

# Ligand Controlled Regioselectivities in C–H Activation - A Case Study on Approaches for the Rationalization and Prediction of Selectivities

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**Abstract:** Achieving regioselectivity in C–H activation remains a major challenge. Controlling or even reversing the regioisomeric outcome through the choice of ligand is even harder to achieve let alone to predict. Herein we investigated ligand effects in the regioselective Pd-catalyzed alkynylation of thiophenes using multivariate linear regression to build predictive models that offer deeper insight into the structural factors driving regioselectivity and enabled the discovery of a more selective ligand. Combining experimental and DFT studies we propose a Curtin-Hammett scenario between the C–H activation and migratory insertion as origin of the ligand-controlled selectivities. A detailed investigation of solvent effects uncovered an inadequate description of solvent-solute dispersion interactions by implicit solvation models. The crucial role of the solvent in substrate coordination is further evidenced by an inverse solvent kinetic isotope effect. Additionally, the often poorly understood role of silver was scrutinized, showing that it serves to mitigate a detrimental side reaction. This study provides generalizable insights for the computational description of challenging regio- and stereoselectivities and is expected to aid future mechanistic investigations in Pd-catalyzed C–H activation that holistically consider the role of all reaction components.

## Introduction

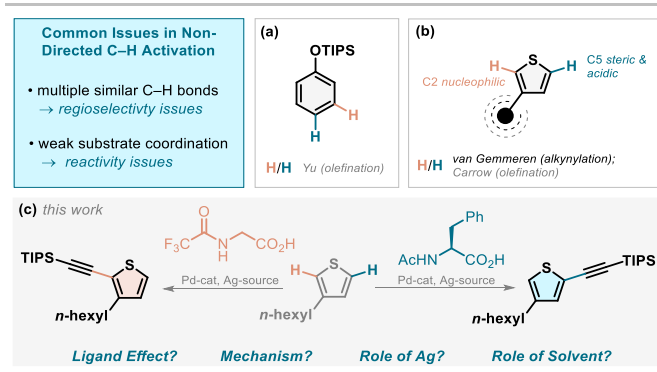
C–H activation generally faces two major challenges: reactivity and selectivity. Nondirected C–H activations, especially when substrate-limited, lack the thermodynamic and kinetic edge provided by directing groups and therefore often suffer from low reactivity. Furthermore, for substrates without a strong electronic or steric bias, the presence of multiple energetically similar C–H bonds renders the selectivity challenging to control.<sup>[1,2]</sup>

Addressing these challenges requires the design of highly active and selective catalysts as well as a fine-tuning of the reaction conditions. Ideally, one would like to identify several sets of catalysts and conditions each allowing the selective functionalization of a molecule in one of several competing positions with full catalyst control.

In the absence of directing groups the selectivity is often governed by the electronic properties of the competing C–H bonds. For instance, electron-rich phenol derivatives are typically functionalized in para and, for small substituents on oxygen, ortho-position, although some sterically sensitive catalysts deliver meta:para mixtures.<sup>[3]</sup>

To date only few examples are reported, where a complete switch in selectivity is based only on the nature of the ligand rather than

the use of a different strategy altogether. A prominent example is the switch between meta- and para olefination of aromatic silyl ethers by Yu (Figure 1).<sup>[4]</sup> Towards the functionalization of heteroarenes,<sup>[5]</sup> Carrow reported a catalyst controlled regioselective olefination.<sup>[6,7]</sup> Unlike these two examples, where completely different ligand classes are employed to access the competing regioisomers, De Vos and Chang independently reported switchable selectivity in indoles arising from different carboxylate ligands.<sup>[8,9]</sup> Recently, we reported a regioselective alkynylation of thiophenes, where under otherwise identical reaction conditions high levels of regioselectivity for either the C2 or C5 position could be achieved, solely through the choice of different N-acyl amino acid ligands.<sup>[10,11]</sup>



**Figure 1.** Literature background and ligand-controlled selectivity studied herein.

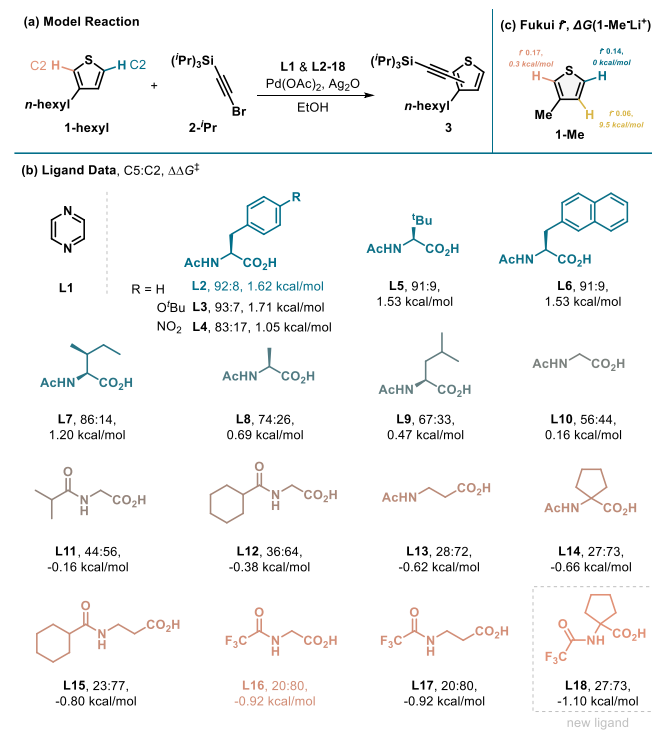
The moderate to good selectivities in all of these systems indicate rather small energy differences (1–2 kcal/mol) between the product forming pathways. We realized that rational insights into these subtle ligand effects could lead to improved catalysts and would potentially be applicable to other arene functionalizations where the regioselectivity still requires improvement.<sup>[3]</sup> Considering that for C–H activations the mechanistic understanding often lags far behind the synthetic utility of such transformations, we became interested in understanding the factors governing the regioselectivity in nondirected C–H activations. We selected our regioselective thiophene alkynylation as a model system and systematically probed various approaches to identify the regioselectivity-controlling factors.

