 | 0.941923000 |
| C | 3.854394000 | -0.682389000 | -1.200396000 |
| H | 2.217823000 | -1.353893000 | -2.523594000 |
| C | 3.993620000 | -0.290196000 | 0.113481000 |
| H | 4.690548000 | -0.725304000 | -1.892212000 |
| O | -3.443974000 | 0.121063000 | -0.837215000 |
| O | -2.474329000 | -1.852596000 | -0.394178000 |
| C | -3.482782000 | -1.170236000 | -0.572085000 |
| C | -4.861351000 | -1.723729000 | -0.503852000 |
| H | -5.398894000 | -1.248721000 | 0.323152000 |
| H | -5.403178000 | -1.483076000 | -1.423218000 |
| H | -4.828956000 | -2.802550000 | -0.353468000 |
| H | -2.508523000 | 0.428053000 | -0.827165000 |
| P | 0.272751000 | -3.608635000 | -0.413989000 |
| H | 0.977514000 | -4.087737000 | -1.536688000 |
| H | 1.168859000 | -4.010556000 | 0.596194000 |
| H | -0.704092000 | -4.618262000 | -0.290340000 |
| C | -0.484369000 | 0.770655000 | -0.437523000 |
| C | -0.133274000 | 1.645011000 | -1.506580000 |
| C | -0.837649000 | 1.518300000 | 0.659104000 |
| C | -0.248221000 | 2.985741000 | -1.206019000 |
| H | 0.201753000 | 1.300285000 | -2.482019000 |
| S | -0.780384000 | 3.240755000 | 0.435703000 |
| Br | -1.354857000 | 0.845659000 | 2.356350000 |
| C | 0.013900000 | 4.074088000 | -2.067903000 |
| N | 0.228501000 | 4.972217000 | -2.780452000 |


| C | 5.179623000 | 0.095417000 | 0.768699000 |
| :--- | :--- | :--- | :--- |
| N | 6.157678000 | 0.414667000 | 1.321362000 |

## Int-15

-------------------------1
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.096654$
$\mathrm{E}_{\mathrm{CCSD}}=-9482.682463$
$\mathrm{G}=-9482.585809$

| ------------------ |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| Pd | -0.278627000 | 1.429597000 | -0.473890000 |
| C | -1.677370000 | -0.061170000 | -0.569517000 |
| C | -2.415444000 | -0.503249000 | -1.650210000 |
| S | -2.090085000 | -0.950610000 | 0.849970000 |
| C | -3.313477000 | -1.553970000 | -1.343137000 |
| H | -2.314033000 | -0.081443000 | -2.647522000 |
| C | -3.269526000 | -1.920372000 | -0.014738000 |
| H | -3.974698000 | -2.029294000 | -2.062078000 |
| P | -2.112322000 | 2.945903000 | -0.567630000 |
| H | -1.989935000 | 4.349437000 | -0.491242000 |
| H | -2.911605000 | 2.840184000 | -1.723514000 |
| H | -3.103458000 | 2.739998000 | 0.412280000 |
| P | 1.552900000 | 2.951931000 | -0.401545000 |
| H | 2.472223000 | 2.745895000 | 0.646564000 |
| H | 2.437583000 | 2.881483000 | -1.495832000 |
| H | 1.404011000 | 4.351804000 | -0.314459000 |
| C | 1.11953000 | -0.083235000 | -0.434410000 |
| C | 1.557109000 | -0.799414000 | -1.578674000 |
| C | 1.733676000 | -0.572180000 | 0.682770000 |
| C | 2.488010000 | -1.781230000 | -1.305718000 |
| H | 1.200758000 | -0.609384000 | -2.588532000 |
| S | 2.851224000 | -1.875311000 | 0.397167000 |
| Br | 1.467517000 | 0.010575000 | 2.470402000 |
| C | 3.109905000 | -2.641900000 | -2.236290000 |
| N | 3.625224000 | -3.350585000 | -3.006828000 |
| C | -4.035713000 | -2.913955000 | 0.625165000 |
| N | -4.666469000 | -3.733559000 | 1.168424000 |

## $\beta$-RE(CNTh/CNTh)

$G_{\text {DFT }}=-2101.774634$
$\mathrm{G}_{\text {CORR DFT }}=0.108452$
$E_{C C S D}=-6910.699308$

```
G=-6910.590856
```

| Pd | -0.001742000 | 1.447669000 | -0.021751000 |
| :--- | :---: | :---: | :---: |
| P | -1.875867000 | 2.982380000 | -0.266495000 |
| P | 1.948431000 | 2.859820000 | -0.422668000 |
| H | 2.306482000 | 3.890006000 | 0.476522000 |
| H | 3.181525000 | 2.165590000 | -0.408146000 |
| H | 2.155890000 | 3.586227000 | -1.617363000 |
| H | -2.070201000 | 4.073244000 | 0.611032000 |
| H | -2.143124000 | 3.671349000 | -1.471423000 |
| H | -3.146385000 | 2.381289000 | -0.106220000 |
| C | 1.659830000 | -0.537152000 | 1.534024000 |
| C | 0.977742000 | -0.346172000 | 0.351443000 |
| S | 2.986516000 | -1.631846000 | 1.393443000 |
| C | 1.554526000 | -1.110239000 | -0.703038000 |
| C | 2.647274000 | -1.845673000 | -0.301657000 |
| H | 1.182072000 | -1.129262000 | -1.724167000 |
| C | -1.014539000 | -0.279503000 | 0.409436000 |
| C | -1.620602000 | -0.634245000 | 1.608589000 |
| S | -1.846512000 | -1.028148000 | -0.924937000 |
| C | -2.725192000 | -1.492952000 | 1.462622000 |
| H | -1.247148000 | -0.300726000 | 2.573210000 |
| C | -2.986858000 | -1.825460000 | 0.147147000 |
| H | -3.315399000 | -1.876490000 | 2.289969000 |
| H | 1.446851000 | -0.104472000 | 2.506206000 |
| C | 3.438057000 | -2.697316000 | -1.105190000 |
| N | 4.095341000 | -3.397403000 | -1.767353000 |
| C | -3.997549000 | -2.672396000 | -0.339785000 |
| N | -4.837495000 | -3.370592000 | -0.756831000 |

## $\beta-\mathrm{RE}(\mathrm{CNTh} / \mathrm{BrCNTh})$

$\mathrm{G}_{\mathrm{DFT}}=-2114.299086$
$\mathrm{G}_{\text {CORR DFT }}=0.094874$
$\mathrm{E}_{\text {CCSD }}=-9482.658526$
$G=-9482.563652$
-----------------------

| Pd | 0.236747000 | 1.491903000 | -0.449552000 |
| :--- | :---: | :---: | :---: |
| P | 2.223465000 | 2.879702000 | -0.659579000 |
| P | -1.559685000 | 3.090710000 | -0.091942000 |
| H | -2.764547000 | 2.527569000 | 0.389956000 |
| H | -1.468755000 | 4.160144000 | 0.826990000 |
| H | -2.110585000 | 3.821407000 | -1.168307000 |


| H | 2.395495000 | 3.804718000 | -1.713972000 |
| :--- | :---: | :---: | :---: |
| H | 2.664844000 | 3.715400000 | 0.390959000 |
| H | 3.422606000 | 2.152445000 | -0.844064000 |
| C | -1.432716000 | -0.719910000 | 0.795829000 |
| C | -0.840567000 | -0.283408000 | -0.371978000 |
| S | -2.834841000 | -1.720008000 | 0.578630000 |
| C | -1.584327000 | -0.771381000 | -1.489666000 |
| C | -2.669907000 | -1.540948000 | -1.150540000 |
| H | -1.322768000 | -0.567106000 | -2.524711000 |
| C | 1.098284000 | -0.363182000 | -0.639584000 |
| C | 1.534341000 | -0.930575000 | -1.832586000 |
| S | 2.073509000 | -0.937376000 | 0.687473000 |
| C | 2.619667000 | -1.813581000 | -1.687614000 |
| H | 1.066027000 | -0.720073000 | -2.790125000 |
| C | 3.038805000 | -1.943745000 | -0.378437000 |
| H | 3.085324000 | -2.351290000 | -2.508345000 |
| Br | -0.900603000 | -0.283834000 | 2.555210000 |
| C | -3.578332000 | -2.159142000 | -2.039254000 |
| N | -4.331818000 | -2.666983000 | -2.770179000 |
| C | 4.079512000 | -2.753903000 | 0.110635000 |
| N | 4.945981000 | -3.418148000 | 0.527755000 |

## Annex 3.5 C-H activation of model thiophenes with steric substituents

## MeTh (3-methylthiophene)

$\mathrm{G}_{\mathrm{DFT}}=-592.085103$
$\mathrm{G}_{\text {CORR DFT }}=0.063961$
$\mathrm{E}_{\text {CCSD }}=-591.3514895$
$G=-591.2875285$

| C | -0.078929000 | -1.057244000 | 0.000000000 |
| :--- | :---: | :---: | :---: |
| C | -0.982912000 | -0.029556000 | 0.000000000 |
| S | 1.559124000 | -0.495966000 | 0.000000000 |
| C | -0.329361000 | 1.242904000 | 0.000000000 |
| C | 1.032466000 | 1.151245000 | 0.000000000 |
| H | -0.865199000 | 2.188923000 | 0.000000000 |
| H | 1.761640000 | 1.952641000 | 0.000000000 |
| H | -0.286408000 | -2.121840000 | 0.000000000 |
| C | -2.468566000 | -0.200750000 | 0.000000000 |
| H | -2.922501000 | 0.267647000 | 0.881724000 |
| H | -2.922501000 | 0.267647000 | -0.881724000 |
| H | -2.747199000 | -1.259150000 | 0.000000000 |

