Using Classifiers to Predict Catalyst Design for Polyketone Microstructure

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ABSTRACT: We applied a classifier method to predict palladium catalysts for the formation of non-alternating polyketones via the copolymerization of CO and ethylene; current examples are limited to using phosphine sulfonate and diphosphazane monoxide supporting ligands. With the reported workflow, we discovered two new classes of palladium complexes capable of achieving the synthesis of non-alternating polyketones with a lower CO content than those made by known palladium catalysts. Our results show that we doubled the number of classes of palladium compounds that can catalyze the formation of this type of polymer. We envision that this methodology can be applied to accelerate catalyst discovery when selectivity is an important outcome.

Polyketones, copolymers of CO and α-olefins, have many properties associated with attractive engineering thermoplastics, such as high melting points, excellent impact performance, and sturdy chemical resistance.[1] The ethylene-CO polyketone microstructure can be either alternating or non-alternating (referring to the ordering of the monomer subunits).[2-4] Non-alternating polyketones, featuring consecutive ethylene units in the polymer chain (Figure 1), behave like polyethylene when the CO content is low, but still retain photodegradability, chemical resistance, and mechanical strength, thus making them a versatile engineering plastic.[5-6]

Despite the advantages of non-alternating polyketones, only a few catalysts capable of preparing these materials have been reported, [2, 7-10] in stark contrast to the numerous reports on alternating polyketone catalysis. Therefore, there are inherent advantages in expanding the scope of catalyst designs for this challenging reaction, such as discovering more facile catalyst synthesis routes, and access to new selectivity or reactivity regimes.

The conventional approach for catalyst exploration is guided by experiments and mechanistic studies to identify promising candidates. However, since the production of new organometallic catalysts requires air-sensitive techniques, it is generally limited to small-scale batch syntheses with similar ligand designs. This approach can thus be time-consuming and inefficient, especially when the outcome does not perform as well as expected. Furthermore, new advances such as integrated catalysis require large datasets that can be tested under different conditions.[11-14]

Machine learning has been used to identify structure-activity relationships in organometallic chemistry, and has the potential to accelerate catalyst exploration when there is insufficient experimental data to generate a model. Two types of models have been used: regression, which predicts continuous values, and classification, which predicts discrete categories (Figure S1).[15-19] For example, regression has been used to describe the relationship between a catalyst structure and polymer molecular weight, comonomer content, or activity.[20-22]

Despite the increasing presence of regression models, the use of a classifier for predicting discrete catalyst structure-activity relationships is not common for organometallic catalysis. A recent example by Doyle and coworkers classifies the reactivity of nickel and palladium monodentate phosphine complexes for cross-coupling reactions into active and inactive using the minimum percent buried volume [$\%V_{bur}$ (min)].[23]

To demonstrate the use of classifiers for polymer synthesis, we devised a method that can predict a particular polymer microstructure. With a judicious selection of catalyst descriptors, a successful classifier can enhance the probability of discovering new designs by narrowing down the search space, thereby reducing time and resources needed for synthesis and experimentation. Herein, we adopt a data-driven methodology to screen virtual catalyst designs with a supervised classifier, thereby accelerating the discovery process.

We focused on palladium complexes because they have been used for a longer time than nickel compounds[10, 24-25] for the synthesis of polyketones and, therefore, there are more examples reported in the literature. Currently, palladium catalysts capable of accessing non-alternating ethylene-CO copolymers are supported by phosphine sulfonate and diphosphazane monoxide ligand classes (Figure 1).[2, 7-9, 26]

The data-driven catalyst discovery process has four stages: data preparation, descriptor selection, classifier prediction and experimental validation (Figure 2). To begin, a training dataset was first curated by obtaining catalyst structures from previous examples that could produce either alternating[27-32] or non-alternating polyketones (Figure 1).[2-4, 7-9, 33-34] We grouped catalysts that have a comparable or higher degree of non-alternation (< 50% CO) than the conventional phosphine sulphonate catalyst into the 'non-alternating' dataset. 25 examples were used for non-alternating polyketones, and 12 examples were used for alternating polyketones (Figure S2). In the 'alternating' dataset, apart from the commonly used symmetrical diphosphines, we also included asymmetric structures and structures with different donor atom combinations. In addition to the training dataset, an 'untested' dataset was curated using compounds that have not been examined for their CO/C_2H_4 copolymerization performance.