## Results and Discussion

## Selectivity Prediction via MLR

Designing selective ligands is often difficult since multifactorial ligand effects on reactivity and selectivity are challenging to evaluate for humans simultaneously. Often, very subtle effects need to be exploited since energy differences as small as 1–3 kcal/mol can cause a reversal of selectivity. Predicting these changes *in silico* remains challenging even in the advent of modern computational methods, since a very sound understanding of ligand effects and the overall reaction mechanism are required.

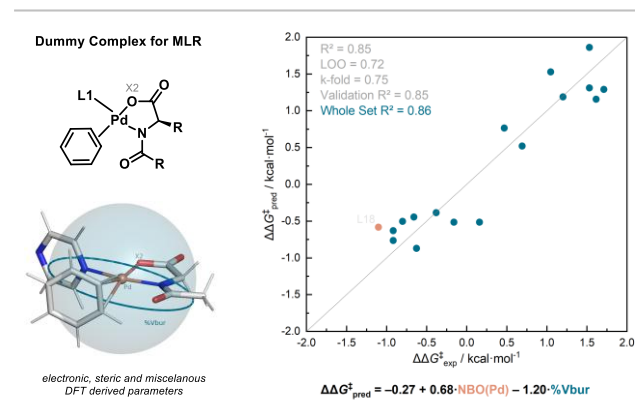
With information from a previous ligand screening at hand (Figure 2), we investigated whether data-science is suited to predict the selectivity in our small dataset. Data science techniques have already been applied to N-acyl amino acid ligands by Sigman,<sup>[12]</sup> Yu,<sup>[13]</sup> Ackermann,<sup>[14]</sup> and Suno,<sup>[15]</sup> for predicting enantioselectivity in C–H functionalization reactions. To date only few studies have investigated the ligand/additive dependent regioselectivity in C–H activation using data modelling.<sup>[9,16]</sup> To the best of our knowledge, regioselectivities controlled by N-acyl amino acid ligands have not been analyzed with data science methods to date, motivating us further to probe the feasibility of this approach. We reasoned that MLR would be a suitable tool, since it is operationally easy, lightweight, and less prone to overfitting in small dataset regimes than common machine learning (ML) models. Additionally, our dataset evenly covers a broad range of experimental selectivities making it well-suited for MLR and MLR enables a direct interpretation of the key parameters and thus molecular effects.<sup>[17–19]</sup>



**Figure 2.** (a) Model reaction for thiophene alkylation with 0.1 mmol **1-hexyl**, **2-SiPr<sub>3</sub>** (1.5 equiv), Pd(OAc)<sub>2</sub> (10 mol%), Ag<sub>2</sub>O (2.0 equiv), **L1** (20 mol%), **L2-18** (30 mol%), EtOH (1 mL), 40°C, 18 h. (b) Overview of the ligands and C5:C2 selectivities. (c) Fukui nucleophilicity index  $f(r)$  and free energy differences ( $\omega\text{B97X-D3BJ/def2-TZVP}$ ) for lithiated thiophene **1-Me** for C2, C5 and C4 positions.

To compute the required descriptors, we chose a model compound that features an N-acyl amino acid ligand coordinated to Pd, the additional pyrazine ligand **L1** and benzene (Figure 3). Benzene was chosen as a dummy substituent at this stage, as it reduces the number of conformers compared to thiophene but offers a similar steric environment, allowing us to efficiently obtain meaningful descriptors. Several steric and electronic parameters were evaluated at the D3BJ PBE0/def2-TZVP level of theory in the gas phase (see SI for details).

A two-parameter model was obtained for the full dataset with reasonable stats (Figure 3). Using normalized parameters, the magnitude of the prefactor indicates the importance of the respective factor in controlling the reaction outcome. Most models obtained in our MLR analysis feature a strong steric parameter, namely the buried volume (%Vbur) and an electronic parameter, the most robust model pairing the %Vbur with the NBO charge on Pd. The MLR model indicates that a more electrophilic Pd catalyst would favor C2 selectivity and more steric bulk would favor C5 selectivity.