## EtTh (3-ethylthiophene)

$\mathrm{G}_{\mathrm{DFT}}=-631.342200$
$\mathrm{G}_{\text {CORR DFT }}=0.090299$
$\mathrm{E}_{\text {CCSD }}=-630.5680706$
$\mathrm{G}=-630.4777716$

| C | -0.426998000 | -1.085154000 | 0.086004000 |
| :--- | :---: | :---: | :---: |
| C | 0.508538000 | -0.109702000 | 0.302114000 |
| S | -2.008020000 | -0.434301000 | -0.187795000 |
| C | -0.072260000 | 1.196418000 | 0.241970000 |
| C | -1.413384000 | 1.180183000 | -0.011662000 |
| H | 0.496496000 | 2.111670000 | 0.389790000 |
| H | -2.092429000 | 2.019676000 | -0.101865000 |
| H | -0.273958000 | -2.158994000 | 0.074285000 |
| C | 1.967410000 | -0.362281000 | 0.540830000 |
| H | 2.279744000 | 0.150723000 | 1.461883000 |
| H | 2.125269000 | -1.434533000 | 0.714697000 |
| C | 2.838468000 | 0.108473000 | -0.620563000 |
| H | 2.718735000 | 1.184701000 | -0.794924000 |
| H | 3.899165000 | -0.082615000 | -0.423829000 |

## Int-17

$G_{\text {DFT }}=-1289.699162$
$\mathrm{G}_{\mathrm{CORRDFT}}=0.116476$
$\mathrm{E}_{\text {CCSD }}=-6099.701013$
$G=-6099.584537$

| Pd | -0.648985000 | 0.355239000 | -0.080554000 |
| :--- | :---: | :---: | :---: |
| C | 1.245306000 | -0.259552000 | 0.003634000 |
| C | 2.128280000 | -0.260021000 | 1.056872000 |
| S | 1.910797000 | -1.049844000 | -1.399841000 |
| C | 3.345316000 | -0.941079000 | 0.723372000 |
| C | 3.381780000 | -1.417166000 | -0.554597000 |
| H | 4.161305000 | -1.068713000 | 1.431979000 |
| H | 4.171444000 | -1.973119000 | -1.047093000 |
| O | -1.867837000 | -1.442515000 | 0.280303000 |
| O | -2.867546000 | 0.489611000 | -0.065629000 |
| C | -2.933968000 | -0.758047000 | 0.163134000 |
| C | -4.263093000 | -1.437032000 | 0.267433000 |
| H | -4.505367000 | -1.889410000 | -0.700868000 |
| H | -4.226905000 | -2.239284000 | 1.009029000 |
| H | -5.047706000 | -0.719634000 | 0.518604000 |
| P | 0.418804000 | 2.290346000 | -0.507878000 |
| H | 1.277844000 | 2.776327000 | 0.492749000 |
| H | 1.272471000 | 2.296454000 | -1.623996000 |
| H | -0.386199000 | 3.417523000 | -0.760440000 |
| C | 1.881078000 | 0.343723000 | 2.404534000 |
| H | 2.608540000 | 1.135097000 | 2.629025000 |
| H | 0.875839000 | 0.773799000 | 2.471551000 |
| H | 1.972093000 | -0.409443000 | 3.196899000 |

## Int-18

$\mathrm{G}_{\mathrm{DFT}}=-1328.955148$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.143789$
$\mathrm{E}_{\text {CCSD }}=-6138.918688$
$G=-6138.774899$
-----------------------

| Pd | -0.725043000 | -0.453503000 | -0.127770000 |
| :--- | :---: | :---: | :---: |
| C | 1.190201000 | -0.088202000 | 0.276520000 |


| C | 2.069117000 | 0.717624000 | -0.406436000 |
| :--- | :---: | :---: | :---: |
| S | 1.876086000 | -0.679782000 | 1.764139000 |
| C | 3.300410000 | 0.879228000 | 0.308528000 |
| C | 3.351935000 | 0.190412000 | 1.485871000 |
| H | 4.117907000 | 1.496582000 | -0.060222000 |
| H | 4.158732000 | 0.142237000 | 2.208284000 |
| O | -1.836418000 | 1.148234000 | 0.892486000 |
| O | -2.946624000 | -0.369045000 | -0.255813000 |
| C | -2.938826000 | 0.670202000 | 0.474354000 |
| C | -4.227013000 | 1.319670000 | 0.871287000 |
| H | -4.566879000 | 0.879802000 | 1.815831000 |
| H | -4.086975000 | 2.391704000 | 1.030123000 |
| H | -4.997948000 | 1.141541000 | 0.117641000 |
| P | 0.241862000 | -2.162237000 | -1.229304000 |
| H | 1.154016000 | -1.825397000 | -2.244136000 |
| H | 1.012514000 | -3.047675000 | -0.456950000 |
| H | -0.617823000 | -3.049761000 | -1.904190000 |
| C | 1.770416000 | 1.430946000 | -1.692454000 |
| H | 2.677364000 | 1.460808000 | -2.313213000 |
| H | 1.014917000 | 0.869974000 | -2.260446000 |
| C | 1.266294000 | 2.852038000 | -1.449645000 |
| H | 0.341380000 | 2.835148000 | -0.859457000 |
| H | 2.005740000 | 3.439489000 | -0.891058000 |
| H | 1.062876000 | 3.371704000 | -2.392987000 |

## $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$

$G_{\text {DFT }}=-1803.224002$
$\mathrm{G}_{\text {CORR DFT }}=0.145026$
$\mathrm{E}_{\text {CCSD }}=-6612.583806$
$G=-6612.43878$
$\qquad$

| Pd | -0.454173000 | -0.650522000 | -0.086814000 |
| :--- | :---: | :---: | :---: |
| O | -2.636868000 | -0.861704000 | -0.085668000 |
| C | -3.388139000 | 0.057052000 | 0.331846000 |
| P | -0.180139000 | -2.907268000 | -0.569909000 |
| O | -2.976772000 | 1.196542000 | 0.729068000 |
| C | -4.871090000 | -0.174298000 | 0.367097000 |
| H | -5.359623000 | 0.524308000 | -0.320047000 |
| H | -5.117053000 | -1.198987000 | 0.083517000 |
| H | -5.252679000 | 0.039734000 | 1.370037000 |
| H | -1.726542000 | 1.300575000 | 0.535014000 |
| C | -0.430135000 | 1.499617000 | 0.255543000 |
| C | 0.416953000 | 2.027087000 | 1.227347000 |


| S | -0.159477000 | 2.385409000 | -1.236774000 |
| :--- | :---: | :---: | :---: |
| C | 1.242210000 | 3.086561000 | 0.794977000 |
| C | 1.036980000 | 3.391561000 | -0.531775000 |
| H | 1.951452000 | 3.612800000 | 1.426899000 |
| H | 0.430794000 | 1.638831000 | 2.243821000 |
| H | 0.575949000 | -3.670796000 | 0.340013000 |
| H | -1.316148000 | -3.728661000 | -0.720325000 |
| H | 0.513532000 | -3.200551000 | -1.758966000 |
| C | 1.544930000 | -0.572279000 | -0.106748000 |
| C | 2.398007000 | -0.226842000 | -1.123258000 |
| S | 2.445560000 | -0.956187000 | 1.334749000 |
| C | 3.776475000 | -0.256722000 | -0.742810000 |
| H | 2.054013000 | 0.057219000 | -2.115098000 |
| C | 3.966992000 | -0.632488000 | 0.556159000 |
| H | 4.592564000 | -0.008981000 | -1.416575000 |
| H | 4.897047000 | -0.741720000 | 1.102072000 |
| H | 1.523444000 | 4.167526000 | -1.113333000 |

## $\beta-\mathrm{CMD}(\mathrm{Th} / \mathrm{Th})$



| Pd | -0.611740000 | -0.628421000 | 0.113997000 |
| :--- | :---: | :---: | :---: |
| O | -2.800623000 | -0.555112000 | 0.128025000 |
| C | -3.398050000 | 0.474183000 | -0.280816000 |
| P | -0.624362000 | -2.929735000 | 0.431306000 |
| O | -2.808784000 | 1.545465000 | -0.640535000 |
| C | -4.897082000 | 0.467082000 | -0.355188000 |
| H | -5.301411000 | -0.503600000 | -0.063454000 |
| H | -5.295553000 | 1.246645000 | 0.301953000 |
| H | -5.213108000 | 0.711662000 | -1.374010000 |
| H | -1.563026000 | 1.451666000 | -0.390556000 |
| H | 0.022624000 | -3.389086000 | 1.593827000 |
| H | -1.853795000 | -3.612892000 | 0.528601000 |
| H | 0.035974000 | -3.713658000 | -0.533962000 |
| C | 1.382108000 | -0.812262000 | 0.123991000 |
| C | 2.266566000 | -0.651231000 | 1.159158000 |
| S | 2.234266000 | -1.209578000 | -1.343091000 |
| C | 3.631902000 | -0.835209000 | 0.774378000 |
| H | 1.955790000 | -0.389921000 | 2.168182000 |
| C | 3.780276000 | -1.141189000 | -0.548122000 |


| H | 4.469045000 | -0.742089000 | 1.461322000 |
| :---: | :---: | :---: | :---: |
| H | 4.691602000 | -1.332872000 | -1.102793000 |
| C | 1.051396000 | 3.021611000 | 1.246648000 |
| C | -0.000314000 | 2.154961000 | 1.261223000 |
| C | -0.272720000 | 1.535761000 | -0.011536000 |
| C | 0.622393000 | 1.994695000 | -0.959681000 |
| S | 1.758275000 | 3.126285000 | -0.336276000 |
| H | -0.586860000 | 1.957768000 | 2.156241000 |
| H | 0.683797000 | 1.711634000 | -2.006019000 |
| H | 1.456106000 | 3.617591000 | 2.056820000 |