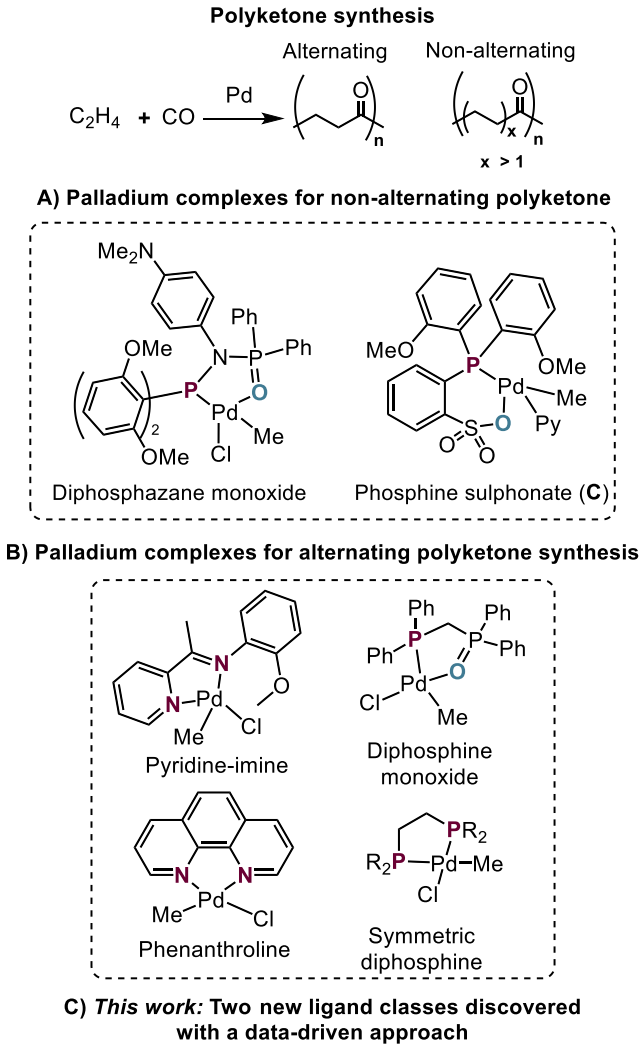


Figure 1. Polyketone synthesis and examples of supporting ligands used for non-alternating copolymerization of ethylene and CO. [2, 7-9, 26]. Classes of palladium complexes used for non-alternating (A) and alternating (B) polyketone training dataset, and successful predictions using the reported algorithm (C).

To broaden the exploration of potential candidates for non-alternating polyketone synthesis beyond phosphine-sulphonates and disphosphazane monoxides, the virtual candidates included compounds with various donor atom combinations. Most of the virtual candidates were inspired by catalysts used in the copolymerization of ethylene and polar monomers.[35-38]

After obtaining a training dataset, we used density functional theory (DFT) to survey various electronic and steric descriptors of the palladium 5-membered keto-alkyl chelating intermediate (Figure 2). We chose to focus on this 5-membered chelate because previous studies suggested that its destabilization enables a greater likelihood for consecutive ethylene insertions.[2, 26, 33]

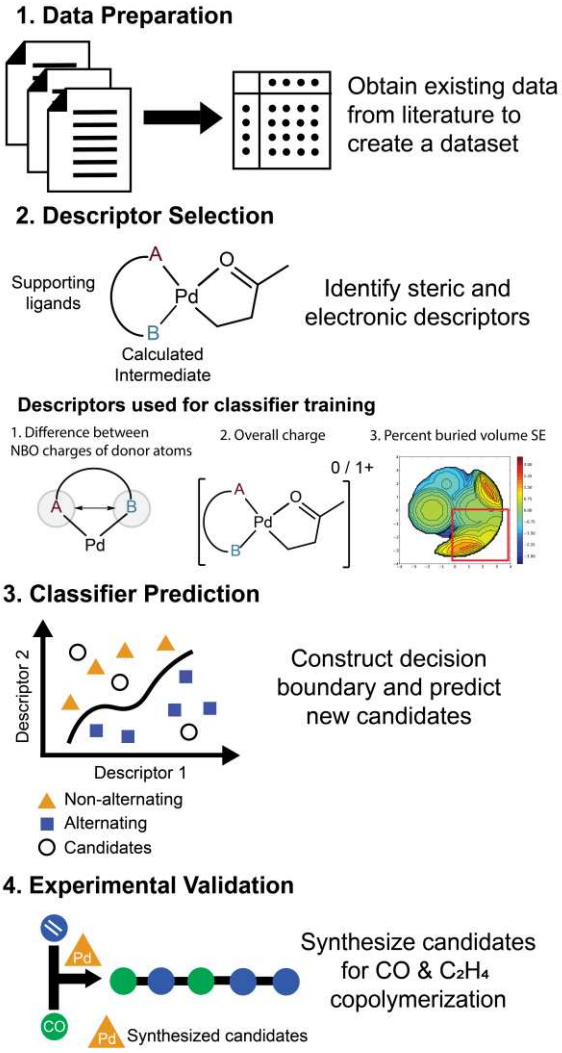


Figure 2. Classifier-assisted catalyst discovery workflow for non-alternating polyketone synthesis. Descriptors chosen for training the classifier (SE = southeast).