**Figure 3.** MLR analysis of the full dataset with the two-parameter equation.

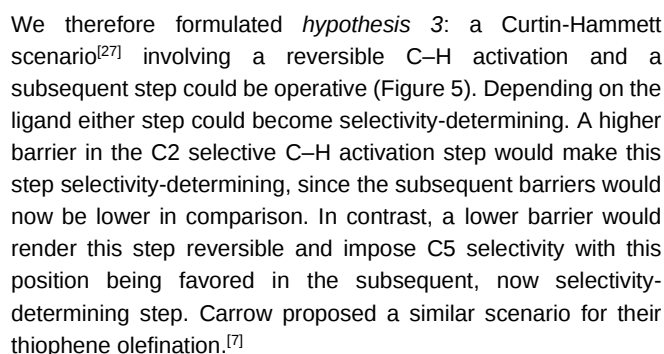
Even more accurate predictions can be reached when limiting the analysis to  $\alpha$ -amino acid-derived ligands. Here, a more refined electronic parameter of the Pd-binding carboxylate oxygen NBO(X2) gives improved out-of-sample predictability for the test/train split. Even the newly synthesized **L18** was predicted well, which showcases the utility of this model for out-of-sample ligand prediction (Figure S6 calc. 1.1 kcal/mol vs exp 1.1 kcal/mol). This ligand was not contained in the original study and constitutes now the most C2 selective ligand for our transformation.

## Initial Mechanistic Hypothesis

Achieving C2 selectivity in thiophenes is possible using electrophilic catalysts since this is the most nucleophilic position as evidenced by the highest  $f$ -Fukui index (Figure 2a). The C5 position is the sterically most accessible and most acidic position as evidenced by the highest relative stability ( $\Delta G$  **1-Me**<sup>+</sup>Li<sup>-</sup>) of lithiated **1** (Figure 2a).

We initially hypothesized that the selectivities in our system could originate from ligand-control in a selectivity determining C–H activation step.

Interestingly, we observed a strong correlation ( $R^2$  0.93) of the experimental  $\Delta\Delta G^\ddagger$  (cf. Figure 2) with the calculated C–H activation barrier  $\Delta G^\ddagger$  in the C2 position (Figure 4b), meaning that the higher the C–H activation barrier the more C2 product was observed. This demonstrated, that while not being the sole factor, the C–H activation step is decisively involved in controlling the regioselectivity.



3

have shown that alkynyl bromides similar to **2** preferentially react via a 1,2-MI. With *hypothesis 3* and the mechanism from Figure 5 in mind, we proceeded to scrutinize the barriers for the MI step with various ligands and bromo(trimethylsilyl)acetylene (**2-SiMe<sub>3</sub>**). Surprisingly, our calculations indicated a preference for the C2 position with **L2**, an experimentally C5-selective ligand. We probed different conformers, the involvement of silver, different ligand orientations, but a preference of C2 over C5 was always pronounced. To probe whether this is a computational artefact, several implicit solvation models (CPCM, SMD, openCOSMORS, dCOSMORS) were tested, with different dispersion corrected DFT functionals and CCSD(T) with complete basis set (CBS) extrapolation. All calculations pointed consistently towards C2 (see SI for further discussion).

After extensively investigating alternate reaction pathways, like an oxidative addition (Pd<sup>II</sup>/Pd<sup>IV</sup>), as suggested for alkynyl iodides,<sup>[29]</sup> or an oxidative addition of alkynyl bromide with an intermittently formed Pd<sup>0</sup> species, followed by a Heck-like insertion of the thiophene,<sup>[31,32]</sup> we concluded, that these alternatives are energetically unfavorable (see SI for further details).

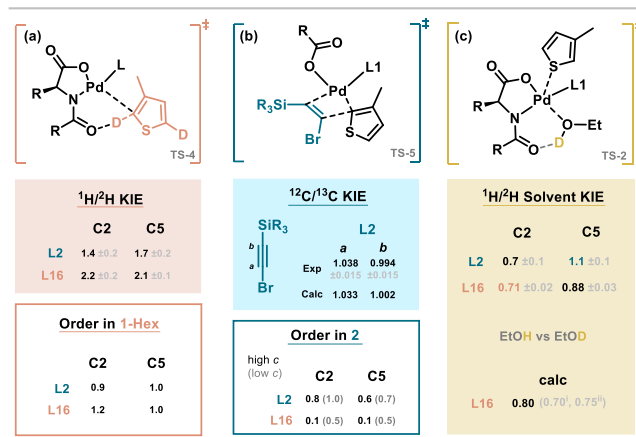
### Mechanistic experiments

To further probe *hypothesis 3* and gain insights into the step(s) besides C–H activation influencing the regioselectivity, we acquired experimental mechanistic data. We selected **L2** and **L16** for our experimental and more detailed computational endeavors and determined the parallel kinetic isotope effects (KIE). Reliable competition KIE data were impossible to obtain for **L2** since significant isotope exchange with the solvent occurred. This phenomenon has previously been observed and was exploited in our (hetero)arene deuteration methodology.<sup>[33–36]</sup> All parallel KIE experiments were conducted in EtOD to avoid misleading results (Figure 6a).

The KIEs (1.4 – 2.1) are larger than the maximum for secondary KIEs. Values for **L2** are smaller than for **L16** and comparably small for a primary KIE.<sup>[37–39]</sup>

We therefore concluded, that the C–H activation is reversible at least for **L2**, which is in line with the calculated KIEs being higher than the experimental values (see SI) and the aforementioned isotope scrambling. The presence of a second step with a similar or higher barrier on the product-forming pathway would explain the truncation of the primary KIE in the C–H activation step.