## $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{MeTh})$

```
G
G
E}\mp@subsup{\textrm{ECSD}}{}{=-6651.807944
G=-6651.636807
```

| Pd | -0.466591000 | -0.754071000 | -0.069146000 |
| :--- | :---: | :---: | :---: |
| O | -2.647518000 | -0.903586000 | -0.264408000 |
| C | -3.395432000 | 0.035937000 | 0.111567000 |
| P | -0.202893000 | -3.063340000 | -0.211109000 |
| O | -2.975140000 | 1.168220000 | 0.520532000 |
| C | -4.883594000 | -0.160273000 | 0.078272000 |
| H | -5.322745000 | 0.542543000 | -0.637267000 |
| H | -5.140412000 | -1.181764000 | -0.207282000 |
| H | -5.306669000 | 0.072735000 | 1.060186000 |
| H | -1.715858000 | 1.252235000 | 0.326085000 |
| C | -0.418268000 | 1.405830000 | 0.055500000 |
| C | 0.326465000 | 2.067086000 | 1.035748000 |
| S | -0.110510000 | 2.164901000 | -1.501331000 |
| C | 1.097580000 | 3.147460000 | 0.537272000 |
| C | 0.964817000 | 3.315992000 | -0.818892000 |
| H | 1.720701000 | 3.783029000 | 1.162144000 |
| H | 0.305537000 | -3.701037000 | 0.937077000 |
| H | -1.307059000 | -3.892675000 | -0.498283000 |
| H | 0.723197000 | -3.526477000 | -1.165076000 |
| C | 1.520541000 | -0.734174000 | 0.168526000 |
| C | 2.257489000 | -1.071736000 | 1.277571000 |
| S | 2.575200000 | -0.284553000 | -1.139763000 |
| C | 3.668541000 | -0.949249000 | 1.083772000 |
| H | 1.805107000 | -1.389669000 | 2.215362000 |
| C | 3.999842000 | -0.537509000 | -0.176044000 |
| H | 4.404238000 | -1.162641000 | 1.854863000 |


| H | 4.984263000 | -0.367017000 | -0.596665000 |
| :--- | ---: | ---: | ---: |
| H | 1.438894000 | 4.069309000 | -1.439366000 |
| C | 0.292576000 | 1.682238000 | 2.476880000 |
| H | 1.229208000 | 1.183179000 | 2.760740000 |
| H | 0.178633000 | 2.560005000 | 3.124037000 |
| H | -0.527561000 | 0.983344000 | 2.678253000 |

## $\alpha-\mathrm{CMD}(\mathrm{Th} / \mathrm{EtTh})$

$\mathrm{G}_{\mathrm{DFT}}=-1881.745243$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.198527$
$\mathrm{E}_{\text {CCSD }}=-6691.024093$
$G=-6690.825566$

| Pd | -0.410953000 | -0.785898000 | -0.190148000 |
| :--- | :---: | :---: | :---: |
| O | -2.592564000 | -1.047420000 | -0.170548000 |
| C | -3.381731000 | -0.085452000 | 0.007911000 |
| P | -0.081005000 | -3.088328000 | -0.336506000 |
| O | -3.015251000 | 1.128605000 | 0.151088000 |
| C | -4.858205000 | -0.350953000 | 0.059679000 |
| H | -5.359112000 | 0.227316000 | -0.723120000 |
| H | -5.071870000 | -1.413184000 | -0.069996000 |
| H | -5.255921000 | -0.006459000 | 1.019527000 |
| H | -1.770693000 | 1.222334000 | 0.033177000 |
| C | -0.444684000 | 1.383192000 | -0.194293000 |
| C | 0.321647000 | 2.132701000 | 0.704312000 |
| S | -0.153541000 | 1.987260000 | -1.822935000 |
| C | 1.099060000 | 3.146622000 | 0.084633000 |
| C | 0.948689000 | 3.184274000 | -1.278184000 |
| H | 1.739020000 | 3.832049000 | 0.636506000 |
| H | 0.697171000 | -3.693670000 | 0.669330000 |
| H | -1.191840000 | -3.956902000 | -0.359295000 |
| H | 0.618591000 | -3.536751000 | -1.473052000 |
| C | 1.587042000 | -0.654088000 | -0.216448000 |
| C | 2.434702000 | -0.448565000 | -1.275462000 |
| S | 2.500932000 | -0.835550000 | 1.256983000 |
| C | 3.815123000 | -0.418323000 | -0.903970000 |
| H | 2.083663000 | -0.304815000 | -2.294646000 |
| C | 4.016107000 | -0.611550000 | 0.432995000 |
| H | 4.625336000 | -0.257053000 | -1.610368000 |
| H | 4.949385000 | -0.636330000 | 0.983726000 |
| H | 1.418679000 | 3.870136000 | -1.975310000 |
| C | 0.345350000 | 1.947193000 | 2.192983000 |
| H | 1.358030000 | 1.612968000 | 2.472031000 |


| H | 0.231881000 | 2.937342000 | 2.659441000 |
| :--- | ---: | ---: | :--- |
| C | -0.683278000 | 0.989640000 | 2.766860000 |
| H | -0.546668000 | -0.028334000 | 2.373596000 |
| H | -0.596533000 | 0.940321000 | 3.857497000 |
| H | -1.704906000 | 1.302295000 | 2.520181000 |

## $\alpha-\mathrm{CMD}(\mathrm{MeTh} / \mathrm{Th})$

|  | $\mathrm{G}_{\mathrm{DFT}}=-1842.486509$ |
| :---: | :---: |
|  | $\mathrm{G}_{\text {CORR DFT }}=0.171016$ |
|  | $\mathrm{E}_{\text {CCSD }}=-6651.805776$ |
|  | $\mathrm{G}=-6651.634760$ |


|  | - | 000 | -0.131003000 |
| :---: | :---: | :---: | :---: |
| O | 0461000 | -0.914021000 | 0 |
| C | -3.452267000 | -0.112422000 | 0.26 |
| P | -0.049326000 | -2.859652000 | -0.676207000 |
| O | -3.088010000 | 0.943887000 | . 882257000 |
| C | -4.927036000 | -0.387871000 | 0.212419000 |
| H | -5.414630000 | 0.393914000 | -0.379 |
|  | -5.129289000 | -1.362558000 | 0.234914000 |
|  | -5.349704000 | -0.340803000 | 1.220431000 |
| H | -1.844652000 | . 145581000 | . 6 |
| C | -0.583070000 | 1.467564000 | 0.372993000 |
| C | 0.272819000 | 2.006465000 | 1.330140000 |
| S | -0.475443000 | 2.463086000 | -1.071588000 |
| C | . 975570000 | 3.161238000 | 0.925776000 |
| , | 0.667509000 | .528274000 | -0.364953000 |
|  | 1.672826000 | 3.709116000 | . 552671000 |
|  | 0.630367000 | -3.612506000 | 0.301006000 |
|  | -1.100933000 | -3.743124000 | -0.997864000 |
|  | 0.808626000 | -3.066227000 | 1.773062000 |
| C | 1.508454000 | -0.518218000 | . 014308000 |
|  | 2.321822000 | -0.831756000 | 1.076529000 |
|  | 2.434800000 | 0.072674000 | -1.336290000 |
| C | 3.704473000 | -0.581759000 | 0.789388000 |
|  | 3.929554000 | -0.095778000 | -0.465889000 |
|  | 4.499060000 | -0.761592000 | 1.511560000 |
|  | 4.871755000 | 0.169238000 | -0.932007000 |
|  | 1.054436000 | 4.375884000 | -0.920547000 |
|  | 1.845438000 | -1.344239000 | 2.401111000 |
|  | 0.752656000 | -1.433342000 | 2.416975000 |
|  | 2.136899000 | -0.670769000 | 3.218229000 |
| H | 2.269521000 | $-2.330625000$ | 2.632523000 |

## $\beta-\mathrm{CMD}(\mathrm{MeTh} / \mathrm{Th})$

$G_{\text {DFT }}=-1842.479961$
$\mathrm{G}_{\text {CORR DFT }}=0.170864$
$\mathrm{E}_{\text {CCSD }}=-6651.801785$
$G=-6651.630921$

| Pd | -0.559889000 | 0.656016000 | 0.199300000 |
| :--- | :---: | :---: | :---: |
| O | -2.737590000 | 0.689057000 | 0.461218000 |
| C | -3.429124000 | -0.040236000 | -0.296195000 |
| P | -0.258946000 | 2.873098000 | 0.798885000 |
| O | -2.936955000 | -0.897031000 | -1.104002000 |
| C | -4.924264000 | 0.078597000 | -0.262994000 |
| H | -5.355127000 | -0.875510000 | 0.057185000 |
| H | -5.241609000 | 0.872234000 | 0.415378000 |
| H | -5.297515000 | 0.277905000 | -1.272241000 |
| H | -1.712941000 | -1.064051000 | -0.821018000 |
| H | 0.336413000 | 3.699509000 | -0.173506000 |
| H | -1.359293000 | 3.670630000 | 1.176690000 |
| H | 0.614327000 | 3.108338000 | 1.877757000 |
| C | 1.429915000 | 0.682644000 | -0.027319000 |
| C | 2.182127000 | 1.064296000 | -1.111423000 |
| S | 2.435143000 | 0.091771000 | 1.264874000 |
| C | 3.584842000 | 0.862402000 | -0.890507000 |
| C | 3.882901000 | 0.346837000 | 0.337477000 |
| H | 4.340087000 | 1.098282000 | -1.638255000 |
| H | 4.854498000 | 0.107932000 | 0.754874000 |
| C | 1.141548000 | -3.091402000 | -0.833243000 |
| C | 0.503986000 | -1.976829000 | -1.287298000 |
| C | -0.484908000 | -1.454809000 | -0.380056000 |
| C | -0.534857000 | -2.230922000 | 0.763933000 |
| S | 0.570218000 | -3.554526000 | 0.741610000 |
| H | 0.727764000 | -1.524156000 | -2.250632000 |
| H | -1.193573000 | -2.105373000 | 1.619276000 |
| H | 1.915773000 | -3.676648000 | -1.316557000 |
| C | 1.627482000 | 1.594074000 | -2.397936000 |
| H | 1.923922000 | 0.966389000 | -3.248927000 |
| H | 0.531740000 | 1.621167000 | -2.370074000 |
| H | 1.987313000 | 2.610104000 | -2.609148000 |