For electronic descriptors, we examined individual natural bond order (NBO) charges of ligand donor atoms, their differences, and the energy gap between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). For steric descriptors, we extracted angles, distances, geometric indices, and percent buried volumes with SambVca 2.1.[39-40] We also wanted to obtain descriptors that highlight steric crowdedness for a specific region within the steric map, but the total and quadrant percent buried volumes calculated by the program were insufficient in achieving this goal. Thus, we constructed two customized descriptors (%Filled_x and %Filled_y) from the generated steric map that would determine the steric crowdedness of specific regions (Figure S5). After gathering various values of steric crowdedness for each specific region, we also calculated the weighted average across all regions as another descriptor.

The descriptors for training the classifier were selected based on the Pearson correlation coefficient between the descriptor values with the target variable (non-alternating / alternating).[41-43] First, we eliminated descriptors that had a high correlation between each other to reduce multicollinearity (> 0.8 or < -0.8, Figure S6-S7). After removing descriptors with high multicollinearity, we categorized the remaining descriptors as either steric or electronic. For each of the two categories of descriptors, we chose those with the

highest coefficient of determination against the binary outcome (alternating versus non-alternating), the difference between the NBO charges of the donor atoms and the percent buried volume of the southeastern (SE) quadrant (Table S7).

Although not obvious at the onset, the chosen electronic and steric descriptors have chemical significance. Past studies with phosphine-sulphonate and diphosphazane monoxide palladium complexes suggested that a high degree of electronic asymmetry tends to favor consecutive ethylene insertions that lower the CO content in the polymer.[9] Since the difference in NBO charges between the two donor atoms can be used to probe the degree of electronic asymmetry within a bidentate ligand, this descriptor has a high correlation coefficient with the target outcomes. Furthermore, Caporaso and coworkers showed that the presence of alkyl or methoxy substituents on the ortho position of the phosphine aryl groups could contribute to the destabilization of the five-membered chelate by increasing steric bulk around the metal center, thereby favoring the non-alternation pathway.[42]

In addition to these two descriptors, we decided to use the overall charge of the supporting ligand as a descriptor as well. Although it does not correlate highly with the target variable, it aided the algorithm in evaluating the steric and electronic influences separately for the cationic and neutrally charged supporting ligands.

After obtaining relevant descriptors, we used Scikit-learn, a free software machine learning library, to train the dataset with various supervised classification model algorithms, including support vector machines, K-nearest neighbors, decision tree, naive bayes, and random forest.[44] The dataset was first standardized, followed by a train-test split of 0.6. Then, a grid optimization algorithm was applied to determine the best hyperparameters for each classification algorithm (Table S8-S9). Since the size of the training dataset is small (n = 25), leave-one-out cross validation was used to improve the generalizability of the classifier and prevent the possibility of overfitting.[45] All optimized classifiers provided high accuracy and cross validation scores (> 80%) during the training stage (Table S10). A 3D decision boundary diagram was subsequently generated to enable a visualization of how the trained model predicts the outcome of our target candidates (Figure 3A, S9-S14). These visualizations demonstrate that the combination of the three chosen descriptors and the classifier algorithm can separate the two types of catalyst designs accurately (regions highlighted in blue and orange in Figure 3A).

The predictions for all 51 virtual candidates are shown in Table S4. From these predictions, we chose 8 candidates (Figure 3B) to test for the formation of non-alternating polyketones. Compounds **1-4** are predicted to form non-alternating polyketones by all algorithms, while the predictions for **5-8** are not consistent, varying from one (**6**) to two (**7**) and three (**5** and **8**) algorithms predicting an alternating structure (Table S4). Compounds **1-8** were synthesized and their reaction with ethylene and CO was carried out at 80 °C under a total pressure of 20 bar, where the C_2H_4/CO gas ratio was 19/1. Compound **C**, (PO-OMe)PdMePy (PO-OMe = P(2-OMe-Ph)$_2$(2-SO_3Ph)), was also tested under the same reaction conditions.[2] The resulting polymer microstructures were characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy (Figure S47-S63), and the molecular weight of the polymers was determined by size exclusion chromatography (SEC, Figures S64-S68).