To get more insights regarding the second selectivity-controlling step, we determined the kinetic orders in thiophene and alkyne for **L2** and **L16** using variable time normalization analysis.<sup>[40,41]</sup> Near unity orders in **1-hexyl** were observed in both cases. For the alkyne **2-Si<sup>i</sup>Pr<sub>3</sub>** a concentration dependent order was observed. An order approaching zero in **2-Si<sup>i</sup>Pr<sub>3</sub>** was observed using **L16**. A broken order slightly below one, that approaches unity at lower concentrations was observed for **L2** (Figure 6a,b). These orders indicate that both reactions feature a high energy TS for the C–H activation step involving the thiophene. Since this step does not involve the alkyne,<sup>[42]</sup> a second TS featuring alkyne must be close in energy, hence explaining the concentration dependence of the kinetic order. We also determined <sup>12</sup>C/<sup>13</sup>C KIEs for the reaction involving **L2** to compare them with our calculated TS (*vide infra*).



**Figure 6.** Experimental investigation of key steps with **L2** and **L16**. Calculations at the ωB97X-D3BJ/def2-TZVP level. (a) Parallel <sup>1</sup>H/<sup>2</sup>H-KIE of **1-hexyl** and **2,5-d<sub>2</sub>-1-hexyl** and order determination for **1-hexyl**. (b) <sup>12</sup>C/<sup>13</sup>C-KIE determination for **2-Si<sup>i</sup>Pr<sub>3</sub>** and comparison with calculated **TS-5-AcO-SiMe<sub>3</sub>**; order determination for **2-Si<sup>i</sup>Pr<sub>3</sub>** at low and high concentrations. (c) Inverse <sup>1</sup>H/<sup>2</sup>H solvent KIE with EtOH/D and comparison with calculated values. <sup>i</sup> D3BJ TPSS/def2-SVP, <sup>ii</sup> D3BJ PBE0/def2-TZVP.

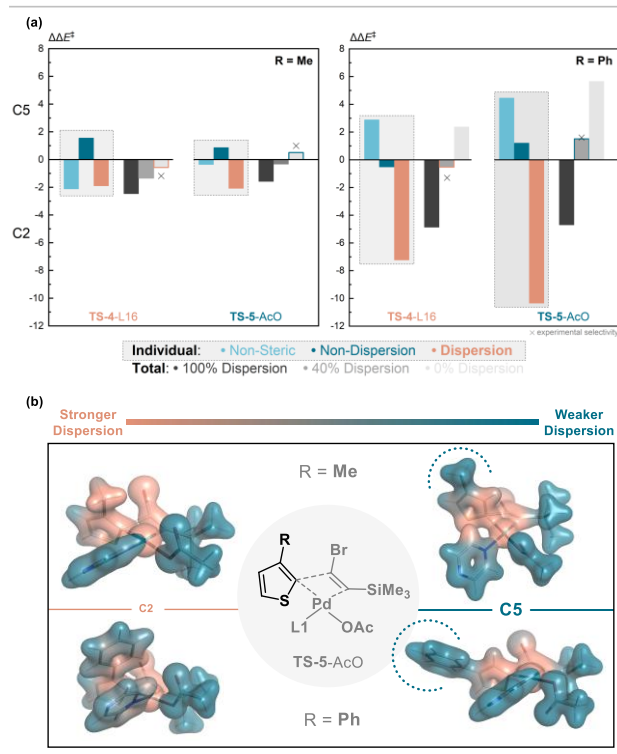
### Investigation of Dispersion Attenuation

The experimental results are in line with a Curtin-Hammett-like scenario involving a C5 selective MI, prompting us to further question the C2 selectivity predicted by our computed TS. Due to the similarity of the system, we turned our attention to the results reported by Carrow.<sup>[7]</sup> In Carrow's case the PCM BP86/6-31G\* basis set and functional for thermochemistry and single point energy reproduce their experimental findings well, despite the generally inadvisable choice of a rather small basis set and the omission of a dispersion correction.<sup>[43]</sup> Unfortunately no detailed discussion regarding the choice of computational methodology was provided. We reoptimized and reinvestigated the structures from Carrow's work and noted, that upon using higher level methods including CCSD(T) the C5 selectivity is not correctly predicted any more. The main factor leading to a correct prediction of the C5 selectivity with BP86/6-31G\* was the absence of a dispersion correction.

Indeed, we found that if the dispersion correction is omitted (see the SI for more details), our computations also predict the experimentally observed C5 selectivity via **TS-5-AcO**, while dispersion corrected DFT results could not predict the experimental C5 selectivity correctly. This effect is even more pronounced for 3-phenyl thiophene (**1-Ph**). Here C2 is predicted to be highly favorable ( $\Delta\Delta G^{\ddagger}_{\text{calc}} = -3.9$  kcal/mol in the MI step), contrasted by the experimental  $\Delta\Delta G^{\ddagger}_{\text{exp}}(\mathbf{L2}) = 1.6$  kcal/mol. The computations for the C–H activation step also overestimate the C2 selectivity ( $\Delta\Delta G^{\ddagger}_{\text{calc}} = -5.2$  kcal/mol) compared to the experimental  $\Delta\Delta G^{\ddagger}_{\text{exp}}(\mathbf{L16}) = -1.3$  kcal/mol at the SMD(EtOH) ωB97X-D3BJ/def2-TZVP//ωB97X-D3BJ/def2-TZVP level of theory.