## $\alpha-$ CMD (MeTh/MeTh)

| $\mathrm{G}_{\text {DFT }}=-1881.752337$ |  |  |  |
| :--- | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.196253$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-6691.028850$ |  |  |  |
| $\mathrm{G}=-6690.832597$ |  |  |  |
| -------------- |  |  |  |
|  |  |  |  |
| Pd | 0.475714000 | 0.734970000 | 0.057275000 |
| O | 2.644157000 | 1.090608000 | 0.081697000 |
| C | 3.472998000 | 0.188410000 | -0.202191000 |
| P | 0.012743000 | 2.994563000 | 0.372104000 |
| O | 3.157233000 | -1.014567000 | -0.483710000 |
| C | 4.937088000 | 0.521699000 | -0.219563000 |
| H | 5.468479000 | -0.132276000 | 0.478906000 |
| H | 5.341541000 | 0.324024000 | -1.217412000 |
| H | 5.106627000 | 1.566255000 | 0.047157000 |
| H | 1.899598000 | -1.171155000 | -0.387009000 |
| C | 0.593994000 | -1.413698000 | -0.211492000 |
| C | 0.300930000 | -2.206392000 | 0.903275000 |
| S | -0.226507000 | -2.084999000 | -1.612191000 |
| C | -0.547579000 | -3.305492000 | 0.620234000 |
| C | -0.916418000 | -3.364680000 | -0.701456000 |
| H | -0.865527000 | -4.031051000 | 1.365442000 |
| H | -0.792238000 | 3.309739000 | 1.483706000 |
| H | 1.056541000 | 3.929374000 | 0.537583000 |
| H | -0.734265000 | 3.624467000 | -0.642648000 |
| C | -1.522164000 | 0.553232000 | 0.052271000 |
| C | -2.417946000 | 0.775618000 | -0.966355000 |
| S | -2.344194000 | 0.088648000 | 1.516982000 |
| C | -3.773960000 | 0.555470000 | -0.553158000 |
| C | -3.902291000 | 0.184924000 | 0.753619000 |
| H | -4.621474000 | 0.674765000 | -1.226044000 |
| H | -4.804859000 | -0.038909000 | 1.310800000 |
| H | -1.542185000 | -4.111950000 | -1.178225000 |
| C | -2.055486000 | 1.173253000 | -2.364163000 |
| H | -2.563710000 | 2.098870000 | -2.666071000 |
| H | -0.975001000 | 1.329209000 | -2.464249000 |
| H | -2.344142000 | 0.396869000 | -3.085509000 |
| C | 0.844273000 | -1.92922000 | 2.267596000 |
| H | 0.070480000 | -1.489223000 | 2.911802000 |
| H | 1.185166000 | -2.849739000 | 2.756239000 |
| H | 1.680441000 | -1.221807000 | 2.227074000 |
|  |  |  |  |

## $\alpha-\mathrm{CMD}(\mathrm{MeTh} / \mathrm{EtTh})$

## $G_{\text {DFT }}=-1921.006625$

$\mathrm{G}_{\text {CORR DFT }}=0.225029$
$\mathrm{E}_{\text {CCSD }}=-6730.245468$
$G=-6730.020439$

| Pd | -0.428990000 | -0.787133000 | -0.020561000 |
| :--- | :---: | :---: | :---: |
| O | -2.590345000 | -1.195057000 | -0.100476000 |
| C | -3.443433000 | -0.287357000 | -0.260790000 |
| P | 0.082131000 | -3.045494000 | 0.203910000 |
| O | -3.160411000 | 0.952714000 | -0.377763000 |
| C | -4.898531000 | -0.650378000 | -0.320808000 |
| H | -5.038985000 | -1.728309000 | -0.224864000 |
| H | -5.435244000 | -0.133476000 | 0.481100000 |
| H | -5.321774000 | -0.302594000 | -1.268400000 |
| H | -1.928134000 | 1.122471000 | -0.312860000 |
| C | -0.587230000 | 1.364446000 | -0.312013000 |
| C | -0.053716000 | 2.256502000 | 0.623459000 |
| S | -0.019593000 | 1.826831000 | -1.914531000 |
| C | 0.779976000 | 3.254227000 | 0.051982000 |
| C | 0.895446000 | 3.146077000 | -1.310387000 |
| H | 1.266906000 | 4.033318000 | 0.635228000 |
| H | 0.853596000 | -3.402937000 | 1.326427000 |
| H | -0.943328000 | -4.011680000 | 0.277626000 |
| H | 0.881379000 | -3.600337000 | -0.814730000 |
| C | 1.564129000 | -0.557600000 | 0.072344000 |
| C | 2.514276000 | -0.679674000 | -0.913741000 |
| S | 2.304595000 | -0.203844000 | 1.611435000 |
| C | 3.842760000 | -0.460587000 | -0.41628000 |
| C | 3.899055000 | -0.197516000 | 0.920773000 |
| H | 4.724222000 | -0.506652000 | -1.053592000 |
| H | 4.767453000 | 0.001196000 | 1.538487000 |
| H | 1.457057000 | 3.790537000 | -1.978631000 |
| C | -0.318419000 | 2.241045000 | 2.101351000 |
| H | 0.649058000 | 2.120117000 | 2.614483000 |
| H | -0.668638000 | 3.244185000 | 2.389245000 |
| C | -1.299427000 | 1.197974000 | 2.604763000 |
| H | -0.949467000 | 0.177897000 | 2.387526000 |
| H | -1.427594000 | 1.283148000 | 3.689155000 |
| H | -2.284565000 | 1.314370000 | 2.137542000 |
| C | 2.242671000 | -1.005621000 | -2.350445000 |
| H | 1.180667000 | -1.218432000 | -2.516369000 |
| H | 2.517125000 | -0.171091000 | -3.009558000 |
| H | 2.822529000 | -1.879474000 | -2.676738000 |
|  |  |  |  |

## $\alpha-$ CMD (EtTh/Th)

$\mathrm{G}_{\mathrm{DFT}}=-1881.741094$
$\mathrm{G}_{\text {CORR DFT }}=0.199148$
$\mathrm{E}_{\mathrm{CCSD}}=-6691.021693$
$\mathrm{G}=-6690.822545$

|  |  |  |  |
| :--- | :---: | :---: | :---: |
| Pd | 0.667606000 | -0.654245000 | -0.032597000 |
| O | 2.827318000 | -0.839307000 | 0.317556000 |
| C | 3.629669000 | 0.078804000 | 0.009970000 |
| P | 0.312797000 | -2.901050000 | 0.428017000 |
| O | 3.279387000 | 1.208731000 | -0.466989000 |
| C | 5.101412000 | -0.140493000 | 0.208890000 |
| H | 5.489260000 | 0.611896000 | 0.902982000 |
| H | 5.301945000 | -1.140236000 | 0.597677000 |
| H | 5.622591000 | 0.000228000 | -0.743211000 |
| H | 2.018326000 | 1.299907000 | -0.482212000 |
| C | 0.687358000 | 1.488401000 | -0.437336000 |
| C | 0.025851000 | 1.981947000 | -1.558321000 |
| S | 0.140801000 | 2.403143000 | 0.959393000 |
| C | -0.881286000 | 3.033518000 | -1.307481000 |
| C | -0.924597000 | 3.370690000 | 0.026392000 |
| H | -1.472704000 | 3.532210000 | -2.069674000 |
| H | -0.338761000 | -3.650141000 | -0.570034000 |
| H | 1.404145000 | -3.745037000 | 0.721428000 |
| H | -0.529241000 | -3.178200000 | 1.522270000 |
| C | -1.319231000 | -0.639949000 | -0.328370000 |
| C | -2.345597000 | -0.534197000 | 0.580036000 |
| S | -1.931517000 | -0.866185000 | -1.944933000 |
| C | -3.633831000 | -0.617558000 | -0.049713000 |
| C | -3.580225000 | -0.799983000 | -1.400256000 |
| H | -4.570045000 | -0.551401000 | 0.501805000 |
| H | -4.398614000 | -0.893571000 | -2.105075000 |
| H | -1.522429000 | 4.147351000 | 0.492103000 |
| C | -2.175162000 | -0.372368000 | 2.064838000 |
| H | -2.539331000 | -1.278043000 | 2.576489000 |
| H | -1.101635000 | -0.301429000 | 2.290361000 |
| C | -2.901593000 | 0.843866000 | 2.630399000 |
| H | -2.547949000 | 1.764854000 | 2.149407000 |
| H | -3.984137000 | 0.777847000 | 2.466584000 |
| H | -2.735253000 | 0.937489000 | 3.709777000 |
| H | 0.203212000 | 1.574523000 | -2.551658000 |
|  |  |  |  |

## $\beta-\mathbf{C M D}(E t T h / T h)$

| $\mathrm{G}_{\text {DFT }}=-1881.734708$ |  |  |  |
| :--- | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.197863$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-6691.017746$ |  |  |  |
| $\mathrm{G}=-6690.819883$ |  |  |  |
| -------------- |  |  |  |
|  |  |  |  |
| Pd | 0.517525000 | -0.710470000 | 0.107665000 |
| O | 2.675033000 | -0.857762000 | 0.480854000 |
| C | 3.417891000 | -0.283547000 | -0.360158000 |
| P | 0.120643000 | -2.910684000 | 0.725040000 |
| O | 2.986280000 | 0.497348000 | -1.270403000 |
| C | 4.900037000 | -0.510013000 | -0.300465000 |
| H | 5.254935000 | -0.862226000 | -1.273923000 |
| H | 5.402657000 | 0.441545000 | -0.099444000 |
| H | 5.158026000 | -1.234017000 | 0.474199000 |
| H | 1.771039000 | 0.826382000 | -0.964705000 |
| H | -0.373970000 | -3.770094000 | -0.274586000 |
| H | 1.191311000 | -3.681546000 | 1.222215000 |
| H | -0.844306000 | -3.128184000 | 1.726758000 |
| C | -1.446660000 | -0.627255000 | -0.279682000 |
| C | -2.474836000 | -0.028863000 | 0.410840000 |
| S | -2.003049000 | -1.278308000 | -1.796985000 |
| C | -3.713806000 | -0.103448000 | -0.306707000 |
| C | -3.628135000 | -0.739500000 | -1.511838000 |
| H | -4.640880000 | 0.315452000 | 0.081015000 |
| H | -4.412126000 | -0.936803000 | -2.233876000 |
| C | -0.669365000 | 3.292145000 | -0.928429000 |
| C | -0.276181000 | 2.06320000 | -1.363708000 |
| C | 0.652261000 | 1.40028000 | -0.485433000 |
| C | 0.907216000 | 2.190726000 | 0.620961000 |
| S | 0.071564000 | 3.698887000 | 0.591139000 |
| H | -0.636583000 | 1.625659000 | -2.291934000 |
| H | 1.583722000 | 1.97565000 | 1.444117000 |
| H | -1.350319000 | 3.993332000 | -1.397504000 |
| C | -2.346194000 | 0.693805000 | 1.724891000 |
| H | -1.752701000 | 1.609546000 | 1.575348000 |
| H | -3.345300000 | 1.028926000 | 2.035794000 |
| C | -1.715683000 | -0.128069000 | 2.841798000 |
| H | -2.283791000 | -1.049210000 | 3.025632000 |
| H | -0.687053000 | -0.415259000 | 2.581999000 |
| H | -1.676470000 | 0.440332000 | 3.778220000 |
|  |  |  |  |