Compounds **1-4** formed non-alternating polyketones with a CO incorporation ranging from 44 to 37% (Table 1, entries 2-5), values lower than most of the reported palladium catalysts (Table S1). However, these compounds did not produce non-alternating polyketones with as low of a CO incorporation as some known nickel catalysts (Table S2).[10] Importantly, compound **C** yielded non-alternating polyketones with a higher CO incorporation (46%) than **1-4** under the same reaction conditions (Table 1, entry 1).

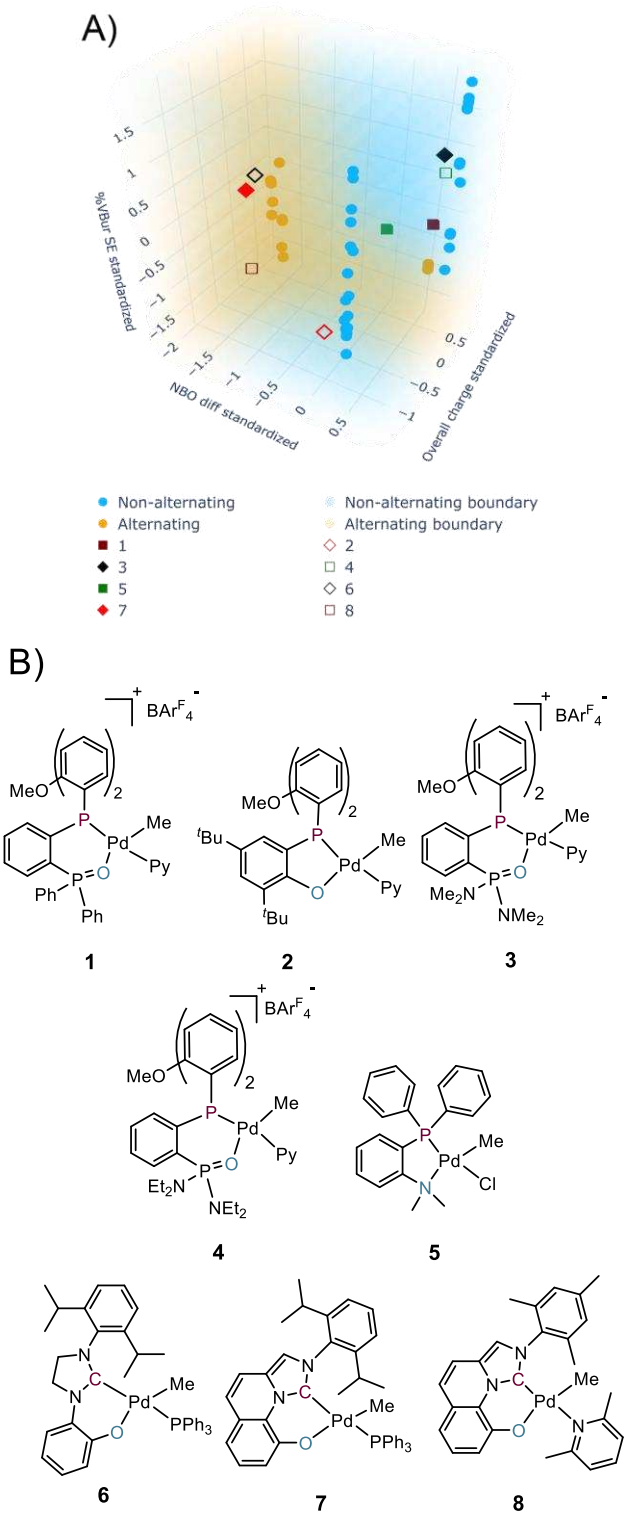
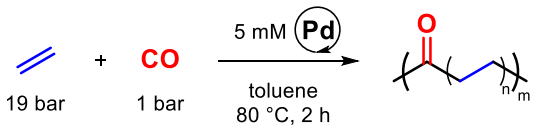


Figure 3. A) Classifier decision boundary trained with the K-nearest neighbors algorithm, using three descriptors. The orange and blue dots represent the catalyst design from the training dataset. The light orange and light blue region represent the region predicted to form alternating and non-alternating polyketones, respectively. The square and diamond data points represent the tested structures. A better visualization for these 3D decision boundaries can be accessed with the GIFs provided as supporting material. B) Structures of Pd complexes that were synthesized and tested experimentally to validate the model.