This is surprising, since generally-speaking DFT-D3 methods outperform conventional DFT functionals without dispersion corrections in most benchmark tests.<sup>[43]</sup> Since the CCSD(T) results also contradict the experimental observations we investigated the nature of the dispersion interactions in more detail to get “the right answer for the right reasons”. We

hypothesized that different levels of intramolecular dispersion interaction could artificially overstabilize the TS leading to the C2 isomer. Using the local energy decomposition (LED)<sup>[44]</sup> scheme with DLPNO-CCSD(T)/def2-TZVP one can decompose the binding energy into several contributions, like non-dispersion, dispersion, geometric preparation, etc. It is thus possible to determine, whether an electronic preference for one isomer competes with dispersion interactions favoring the other isomer. We performed this analysis for the C–H activation step with **L16** and the MI step with acetate (see SI for other ligands). The results show that for both **1-Me** and **1-Ph** the combined non-steric and non-dispersive contributions favor the C5 isomer and the dispersion effect favors C2 in the MI step (Figure 7a).



**Figure 7.** (a) Comparison of the relative  $\Delta\Delta E^\ddagger$  (C2 vs C5) in kcal/mol different decomposed contributions from the LED analysis at the DLPNO-CCSD(T)/def2-TZVPP level of theory. (b) Dispersion interaction density mapped on the electron density for **TS-5-AcO** for C2 and C5 for **1-Me** and **1-Ph**.

Notably, the substituent in C3 position points outwards during the C5-functionalization pathway and towards the Pd-complex during the C2-functionalization pathway. In case of C2 functionalization intramolecular dispersion interactions can stabilize the intermediates and TS relative to the respective C5 isomers. In vacuo, this is a realistic behavior, but in solution solvent-solute interactions are expected to a) truncate these intramolecular dispersion interactions and b) stabilize the C5 isomers by solvent-solute interactions. This can be visualized by inspecting the dispersion interaction densities (Figure 7b), where the different levels of intramolecular dispersion interactions with the C3 substituent are clearly visible.

In the end the C2 vs C5 selectivity depends on the competing isomeric TS rather than the respective ground states (GS). For solution GS conformers determined by vibrational circular

dichroism, it has already been discussed, that implicit solvation models can perform poorly especially when neglecting crucial explicit solvent interactions.<sup>[45,46]</sup> It was found that omitting dispersion corrections led to superior geometric results<sup>[47]</sup> or reaction enthalpies for ligand coordination reactions.<sup>[48]</sup> This is likely due to the poor performance of the implicit solvation models rather than the dispersion correction itself.<sup>[49]</sup> Several models,<sup>[50–55]</sup> often termed molecular balance, have been developed to quantify the attenuation of dispersion interactions due to solvent-solute interactions. Experimentally, Chen showed an attenuation of the predicted dispersion interactions in dichloromethane<sup>[56]</sup> and other solvents of up to 70%.<sup>[57]</sup>

Overall, **1-Ph** has a larger dispersion contribution stabilizing C2 (7–10 kcal/mol) compared to **1-Me** (~2 kcal/mol). A full attenuation of intramolecular dispersion interactions in case of **1-Me** for **TS-4** and **TS-5** results in experimentally correct selectivities. The predicted C5 selectivity for the MI is now in agreement with experiment and the C2 selectivity in the C–H activation TS is not overestimated any more. In case of **TS-4-L16** for **1-Me** the non-steric factors like electronics favor C2 selectivity whereas in case of **TS-5-AcO** mainly non-dispersion effects like steric repulsion favor the C5 selectivity. In addition to solvent-solute effects, an overestimation of alkyl dispersion interaction could play an additional minor role.<sup>[58]</sup>

A lower degree of dispersion attenuation for **1-Ph** is expected due to the larger nature of the substituent and the overall larger dispersion contribution. It is reasonable to assume, that a certain amount of dispersion will not be truncated and some intramolecular dispersion persists. A 60% attenuation of dispersion interaction in case of **1-Ph** yields qualitatively good results for the MI and C–H activation step (Figure 7a, framed boxes). Upon using non-dispersion corrected structures, larger basis sets, other carboxylates and implicit solvation models the precise values for attenuation might change, but the overall effect is expected to be identical and to show at least a reasonable qualitative agreement with experiment.

The work-flow above enables an estimation of how much truncation of dispersion interaction is required for an agreement with experiment and shows, if other factors can be used to predict the regioselectivity correctly.

A conceptual alternative would be to study the system with explicit solvation. However, obtaining quantitatively meaningful results with explicit solvation is very challenging since extensive conformational sampling of all solvent molecules is required and many additional solvent molecules are required for adequate solvent-solute interactions thus rendering the system prohibitively large for long QM/MD simulations and high level DFT methods. We nevertheless carried out preliminary calculations with explicit solvation for **1-Ph** (see SI), which qualitatively corroborate to the conclusion that the C5 isomer is preferred in the MI step (**TS-5**).