## $\alpha-\operatorname{CMD}(E t T h / M e T h)$

| $\mathrm{G}_{\text {DFT }}=-1921.008151$ |  |  |  |
| :--- | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.222999$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-6730.24549$ |  |  |  |
| $\mathrm{G}=-6730.022491$ |  |  |  |
| --------------- |  |  |  |
|  |  |  |  |
| Pd | 0.594636000 | 0.732837000 | 0.086569000 |
| O | 2.741555000 | 1.128876000 | -0.162843000 |
| C | 3.570926000 | 0.216260000 | -0.407720000 |
| P | 0.130853000 | 3.000716000 | 0.345508000 |
| O | 3.266806000 | -1.015773000 | -0.536678000 |
| C | 5.021414000 | 0.570954000 | -0.565017000 |
| H | 5.362573000 | 0.270631000 | -1.560849000 |
| H | 5.182159000 | 1.641436000 | -0.426413000 |
| H | 5.614944000 | 0.008164000 | 0.162315000 |
| H | 2.023762000 | -1.178594000 | -0.365519000 |
| C | 0.723671000 | -1.421063000 | -0.130773000 |
| C | 0.473413000 | -2.201062000 | 1.002526000 |
| S | -0.156710000 | -2.101644000 | -1.489794000 |
| C | -0.395861000 | -3.295531000 | 0.766827000 |
| C | -0.821183000 | -3.364769000 | -0.537295000 |
| H | -0.687543000 | -4.011345000 | 1.531965000 |
| H | -0.550552000 | 3.366280000 | 1.522492000 |
| H | 1.171987000 | 3.952807000 | 0.343623000 |
| H | -0.733554000 | 3.569424000 | -0.610406000 |
| C | -1.384163000 | 0.524602000 | 0.358727000 |
| C | -2.419089000 | 0.694370000 | -0.530748000 |
| S | -1.985328000 | 0.177248000 | 1.958035000 |
| C | -3.701341000 | 0.524993000 | 0.092097000 |
| C | -3.637630000 | 0.247402000 | 1.426340000 |
| H | -4.641897000 | 0.615097000 | -0.448549000 |
| H | -4.449953000 | 0.072907000 | 2.122715000 |
| H | -1.472453000 | -4.111579000 | -0.979417000 |
| C | 1.082263000 | -1.916519000 | 2.337009000 |
| H | 1.471857000 | -2.830633000 | 2.800931000 |
| H | 1.897793000 | -1.188786000 | 2.254043000 |
| C | -2.256924000 | 1.028169000 | -1.987805000 |
| H | -2.629479000 | 2.048158000 | -2.176558000 |
| H | -1.183824000 | 1.044769000 | -2.226734000 |
| C | -2.977178000 | 0.056365000 | -2.917169000 |
| H | -2.616897000 | -0.968378000 | -2.761398000 |
| H | -4.059750000 | 0.058935000 | -2.740901000 |
| H | -2.813058000 | 0.319336000 | -3.968505000 |
| H | 0.333632000 | -1.499396000 | 3.024655000 |
|  |  |  |  |

## $\alpha-\operatorname{CMD}(E t T h / E t T h)$

| $\mathrm{G}_{\text {DFT }}=-1960.263390$ |  |  |  |
| :---: | :---: | :---: | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.251516$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-6769.462795$ |  |  |  |
| $\mathrm{G}=-6769.211279$ |  |  |  |
| Pd | -0.526181000 | -0.788012000 | -0.307959000 |
| O | -2.606627000 | -1.485029000 | -0.155718000 |
| C | -3.383472000 | -0.927042000 | 0.663851000 |
| P | 0.241715000 | -2.869026000 | $-1.005508000$ |
| O | -3.093473000 | 0.126601000 | 1.320385000 |
| C | -4.748068000 | -1.512357000 | 0.886453000 |
| H | -5.499936000 | -0.823749000 | 0.486473000 |
| H | -4.846907000 | -2.481793000 | 0.395052000 |
| H | -4.938334000 | -1.610983000 | 1.959227000 |
| H | -2.028731000 | 0.648326000 | 0.802600000 |
| C | -1.059741000 | 1.260946000 | 0.133579000 |
| C | -0.322196000 | 2.198745000 | 0.858958000 |
| S | -1.644910000 | 2.015234000 | $-1.348001000$ |
| C | -0.253187000 | 3.472428000 | 0.237938000 |
| C | -0.916282000 | 3.520337000 | -0.963281000 |
| H | 0.260033000 | 4.331024000 | 0.664350000 |
| H | 1.179332000 | -3.527859000 | -0.184860000 |
| H | -0.672153000 | -3.918061000 | -1.238317000 |
| H | 0.953171000 | -2.872576000 | -2.220478000 |
| C | 1.399094000 | -0.241342000 | -0.440283000 |
| C | 2.455073000 | -0.521273000 | 0.396187000 |
| S | 1.915498000 | 0.705534000 | -1.807194000 |
| C | 3.684948000 | 0.048002000 | -0.077810000 |
| C | 3.560778000 | 0.736051000 | -1.249366000 |
| H | 4.629434000 | -0.049040000 | 0.455202000 |
| H | 4.326291000 | 1.256393000 | -1.813801000 |
| H | -1.009994000 | 4.370116000 | -1.631338000 |
| C | 0.277459000 | 1.903666000 | 2.200544000 |
| H | -0.323516000 | 2.407042000 | 2.973905000 |
| H | 0.192168000 | 0.825908000 | 2.394434000 |
| C | 1.731171000 | 2.350009000 | 2.323513000 |
| H | 1.827984000 | 3.438119000 | 2.229841000 |
| H | 2.144729000 | 2.065630000 | 3.297884000 |
| H | 2.346995000 | 1.887484000 | 1.540739000 |
| C | 2.361318000 | -1.286448000 | 1.686479000 |
| H | 1.326855000 | -1.635244000 | 1.818764000 |
| H | 2.556328000 | -0.602274000 | 2.528585000 |
| C | 3.327050000 | -2.464243000 | 1.772748000 |


| H | 3.160844000 | -3.176663000 | 0.953620000 |
| :--- | :--- | :--- | :--- |
| H | 4.370556000 | -2.133344000 | 1.706248000 |
| H | 3.211166000 | -3.004215000 | 2.719287000 |

## Annex 3.6 Cross-coupling of a thienyl fragment with other thiophene-based substrates

## 2Br3EtTh (2-bromo-3-ethylthiophene)

$\mathrm{G}_{\mathrm{DFT}}=-643.854882$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.077404$
$\mathrm{E}_{\text {CCSD }}=-3202.524675$
$G=-3202.447271$

| C | -0.057077000 | -0.368882000 | 0.078060000 |
| :--- | :---: | :---: | :---: |
| C | -0.972052000 | 0.619951000 | 0.329795000 |
| S | -0.772712000 | -1.919766000 | -0.229339000 |
| C | -2.298803000 | 0.090189000 | 0.261801000 |
| C | -2.351157000 | -1.243500000 | -0.023730000 |
| H | -3.182230000 | 0.702059000 | 0.429386000 |
| H | -3.223284000 | -1.879074000 | -0.121892000 |
| C | -0.663231000 | 2.063428000 | 0.577502000 |
| H | -1.402370000 | 2.469261000 | 1.280821000 |
| H | 0.317077000 | 2.155069000 | 1.062899000 |
| C | -0.679833000 | 2.875353000 | -0.716140000 |
| H | -1.658535000 | 2.809405000 | -1.207084000 |
| H | -0.467622000 | 3.932394000 | -0.522342000 |
| H | 0.072589000 | 2.500049000 | -1.420611000 |
| Br | 1.829734000 | -0.176918000 | 0.032129000 |

## Int-4

$\mathrm{G}_{\mathrm{DFT}}=-1250.436876$
$\mathrm{G}_{\text {CORR DFT }}=0.090706$
$\mathrm{E}_{\text {CCSD }}=-6060.479804$
$\mathrm{G}=-6060.389098$

| Pd | -0.543546000 | 0.391847000 | 0.038181000 |
| :--- | :---: | :---: | :---: |
| C | 1.347922000 | -0.187440000 | 0.217213000 |
| C | 2.242911000 | -0.050577000 | 1.248197000 |
| S | 2.014785000 | -1.160360000 | -1.062161000 |
| C | 3.460207000 | -0.764780000 | 1.025647000 |
| H | 2.038672000 | 0.528157000 | 2.145893000 |
| C | 3.488674000 | -1.410548000 | -0.177640000 |
| H | 4.279688000 | -0.795148000 | 1.738254000 |
| H | 4.277054000 | -2.025176000 | -0.596844000 |
| O | -1.712524000 | -1.453188000 | 0.266788000 |
| O | -2.763072000 | 0.453683000 | -0.066816000 |


| C | -2.795789000 | -0.804029000 | 0.109991000 |
| :--- | :---: | :--- | :---: |
| C | -4.104344000 | -1.528473000 | 0.102386000 |
| H | -4.372391000 | -1.759899000 | -0.934761000 |
| H | -4.032681000 | -2.468316000 | 0.654660000 |
| H | -4.894191000 | -0.898472000 | 0.519321000 |
| P | 0.476301000 | 2.376286000 | -0.266471000 |
| H | 1.218992000 | 2.868236000 | 0.820343000 |
| H | 1.426523000 | 2.444594000 | -1.298793000 |
| H | -0.352332000 | 3.473627000 | -0.567316000 |