In comparison with the control compound **C** (Table 1, entry 1), **1** generated polyketones with a higher molecular weight and a monomodal distribution (Table 1, entry 2), while the polyketones synthesized by **2**-**4** showed similar or lower molecular weights than **C** with bimodal distributions (Table 1, entries 3-5). The vinyl end group observed in the ^{1}H NMR spectra of the polyketones suggested that the chain termination involves β-H elimination resulting in low molecular weights of polymers (Figure S47, S50, S53, S57, S60).[10, 46-48] Compounds **5**-**8** displayed no CO/ethylene copolymerization activity. For carbene-based compounds **6**-**8**, the presence of CO may have led to catalyst poisoning, since these compounds could achieve high ethylene homopolymerization activity (23 g/mmol·h), while the decomposition of the compounds into Pd(0) black was observed in the presence of CO even at room temperature (Table S11).[9, 49-50]

Table 1. Copolymerization of ethylene and CO by selected Pd complexes.[a]



Entry	Cat.	Activity (g/mmol·h)	CO (%)[b]	M_n (g/mol)[c]	$Đ$[d]
1	**C**	1.8	46	2,660	1.55
2	**1**	0.49	40	6,470	1.11
3	**2**	0.63	43	1,840	1.32[d]
4	**3**	1.11	37	2,320	1.51
5	**4**	0.67	43	1,610	1.29[d]
6[e]	**5**	0	-	-	-
7	**6**	0	-	-	-
8	**7**	0	-	-	-
9	**8**	0	-	-	-

[a] All copolymerizations were carried out at 80 °C for 2 hours with C_2H_4/CO = 19/1 using 5 mM Pd catalyst. Catalyst **C** represents the Pd catalyst supported by the phosphine-sulphonate ligand from previous literature. [b] CO incorporation was determined by ^{1}H NMR spectroscopy (see SI, Section 1 for details). [c] M_n and $Đ$ were determined by SEC measurements in chloroform at 40 °C and a flow rate of 0.70 mL/min and were calibrated with narrow-dispersity polystyrene standards (see SI, Section 1 for details and Figures S64-S68). [d] Bimodal distribution. [e] 1 equiv of $NaBAr^F$ was added.

Attenuated total reflectance infrared (ATR-IR) spectroscopy was also employed to investigate the presence of the carbonyl group in polyketones. The ATR-IR spectra of the obtained polymers from the reactions with **1**-**4** revealed that all non-alternating polyketones have an almost identical C=O stretching at 1693 cm^{-1}, due to the similar degree of CO incorporation (Figure S69).[11] Importantly, polyethylene was not observed at 1468 cm^{-1}, suggesting that the obtained polymers are not a mixture of polyethylene and alternating polyketone.

In summary, we designed a data-driven approach using a classifier that can assist in predicting the selectivity of ethylene-CO copolymerization. This method was developed to discover catalysts with CO incorporation < 50%, without any training or predictions about catalytic activity. With three descriptors, namely the difference in NBO charge between ligand donor atoms, the overall charge, and the percent buried volume of the southeast quadrant, we were able to achieve a satisfying predictive performance and obtain two new classes of compounds that could produce non-alternating polyketones with a degree of non-alternation greater than the conventional phosphine sulphonate catalysts. Our method expands the structural diversity of palladium catalysts capable of producing ethylene/CO copolymers with a varying CO content, and validates the descriptor-based approach with a relatively small set of inputs that could be broadly appropriate for organometallic chemistry. We envision that this methodology can be applied to accelerate catalyst discovery when selectivity is an important outcome. In addition, since nickel-based catalysts are of high interest due to their low cost, we are currently pursuing the development of new models to predict their performance as future work. Due to the scarcity of known nickel-based catalyst for non-alternating polyketone synthesis, using a predictive algorithm would overcome the limitation of data sparsity. Future studies will leverage statistical analysis and machine learning to target multiple properties simultaneously.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Computational details, polymerization and characterization data, NMR spectra (PDF)
Repository with relevant files to train the binary classifier and plot decision boundaries for the catalyst designs at https://github.com/pldresearch/classifier-polyketone

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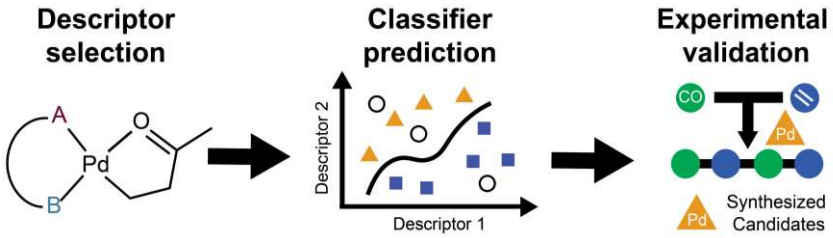
TOC Graphic


Descriptor selection
Classifier prediction
Experimental validation
A
O
Pd
B
Descriptor 2
Descriptor 1
CO
Pd
Pd
Synthesized Candidates