We concluded that an attenuation of intramolecular dispersion interactions due to solvent-solute dispersion interaction is likely operative in our system, since a) alternate pathways explaining the observed selectivities were probed and found to have prohibitively high barriers, b) literature reports show ground state dispersion attenuation in related systems, c) an attenuation was shown to predict the correct isomer in case of the MI **TS-5** and improve the agreement with the observed selectivity in the C–H

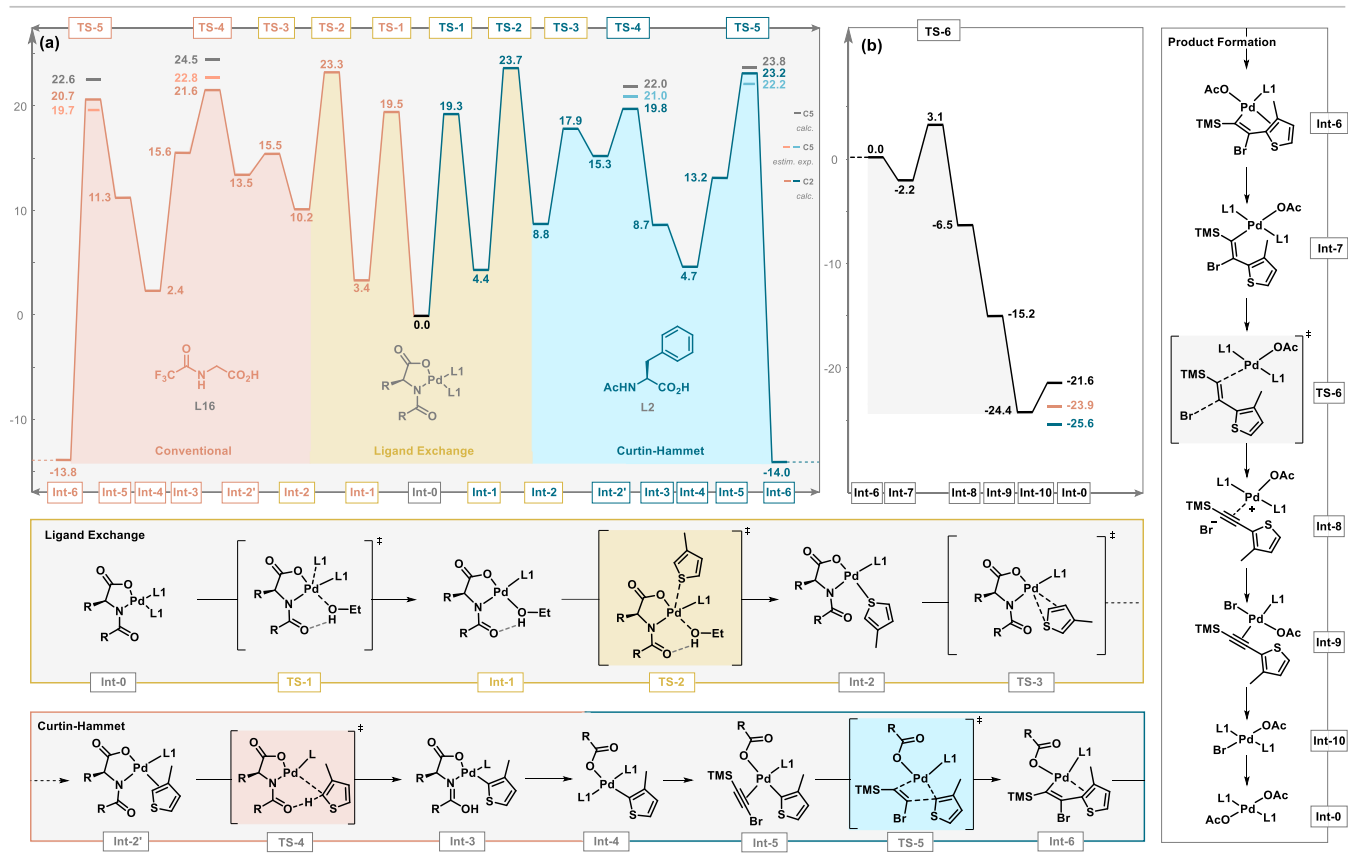
activation **TS-4**, and d) preliminary calculations with explicit solvation corroborate to this interpretation. Notably, to the best of our knowledge this study constitutes a first report, in which an attenuation of dispersion interactions on TS was shown to be key for the qualitatively correct prediction of regioselectivities.

### Detailed Mechanistic Picture

To verify if the suggested Curtin-Hammett-like scenario is indeed responsible for the regioselective C–H functionalization, the full reaction pathway was investigated using DFT. Several functional combinations were benchmarked and dCOSMORS (EtOH)  $\omega$ B97X-D3BJ/def2-QZVPP// $\omega$ B97X-D3BJ/def2-TZVP was selected, as it accurately predicts experimental results and is most in line with DLPNO-CCSD(T)/CBS results (Figure 8). The calculations indeed confirm a higher barrier for the C–H activation (**TS-4**) when using **L16** and a higher barrier for the MI (**TS-5**) with **L2**. This is in line with a Curtin-Hammett-like scenario, in which the C–H activation is reversible for **L2** and only the higher barrier imposes the selectivity. The MI is exergonic and irreversible ( $\Delta G^\ddagger > 30$  kcal/mol for the reverse reaction). The MI is followed by an additional **L1** coordination (**Int-7**), a  $\beta$ -bromide elimination (**TS-6**), bromide coordination (**Int-9**) and product liberation (**Int-10**). The possibility of an inverse MI and a subsequent silyl migration as investigated by Paton<sup>[28]</sup> was also evaluated. The comparison of calculated and experimental  $^{12}\text{C}/^{13}\text{C}$  KIEs with **L2** allowed us to exclude this scenario.