## Int-18

```
G
G
E}\mp@subsup{\textrm{ECSD}}{\mathrm{ C -6138.918688}}{
G=-6138.774899
```

|  |  |  |  |
| :--- | :---: | :---: | :---: |
| Pd | -0.725043000 | -0.453503000 | -0.127770000 |
| C | 1.190201000 | -0.088202000 | 0.276520000 |
| C | 2.069117000 | 0.717624000 | -0.406436000 |
| S | 1.876086000 | -0.679782000 | 1.764139000 |
| C | 3.300410000 | 0.879228000 | 0.308528000 |
| C | 3.351935000 | 0.190412000 | 1.485871000 |
| H | 4.117907000 | 1.496582000 | -0.060222000 |
| H | 4.158732000 | 0.142237000 | 2.208284000 |
| O | -1.836418000 | 1.148234000 | 0.892486000 |
| O | -2.946624000 | -0.369045000 | -0.255813000 |
| C | -2.938826000 | 0.670202000 | 0.474354000 |
| C | -4.227013000 | 1.319670000 | 0.871287000 |
| H | -4.566879000 | 0.879802000 | 1.815831000 |
| H | -4.086975000 | 2.391704000 | 1.030123000 |
| H | -4.997948000 | 1.141541000 | 0.117641000 |
| P | 0.241862000 | -2.162237000 | -1.229304000 |
| H | 1.154016000 | -1.825397000 | -2.244136000 |
| H | 1.012514000 | -3.047675000 | -0.456950000 |
| H | -0.617823000 | -3.049761000 | -1.904190000 |
| C | 1.770416000 | 1.430946000 | -1.692454000 |
| H | 2.677364000 | 1.460808000 | -2.313213000 |
| H | 1.014917000 | 0.869974000 | -2.260446000 |
| C | 1.266294000 | 2.852038000 | -1.449645000 |
| H | 0.341380000 | 2.835148000 | -0.859457000 |
| H | 2.005740000 | 3.439489000 | -0.891058000 |
| H | 1.062876000 | 3.371704000 | -2.392987000 |

## $\alpha$-CMD

| $\mathrm{G}_{\text {DFT }}=-1815.744609$ |  |  |  |
| :--- | :---: | :--- | :---: |
| $\mathrm{G}_{\text {CORR DFT }}=0.132665$ |  |  |  |
| $\mathrm{E}_{\text {CCSD }}=-9184.541396$ |  |  |  |
| $\mathrm{G}=-9184.408731$ |  |  |  |
| ------------ |  |  |  |
|  |  |  |  |
| Pd | 1.605185000 | 0.216097000 | -0.055386000 |
| O | 2.989933000 | -1.447785000 | -0.399837000 |
| C | 2.826526000 | -2.563982000 | 0.157475000 |
| P | 3.131878000 | 1.779007000 | -0.822414000 |
| O | 1.819645000 | -2.865351000 | 0.880094000 |
| C | 3.863661000 | -3.631959000 | -0.033704000 |
| H | 4.735347000 | -3.244593000 | -0.563810000 |
| H | 4.161724000 | -4.035350000 | 0.938566000 |
| H | 3.425755000 | -4.456913000 | -0.605413000 |
| H | 0.954787000 | -1.940338000 | 0.824849000 |
| C | -0.030029000 | -1.040836000 | 0.679960000 |
| C | -0.778158000 | -0.593037000 | 1.766224000 |
| S | -1.132741000 | -1.401984000 | -0.640416000 |
| C | -2.171254000 | -0.530739000 | 1.564111000 |
| C | -2.501312000 | -0.939336000 | 0.291533000 |
| H | -2.902021000 | -0.206460000 | 2.298341000 |
| H | -0.304590000 | -0.303625000 | 2.701923000 |
| Br | -4.249478000 | -0.985771000 | -0.430469000 |
| H | 3.576267000 | 2.721477000 | 0.123827000 |
| H | 4.358853000 | 1.345142000 | -1.364409000 |
| H | 2.681838000 | 2.645058000 | -1.835848000 |
| C | 0.448571000 | 1.820636000 | 0.255361000 |
| C | 0.492086000 | 2.727086000 | 1.285503000 |
| S | -0.836719000 | 2.216770000 | -0.848249000 |
| C | -0.522425000 | 3.730292000 | 1.200304000 |
| H | 1.217422000 | 2.671555000 | 2.094717000 |
| C | -1.319881000 | 3.591335000 | 0.099621000 |
| H | -0.649640000 | 4.523262000 | 1.932537000 |
| H | -2.152639000 | 4.208948000 | -0.216665000 |
|  |  |  |  |
|  |  |  |  |

## $\beta$-CMD

$G_{\text {DFT }}=-1815.738077$
$\mathrm{G}_{\text {CORR DFT }}=0.131771$
$\mathrm{E}_{\text {CCSD }}=-9184.536345$
$G=-9184.404574$

| Pd | -1.618850000 | 0.315569000 | 0.101338000 |
| :--- | :---: | :---: | :---: |
| O | -3.278127000 | -1.111821000 | 0.081444000 |
| C | -3.127288000 | -2.219055000 | -0.495904000 |
| P | -3.013215000 | 2.144941000 | 0.337066000 |
| O | -2.014979000 | -2.633830000 | -0.966418000 |
| C | -4.308206000 | -3.129346000 | -0.655790000 |
| H | -4.474373000 | -3.322179000 | -1.720430000 |
| H | -4.092492000 | -4.092871000 | -0.183826000 |
| H | -5.205119000 | -2.690976000 | -0.215430000 |
| H | -1.097346000 | -1.881503000 | -0.582742000 |
| H | -2.910241000 | 3.154822000 | -0.637453000 |
| H | -4.407841000 | 1.943270000 | 0.366725000 |
| H | -2.830394000 | 2.911321000 | 1.502739000 |
| C | -0.144772000 | 1.664871000 | 0.153764000 |
| C | 0.623294000 | 2.057372000 | 1.219479000 |
| S | 0.409295000 | 2.425374000 | -1.310998000 |
| C | 1.674581000 | 2.956221000 | 0.857155000 |
| H | 0.461909000 | 1.696325000 | 2.232808000 |
| C | 1.692968000 | 3.249816000 | -0.476551000 |
| H | 2.388419000 | 3.366055000 | 1.566784000 |
| H | 2.369006000 | 3.900912000 | -1.018677000 |
| C | 2.290998000 | -1.128201000 | 0.037805000 |
| C | 1.180290000 | -0.967144000 | -0.730025000 |
| C | -0.039080000 | -1.219766000 | -0.009931000 |
| C | 0.235255000 | -1.576738000 | 1.297444000 |
| S | 1.920992000 | -1.603978000 | 1.672974000 |
| H | 1.225005000 | -0.663357000 | -1.772482000 |
| H | -0.477544000 | -1.843644000 | 2.073426000 |
| Br | 4.094525000 | -0.870679000 | -0.492157000 |

## $\gamma$-CMD

$G_{\text {DFT }}=-1815.741028$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.132657$
$\mathrm{E}_{\text {CCSD }}=-9184.540316$
$\mathrm{G}=-9184.407659$

| Pd | -0.102985000 | -1.112923000 | 0.015860000 |
| :--- | :--- | :--- | :---: |
| O | -2.167737000 | -1.816738000 | 0.162769000 |
| C | -2.996279000 | -1.210661000 | 0.893080000 |
| P | 0.524589000 | -3.011638000 | -1.134605000 |
| O | -2.729078000 | -0.158628000 | 1.557636000 |


| C | -4.396530000 | -1.742172000 | 0.996078000 |
| :--- | :---: | :---: | :---: |
| H | -5.091656000 | -1.002060000 | 0.586459000 |
| H | -4.501866000 | -2.683103000 | 0.453533000 |
| H | -4.659155000 | -1.883978000 | 2.048752000 |
| H | -1.532801000 | 0.247254000 | 1.280932000 |
| H | 1.540368000 | -3.800595000 | -0.563877000 |
| H | -0.457614000 | -3.985319000 | -1.403513000 |
| H | 1.062782000 | -2.805544000 | -2.417591000 |
| C | 1.808559000 | -0.562690000 | -0.202368000 |
| C | 2.361361000 | 0.293390000 | -1.119581000 |
| S | 3.021081000 | -1.125496000 | 0.913832000 |
| C | 3.759298000 | 0.513836000 | -0.915858000 |
| H | 1.784671000 | 0.771766000 | -1.908767000 |
| C | 4.263428000 | -0.182381000 | 0.145804000 |
| H | 4.363253000 | 1.167196000 | -1.540023000 |
| H | 5.280090000 | -0.205420000 | 0.521021000 |
| C | 1.062837000 | 2.478618000 | 1.921354000 |
| C | 0.515668000 | 1.239783000 | 2.060876000 |
| C | -0.385718000 | 0.853896000 | 1.005071000 |
| C | -0.469735000 | 1.889958000 | 0.097692000 |
| S | 0.499218000 | 3.267331000 | 0.477767000 |
| H | 0.749317000 | 0.589247000 | 2.900325000 |
| H | 1.763568000 | 2.992090000 | 2.570109000 |
| Br | -1.534859000 | 1.916331000 | -1.473129000 |