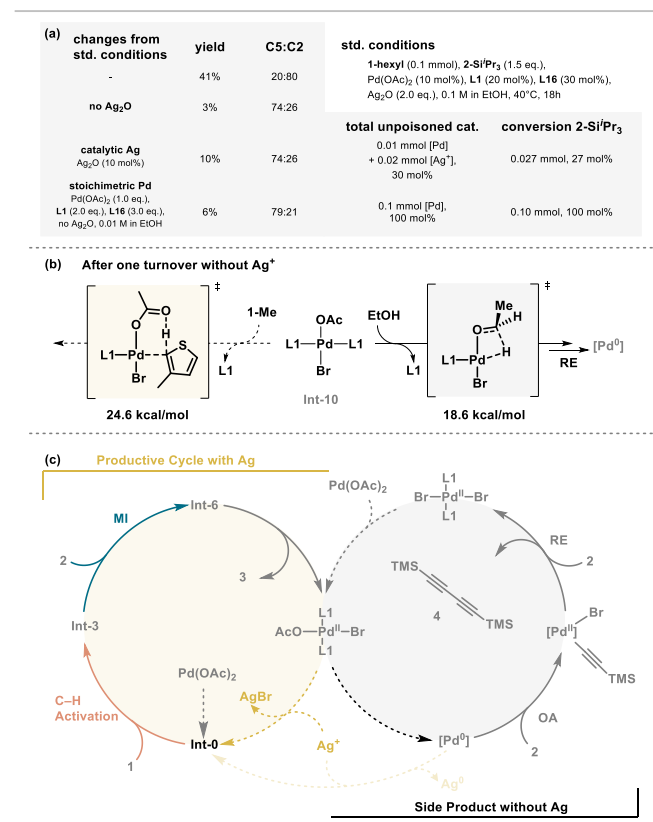
During the KIE studies we noted that reactions using either **L2** or **L16** both feature an inverse solvent KIE (Figure 6c) in EtOH/D.<sup>[59,60]</sup> The effect is more pronounced for **L16** and in both cases more for C2 than for C5. Explicit coordination of EtOH in **TS-4** was probed and found unfavorable. It seemed reasonable that upon ligand decooordination from the resting state (**Int-0**), an intermediate EtOH coordination to the metal would take place giving **Int-1**. The subsequent ligand exchange from EtOH to substrate would then give rise to an inverse solvent KIE.

Comparing the relative barriers for associative and dissociative ligand exchange pathways the formation of **Int-2** was indeed found to be more favorable through the intermediacy of **Int-1** rather than directly from **Int-0** (2.0 kcal/mol for **L16** and 2.8 kcal/mol for **L2**). We calculated the KIEs and found that it is in good agreement with the experimentally observed values (Figure 6b). Please note that the calculated barriers for ligand exchange reactions with EtOH are lower than **TS-4** with CPCM or SMD (see SI) which indicates a larger degree of uncertainty in addition to the difficulty of modelling EtOH as bulk solvent. Molecular dynamics simulations with umbrella sampling could in principle be used for solvent-ligand exchange reactions, but are either computationally prohibitively costly or would require ML learned force-fields for comparable accuracy.<sup>[61,62]</sup> The reaction orders suggest that **TS-4** or **TS-5** are indeed turnover-limiting but **TS-2**, **TS-4**, and **TS-5** are all energetically very similar as evidenced by the KIEs for **1-hexyl**, **2-Si<sup>i</sup>Pr<sub>3</sub>**, and EtOH/D (Figure 6).



**Figure 9.** Free energy pathways at the dCOSMORS(EtOH)  $\omega$ B97X-D3BJ/def2-TZVPP/ $\omega$ B97X-D3BJ/def2-TZVP level of theory for (a) the initial C–H activation and MI for **L2** and **L16** with EtOH ligand exchange (grey background) and (b) the remaining steps for product generation (white background) using acetate as the carboxylate ligand.

The results explain the experimental observations well, but should be interpreted taking into consideration the fundamentally challenging nature of this system. Even high level methods with “chemical accuracy” show errors of at least 1 kcal/mol in the gas phase and additional errors due to implicit solvation models (e.g. errors of 2-3 kcal/mol for COSMO-RS) are expected.<sup>[43,49,63]</sup> Irrespective of possible influence of ligand-exchange processes on the turnover-frequency, the selectivity is imposed by **TS-4** vs **TS-5**. This can be seen from the coordination of **1-Me** to the catalyst via the S-atom in **TS-2** and **Int-2**. Only in the subsequent steps regioisomeric intermediates and TS occur, e.g. **Int-2'**, which can equilibrate via comparably low TS such as **TS-3**. Considering the various roles silver salts are known to play in C–H activation,<sup>[64–69]</sup> we investigated computationally whether silver would lower any of the barriers, but, unlike in some related systems,<sup>[28]</sup> found that the redox neutral (Pd<sup>II</sup>/Pd<sup>II</sup>) pathway itself neither requires silver as oxidant, nor for bromide stripping in the steps following the MI.



**Figure 9.** (a) Control experiments to study the role of silver. (b) C–H activation vs Pd<sup>0</sup> formation in the absence of silver and presence of bromide. (c) Simplified catalytic cycles rationalizing the role of silver in suppressing side product formation.