## $\alpha-\mathrm{CMD}(\mathrm{Et} / 2 \mathrm{Br} 3 \mathrm{EtTh})$

$G_{\text {DFT }}=-1972.785874$
$\mathrm{G}_{\text {CORR DFT }}=0.238445$
$\mathrm{E}_{\text {CCSD }}=-9341.419651$
$G=-9341.181206$

| Pd | 1.776904000 | -0.026191000 | -0.272229000 |
| :--- | :---: | :--- | :---: |
| O | 3.293087000 | -1.608236000 | -0.103766000 |
| C | 3.132091000 | -2.606486000 | 0.642473000 |
| P | 3.275217000 | 1.438451000 | -1.271226000 |
| O | 2.063386000 | -2.848862000 | 1.298433000 |
| C | 4.248355000 | -3.598603000 | 0.789418000 |
| H | 4.494789000 | -3.717230000 | 1.849098000 |
| H | 3.913819000 | -4.575214000 | 0.424980000 |
| H | 5.132469000 | -3.281402000 | 0.233951000 |
| H | 1.176521000 | -2.024719000 | 0.991571000 |
| C | 0.163762000 | -1.210125000 | 0.600890000 |


| C | -0.653076000 | -0.554315000 | 1.515945000 |
| :--- | :---: | :---: | :---: |
| S | -0.858438000 | -1.879200000 | -0.659835000 |
| C | -2.041969000 | -0.558352000 | 1.248719000 |
| C | -2.280579000 | -1.252084000 | 0.078859000 |
| H | 3.541794000 | 2.633037000 | -0.574933000 |
| H | 4.586086000 | 1.012246000 | -1.569574000 |
| H | 2.880157000 | 1.968222000 | -2.514010000 |
| C | 0.500413000 | 1.514900000 | -0.474201000 |
| C | 0.375940000 | 2.651532000 | 0.289702000 |
| S | -0.579822000 | 1.555232000 | -1.841911000 |
| C | -0.600809000 | 3.556700000 | -0.244588000 |
| C | -1.197647000 | 3.114198000 | -1.388807000 |
| H | -0.846448000 | 4.509102000 | 0.222780000 |
| H | -1.965478000 | 3.595988000 | -1.983557000 |
| C | 1.136975000 | 2.929607000 | 1.555916000 |
| H | 1.756645000 | 3.831503000 | 1.428602000 |
| H | 1.833851000 | 2.099336000 | 1.741543000 |
| C | 0.229049000 | 3.117981000 | 2.768363000 |
| H | -0.451204000 | 3.967728000 | 2.630807000 |
| H | -0.391524000 | 2.227879000 | 2.937526000 |
| H | 0.812170000 | 3.302107000 | 3.677765000 |
| H | -0.238084000 | -0.056054000 | 2.392832000 |
| C | -3.068796000 | 0.156320000 | 2.071143000 |
| H | -3.991671000 | -0.437502000 | 2.118703000 |
| H | -2.697316000 | 0.242879000 | 3.101018000 |
| C | -3.370139000 | 1.544802000 | 1.509313000 |
| H | -2.455966000 | 2.151130000 | 1.451853000 |
| H | -3.777157000 | 1.475765000 | 0.492469000 |
| H | -4.098689000 | 2.074529000 | 2.133070000 |
| Br | -3.981761000 | -1.524785000 | -0.711539000 |

## $\beta-\mathrm{CMD}(\mathrm{Et} / 2 \mathrm{Br} 3 \mathrm{EtTh})$

$\mathrm{G}_{\mathrm{DFT}}=-1972.777791$
$\mathrm{G}_{\text {CORR DFT }}=0.239176$
$\mathrm{E}_{\mathrm{CCSD}}=-9341.415580$
$\mathrm{G}=-9341.176404$

| Pd | -1.593143000 | 0.397908000 | 0.089389000 |
| :--- | :---: | :---: | :---: |
| O | -1.997559000 | 2.541427000 | 0.332566000 |
| C | -1.585636000 | 3.332023000 | -0.555677000 |
| P | -3.465482000 | -0.224745000 | 1.288948000 |
| O | -0.821067000 | 2.985755000 | -1.516753000 |
| C | -1.974596000 | 4.778765000 | -0.481918000 |


| H | -2.260097000 | 5.143568000 | -1.472298000 |
| :--- | :---: | :---: | :---: |
| H | -2.787110000 | 4.931559000 | 0.230510000 |
| H | -1.102173000 | 5.358700000 | -0.160191000 |
| H | -0.375239000 | 1.811924000 | -1.292757000 |
| H | -4.306826000 | 0.770830000 | 1.826763000 |
| H | -4.399557000 | -1.034926000 | 0.617336000 |
| H | -3.225507000 | -1.015721000 | 2.428320000 |
| C | -1.396148000 | -1.592817000 | -0.121828000 |
| C | -0.787723000 | -2.533025000 | 0.673221000 |
| S | -2.093627000 | -2.328142000 | -1.543099000 |
| C | -0.862332000 | -3.850137000 | 0.105245000 |
| C | -1.529928000 | -3.906759000 | -1.082010000 |
| H | -0.430815000 | -4.725225000 | 0.588968000 |
| H | -1.737049000 | -4.769546000 | -1.704784000 |
| C | 2.572046000 | 0.236460000 | -0.518306000 |
| C | 1.491258000 | 0.977682000 | -0.128459000 |
| C | 0.339673000 | 0.711628000 | -0.969390000 |
| C | 0.646636000 | -0.194637000 | -1.962742000 |
| S | 2.264841000 | -0.775906000 | -1.901759000 |
| H | -0.011819000 | -0.578632000 | -2.735644000 |
| C | -0.086746000 | -2.262339000 | 1.972786000 |
| H | -0.466100000 | -2.952835000 | 2.741778000 |
| H | -0.334005000 | -1.247435000 | 2.313802000 |
| C | 1.428508000 | -2.408868000 | 1.862136000 |
| H | 1.707270000 | -3.421397000 | 1.543928000 |
| H | 1.827337000 | -1.705239000 | 1.119147000 |
| H | 1.922979000 | -2.209628000 | 2.820940000 |
| Br | 4.298190000 | 0.216460000 | 0.279098000 |
| C | 1.500251000 | 1.963115000 | 1.001196000 |
| H | 2.518590000 | 2.352673000 | 1.131093000 |
| H | 0.871316000 | 2.820434000 | 0.725259000 |
| C | 1.009223000 | 1.373531000 | 2.320031000 |
| H | 1.054636000 | 2.117197000 | 3.123276000 |
| H | -0.032831000 | 1.034269000 | 2.229570000 |
| H | 1.619822000 | 0.510312000 | 2.615969000 |

# Annex 3.7 Unpublished results for the cross-coupling of a thienyl fragment with 2iodothiophene and thieno[3,2-b] thiophene 

## ITh (2-iodothiophene)

$\mathrm{G}_{\mathrm{DFT}}=-563.580487$
$\mathrm{G}_{\text {CORR DFT }}=0.024535$
$\mathrm{E}_{\text {CCSD }}=-7469.544325$
$G=-7469.519790$

| ------------------ |  |  |  |
| :--- | :---: | :---: | :---: |
|  |  |  |  |
| C | 3.019989000 | -0.204889000 | 0.000004000 |
| C | 2.705119000 | 1.124945000 | 0.000002000 |
| S | 1.604688000 | -1.199607000 | -0.000002000 |
| C | 1.300873000 | 1.364727000 | -0.000003000 |
| C | 0.583595000 | 0.200641000 | -0.000005000 |
| H | 0.845914000 | 2.350451000 | -0.000014000 |
| H | 3.450687000 | 1.914083000 | 0.000008000 |
| I | -1.502441000 | 0.012894000 | 0.000001000 |
| H | 4.000325000 | -0.666744000 | 0.000007000 |

## $\alpha$-CMD-I

$G_{\text {DFT }}=-1813.990415$
$\mathrm{G}_{\text {CORR DFT }}=0.131722$
$\mathrm{E}_{\text {CCSD }}=-13529.999398$
$G=-13529.867676$

| Pd | 1.990798000 | 0.158727000 | -0.061438000 |
| :--- | :---: | :--- | :---: |
| O | 3.290931000 | -1.571706000 | -0.419794000 |
| C | 3.069762000 | -2.687610000 | 0.116214000 |
| P | 3.582578000 | 1.643485000 | -0.855990000 |
| O | 2.049851000 | -2.949103000 | 0.837293000 |
| C | 4.047028000 | -3.806347000 | -0.097820000 |
| H | 3.559488000 | -4.602877000 | -0.669587000 |
| H | 4.930838000 | -3.459766000 | -0.635995000 |
| H | 4.336584000 | -4.232668000 | 0.867283000 |
| H | 1.245383000 | -1.981907000 | 0.813424000 |
| C | 0.312703000 | -1.012454000 | 0.710080000 |
| C | -0.361184000 | -0.522478000 | 1.826320000 |
| S | -0.866188000 | -1.284109000 | -0.564080000 |
| C | -1.753263000 | -0.361989000 | 1.675731000 |
| C | -2.166872000 | -0.734362000 | 0.415532000 |
| H | -2.425582000 | 0.010549000 | 2.442927000 |


| H | 0.166060000 | -0.271154000 | 2.744425000 |
| :--- | :---: | :---: | :---: |
| H | 4.079011000 | 2.572872000 | 0.077354000 |
| H | 4.783662000 | 1.151545000 | -1.406669000 |
| H | 3.163033000 | 2.521555000 | -1.872452000 |
| C | 0.916165000 | 1.819218000 | 0.254924000 |
| C | 1.021002000 | 2.730124000 | 1.276911000 |
| S | -0.363217000 | 2.274241000 | -0.833233000 |
| C | 0.058719000 | 3.783945000 | 1.198430000 |
| H | 1.754030000 | 2.642774000 | 2.076365000 |
| C | -0.760599000 | 3.678803000 | 0.109991000 |
| H | -0.016786000 | 4.587353000 | 1.926454000 |
| H | -1.564983000 | 4.336299000 | -0.199319000 |
| I | -4.126088000 | -0.608019000 | -0.309417000 |