We conducted control experiments (Figure 9a) which confirm that silver is required for product formation and only traces of product are formed in the absence of silver. Interestingly, even in the presence of stoichiometric amounts of Pd but absence of silver, only little product formation was observed. The reagent **2-Si<sup>i</sup>Pr<sub>3</sub>** was nevertheless consumed to a large degree. We could trace back the high conversion of the bromo alkyne to an alkyne-alkyne

homocoupling forming a Glaser-like product **4**. The conversion of alkyne was correlated to the amount of Pd-catalyst available. When adding catalytic amounts of silver (20 mol% Ag<sup>+</sup>) and Pd (10 mol%), 27 mol% of **2-Si<sup>i</sup>Pr<sub>3</sub>** were consumed. Consequently, in the stoichiometric experiment one equivalent of **2-Si<sup>i</sup>Pr<sub>3</sub>** was consumed. These experiments show that silver is needed to enable the desired thiophene alkynylation reactivity, but can also promote catalyst turnover in the alkyne homocoupling side-reaction.

We investigated the formation of the side-product computationally (Figure 9b, for more details see SI) and found that in the presence of bromide ions, e.g. after completing the initial catalytic cycle, Pd(0) forms rapidly and a subsequent oxidative addition of alkyne triggers homocoupling, which proceeds faster than thiophene alkynylation. Ag<sub>2</sub>O acts as a base and halide scavenger to formally trap HBr and can also reoxidize Pd<sup>0</sup> that is formed in side reactions. In the absence of silver, Pd(OAc)<sub>2</sub> is gradually converted to a fully inactive palladium dibromide species. These mechanistic findings are summarized in Figure 9c.

## Conclusion

Several important conclusions can be drawn from this study:

- MLR can be used to predict ligand effects on the regioselectivity of nondirected C–H activation processes
- Traditional implicit solvation may fail to (even qualitatively) describe the regioselectivity for such complex systems
- LED analysis and visualizing dispersion interactions can help to understand if an attenuation of dispersion interactions could be responsible for inaccurate predictions
- A Curtin-Hammett scenario with a switch in selectivity determining step **TS-4** vs **TS-5** is responsible for the different selectivities observed with ligands **L2** and **L16**
- Ethanol plays a crucial role to facilitate substrate coordination by prior direct coordination to the catalyst center
- The role of silver is to suppress the undesired formation of homocoupled alkyne and recycle the catalyst

MLR is able to bridge the gap between two distinct mechanistic regimes (**TS-4** and **TS-5**) and predicts ligand-dependent selectivities with good accuracy, only using a simple model compound and well interpretable descriptors. This is noteworthy especially in light of the failure of even high quality CCSD(T) with implicit solvation to qualitatively predict the correct regioisomeric outcome. We provide an explanation and visualization method showing why the relative stabilities of **TS-5** were incorrectly modelled with implicit solvation. We expect this work will prove highly useful as a basis for future computational studies aiming to assess challenging selectivities. Notably, a very recent theoretical study by Bistoni in the field of asymmetric organocatalysis, also showcases the need for methods to study computational shortcomings due to explicit solvent-solute effects.<sup>[70]</sup> Alcoholic solvents, including hexafluoroisopropanol (HFIP), are often vital in palladium catalyzed C–H activation despite their

often ambiguous role.<sup>[71]</sup> It is commonly assumed that hydrogen bonding lowers the C–H activation barrier. We herein introduce an additional explanation for the role of alcoholic solvents: the direct coordination to the metal center and simultaneous H-bond to the ligand as a way to increase the rate of substrate coordination.

We furthermore provide evidence for the role of silver in our transformation. Understanding the roles of silver in C–H functionalization is crucial for developing silver free variants - one of the major challenges in the field of C–H activation.<sup>[64]</sup> The role of silver to suppress detrimental side reactions has not been described to date and may be quite prevalent considering the widespread use of alkynyl bromides in C–H activation.

Overall, this study offers new directions for a holistic investigation of reaction mechanisms in C–H activation taking into consideration all reaction partners. Several methodological aspects are expected to prove useful in the future and the study opens up new perspectives concerning solvent effects and the role of silver salts in the field of C–H activation.

## Supporting Information

The authors have cited the following additional references within the Supporting Information.<sup>[72–147]</sup> Coordinates as xyz files, descriptor datasheets and further supporting material was deposited at the open access repository ZENODO DOI: 10.5281/zenodo.15126469.

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## Conflict of Interests

The authors declare no conflict of interest.

**Keywords:** Catalysis • Selectivity Prediction • Mechanism • Dispersion • C–H activation

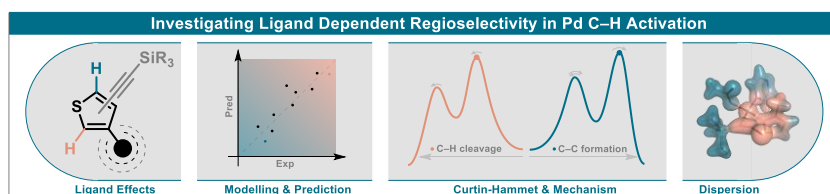
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## Short Summary



### Description

Strategies to understand ligand effects on regioselectivities of C-H activation processes were investigated using an alkynylation of thiophenes as model system. The results shed light on the role of dispersion models for the correct prediction of reaction outcomes and propose new roles for solvent and silver additive. The utility of multivariate linear regression in predicting selectivities across mechanistic regimes is demonstrated.