## $\beta$-CMD-I

```
G
G
E
G=-13529.864163
```

| Pd | -1.989661000 | 0.275062000 | 0.094698000 |
| :--- | :---: | :---: | :---: |
| O | -3.581782000 | -1.227159000 | 0.049106000 |
| C | -3.376810000 | -2.314870000 | -0.547262000 |
| P | -3.463429000 | 2.045314000 | 0.321180000 |
| O | -2.242502000 | -2.670553000 | -1.016117000 |
| C | -4.512562000 | -3.275891000 | -0.733214000 |
| H | -4.645722000 | -3.477769000 | -1.800696000 |
| H | -4.265250000 | -4.228177000 | -0.253723000 |
| H | -5.437372000 | -2.877458000 | -0.313110000 |
| H | -1.367786000 | -1.893547000 | -0.609218000 |
| H | -4.849388000 | 1.789487000 | 0.341219000 |
| H | -3.320948000 | 2.819304000 | 1.487566000 |
| H | -3.395740000 | 3.059612000 | -0.652170000 |
| C | -0.571078000 | 1.681647000 | 0.167021000 |
| C | 0.188801000 | 2.081465000 | 1.235680000 |
| S | -0.053531000 | 2.489887000 | -1.285837000 |
| C | 1.204420000 | 3.024687000 | 0.885345000 |
| H | 0.048474000 | 1.693904000 | 2.242275000 |
| C | 1.202826000 | 3.346599000 | -0.441955000 |
| H | 1.907602000 | 3.445879000 | 1.599045000 |
| H | 1.851460000 | 4.032348000 | -0.974757000 |
| C | 1.976482000 | -0.990758000 | 0.147971000 |
| C | 0.884904000 | -0.870479000 | -0.654936000 |


| C | -0.350314000 | -1.191507000 | 0.009497000 |
| :--- | :---: | :---: | :---: |
| C | -0.111317000 | -1.558147000 | 1.321124000 |
| S | 1.558963000 | -1.511837000 | 1.757415000 |
| H | 0.947749000 | -0.540828000 | -1.689131000 |
| H | -0.840172000 | -1.872675000 | 2.063878000 |
| I | 3.964872000 | -0.553702000 | -0.353958000 |

## $\gamma$-CMD-I

$\mathrm{G}_{\mathrm{DFT}}=-1813.987317$
$\mathrm{G}_{\mathrm{CORR} \mathrm{DFT}}=0.131319$
$\mathrm{E}_{\text {CCSD }}=-13530.000302$
$G=-13529.868983$

| Pd | -0.472391000 | 1.181701000 | 0.005647000 |
| :--- | :---: | :---: | :---: |
| O | 1.216221000 | 2.558670000 | 0.229601000 |
| C | 2.104833000 | 2.332898000 | 1.093197000 |
| P | -1.556111000 | 2.660309000 | -1.399361000 |
| O | 2.116155000 | 1.315718000 | 1.858507000 |
| C | 3.241624000 | 3.302702000 | 1.236744000 |
| H | 4.165669000 | 2.815345000 | 0.907756000 |
| H | 3.072664000 | 4.199940000 | 0.639019000 |
| H | 3.372849000 | 3.568020000 | 2.289777000 |
| H | 1.164805000 | 0.506592000 | 1.530179000 |
| H | -2.820111000 | 3.123841000 | -0.989551000 |
| H | -0.914553000 | 3.873283000 | -1.719454000 |
| H | -1.875708000 | 2.175867000 | -2.680627000 |
| C | -2.060728000 | 0.000331000 | -0.290447000 |
| C | -2.194419000 | -1.075646000 | -1.129649000 |
| S | -3.515802000 | 0.231015000 | 0.638897000 |
| C | -3.462250000 | -1.726860000 | -1.016918000 |
| H | -1.403805000 | -1.409126000 | -1.799028000 |
| C | -4.287827000 | -1.140181000 | -0.100337000 |
| H | -3.744545000 | -2.600012000 | -1.599316000 |
| H | -5.295988000 | -1.420467000 | 0.182437000 |
| C | -0.595697000 | -2.399821000 | 2.256457000 |
| C | -0.515241000 | -1.041086000 | 2.265416000 |
| C | 0.324033000 | -0.479962000 | 1.236957000 |
| C | 0.859589000 | -1.504687000 | 0.482182000 |
| S | 0.365201000 | -3.082691000 | 0.979181000 |
| H | -1.048705000 | -0.427533000 | 2.987763000 |
| H | -1.154782000 | -3.055471000 | 2.914700000 |
| I | 2.166433000 | -1.294105000 | -1.145826000 |

## Thth (thieno[3,2-b]thiophene)

```
\(G_{\text {DFT }}=-1027.132178\)
```

$\mathrm{G}_{\mathrm{CORRDFT}}=0.049232$
$\mathrm{E}_{\text {CCSD }}=-1025.853504$
$\mathrm{G}=-1025.804272$

| C | 0.183433000 | 0.669966000 | -0.000008000 |
| :--- | :---: | :--- | :---: |
| C | -0.183432000 | -0.669967000 | -0.000006000 |
| C | 0.914952000 | -1.573670000 | -0.000002000 |
| C | 2.101783000 | -0.899540000 | 0.000002000 |
| S | 1.913833000 | 0.834630000 | 0.000002000 |
| H | 0.837038000 | -2.655472000 | 0.000002000 |
| H | 3.101129000 | -1.318654000 | 0.000007000 |
| S | -1.913836000 | -0.834631000 | 0.0000001000 |
| C | -2.101782000 | 0.899542000 | 0.000004000 |
| C | -0.914949000 | 1.573671000 | -0.000003000 |
| H | -3.101128000 | 1.318657000 | 0.000012000 |
| H | -0.837029000 | 2.655473000 | -0.000004000 |

## $\alpha-\mathrm{CMD}$ (Th/Thth)

$\mathrm{G}_{\mathrm{DFT}}=-2277.530589$
$\mathrm{G}_{\mathrm{CORRDFT}}=0.155203$
$\mathrm{E}_{\mathrm{CCSD}}=-7086.307737$
$G=-7086.152534$

| --------------------- |  |  |  |
| :--- | :---: | :--- | :---: |
|  |  |  |  |
| Pd | 1.396201000 | 0.217443000 | -0.207699000 |
| O | 2.924288000 | -1.354883000 | -0.321340000 |
| C | 2.803888000 | -2.434351000 | 0.310654000 |
| P | 2.892938000 | 1.805825000 | -1.009948000 |
| O | 1.762088000 | -2.769208000 | 0.970087000 |
| C | 3.937257000 | -3.417198000 | 0.305238000 |
| H | 4.215488000 | -3.659985000 | 1.335353000 |
| H | 3.605761000 | -4.347565000 | -0.167120000 |
| H | 4.800217000 | -3.019305000 | -0.231071000 |
| H | 0.857745000 | -1.947502000 | 0.775979000 |
| H | 4.177949000 | 1.382489000 | -1.405572000 |
| H | 2.492630000 | 2.528139000 | -2.149336000 |
| H | 3.223778000 | 2.875656000 | -0.156090000 |
| C | 0.063171000 | 1.705385000 | -0.131807000 |
| C | -1.016530000 | 1.959239000 | -0.938290000 |


| S | 0.128104000 | 2.858085000 | 1.173815000 |
| :--- | :---: | :---: | :---: |
| C | -1.804242000 | 3.068184000 | -0.498438000 |
| H | -1.264672000 | 1.355735000 | -1.808393000 |
| C | -1.316873000 | 3.658904000 | 0.632758000 |
| H | -2.700826000 | 3.409582000 | -1.009385000 |
| H | -1.707767000 | 4.511772000 | 1.175667000 |
| C | -2.315335000 | -1.356335000 | -0.533166000 |
| C | -2.688878000 | -0.905974000 | 0.736424000 |
| C | -4.094320000 | -0.775643000 | 0.905426000 |
| C | -4.759906000 | -1.112867000 | -0.239228000 |
| S | -3.714948000 | -1.610297000 | -1.541463000 |
| H | -4.587799000 | -0.441806000 | 1.811805000 |
| H | -5.831226000 | -1.095254000 | -0.406210000 |
| S | -1.294170000 | -0.645096000 | 1.721862000 |
| C | -0.191676000 | -1.135461000 | 0.431005000 |
| C | -0.924956000 | -1.494541000 | -0.698923000 |
| H | -0.444980000 | -1.848095000 | -1.609537000 |

## $\beta-\operatorname{CMD}(T h / T h t h)$

$\mathrm{G}_{\mathrm{DFT}}=-2277.525131$
$\mathrm{G}_{\text {CORR DFT }}=0.156539$
$\mathrm{E}_{\text {CCSD }}=-7086.306814$
$\mathrm{G}=-7086.150275$

| Pd | -1.217520000 | 0.445580000 | 0.211001000 |
| :--- | :---: | :---: | :---: |
| O | -3.031768000 | -0.779868000 | 0.092563000 |
| C | -3.012433000 | -1.789385000 | -0.660069000 |
| P | -2.450234000 | 2.388335000 | 0.490271000 |
| O | -1.958529000 | -2.241502000 | -1.219560000 |
| C | -4.290322000 | -2.529763000 | -0.921913000 |
| H | -4.210763000 | -3.540369000 | -0.508251000 |
| H | -5.142432000 | -2.016193000 | -0.473758000 |
| H | -4.439185000 | -2.634026000 | -2.000859000 |
| H | -0.951604000 | -1.696217000 | -0.681171000 |
| H | -3.829813000 | 2.250954000 | 0.740905000 |
| H | -2.070480000 | 3.243806000 | 1.540289000 |
| H | -2.469223000 | 3.308569000 | -0.575251000 |
| C | 0.411445000 | 1.598917000 | 0.300563000 |
| C | 1.408558000 | 1.630508000 | 1.240906000 |
| S | 0.773694000 | 2.698614000 | -1.002279000 |
| C | 2.471655000 | 2.526064000 | 0.909381000 |
| H | 1.402778000 | 1.009004000 | 2.133818000 |
| C | 2.276615000 | 3.178686000 | -0.275242000 |


| H | 3.350457000 | 2.673284000 | 1.531822000 |
| :--- | :---: | :---: | :---: |
| H | 2.916423000 | 3.904221000 | -0.764188000 |
| C | 1.459843000 | -1.293287000 | -0.397692000 |
| C | 2.411965000 | -1.801357000 | 0.473308000 |
| C | 3.745905000 | -1.756892000 | -0.016176000 |
| C | 3.781980000 | -1.213682000 | -1.269797000 |
| S | 2.211362000 | -0.746884000 | -1.862560000 |
| H | 4.624594000 | -2.104195000 | 0.516994000 |
| H | 4.651133000 | -1.055754000 | -1.897920000 |
| S | 1.662719000 | -2.318883000 | 1.959813000 |
| C | 0.103814000 | -1.843061000 | 1.354061000 |
| C | 0.106128000 | -1.306109000 | 0.077952000 |
| H | -0.765391000 | -2.023233000 | 1.982143000 |

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