

Kernel Methods for Predicting Yields of Chemical Reactions

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Abstract

The use of machine learning methods for the prediction of reaction yield is an emerging area. We demonstrate the applicability of support vector regression (SVR) for predicting reaction yields, using combinatorial data. Molecular descriptors used in regression tasks related to chemical reactivity have often been based on time-consuming, computationally demanding quantum chemical calculations, usually density functional theory. Structure-based descriptors (molecular fingerprints and molecular graphs) are quicker and easier to calculate, and are applicable to any molecule. In this study, SVR models built on structure-based descriptors were compared to models built on quantum chemical descriptors. The models were evaluated along the dimension of each reaction component in a set of Buchwald-Hartwig amination reactions. The structure-based SVR models out-performed the quantum chemical SVR models, along the dimension

of each reaction component. The applicability of the models was assessed with respect to similarity to training. Prospective predictions of unseen Buchwald-Hartwig reactions are presented for synthetic assessment, to validate the generalisability of the models, with particular interest along the aryl halide dimension.

Introduction

Advances in medicinal chemistry rely on the discovery and synthesis of novel molecules. Time, cost and efficiency pressures in the pharmaceutical industry are key drivers in accelerating drug design and development. The success of artificial intelligence and machine learning in other fields, such as image recognition and text processing, has sparked increased interest in their application to drug discovery.¹⁻³ This attention includes the design and optimisation of small molecules. The availability of large reaction datasets and high-performance computing have been key in the development of computer-aided chemistry,⁴ for example in: molecular design,⁵ retrosynthetic planning tools,⁶⁻¹⁰ reaction prediction¹⁰⁻¹² and the optimisation of reaction conditions.¹³⁻¹⁵

Whilst the prediction of biological activities and molecular properties using quantitative structure-activity or structure-property relationship (QSAR/QSPR) models has been well-studied,^{1,16} reactivity prediction, has been explored much less. This is largely due to a lack of appropriately curated data, for example, on reaction yield and enantiomeric excess (%ee). Performing a large number of experimental reactions is expensive, time-consuming, resource-consuming and requires synthetic chemists. High-throughput chemistry, along with batch and flow systems, have recently opened up opportunities to generate reaction data for use in machine learning.¹⁷⁻¹⁹

Support vector machines (SVM) are a supervised learning technique that can be applied to classification and regression problems, whereby the label is either a class/category or continuous value, respectively.²⁰ For non-linear relationships, SVMs use a kernel function to map data from an input space to a high-dimensional feature space, where classification or re-

gression is performed linearly. The kernel function computes the inner product in the feature space directly, without applying the non-linear transformations at a higher computational cost. Different types of kernels have been assessed for both classification and regression problems related to chemo-²¹ and bioinformatics.²²⁻²⁶ Applications of SVMs in chemistry include bioactivity prediction, toxicity-related properties and physicochemical property prediction.^{1,26-29}

A dataset consisting of chemical structures or reactions must be converted to a machine readable format before it is presented to a machine learning algorithm. Molecular descriptors are based on the structural, physiochemical, electronic, or topological nature of molecules. Quantum chemical descriptors are common for the prediction of chemical reactivity.^{19,30-32} They have also been used to build kernel-based QSAR and QSPR models, employing the Gaussian radial basis function (RBF) kernel.³³⁻³⁵ Site-specific, atomic properties including NMR shifts, vibrational frequencies, vibrational intensities and partial atomic charges have been used, along with global descriptors such as HOMO (Highest Occupied Molecular Orbital) energies, LUMO (Lowest Unoccupied Molecular Orbital) energies, dipole moment and polar surface area. Three-dimensional steric descriptors have been included in models of catalyst selectivity to improve predictions, by capturing important conformational information.^{31,32} Quantum chemical descriptors are typically calculated using density functional theory (DFT), which can be computationally demanding. Therefore, quantum chemical descriptors may not always be appropriate for large datasets, particularly if the dataset contains large molecules. Site-specific descriptors require overlapping, common structural features within the molecules.^{19,30,31} Reaction components that consist of a large variety of molecules with no key shared atoms between them all, require alternative representations such as structure-based descriptors.

A chemical hashed fingerprint defines the two-dimensional topology of a molecule in the form of a vector of binary bits. For example, MACCS Keys³⁶ depict the presence or absence of a set of predefined structural fragments, while other fingerprints consider each atom and

its local environment. Morgan circular fingerprints³⁷ encode the neighbourhood within a particular radius of each atom, whereas RDK fingerprints³⁸ encode topological paths up to a specified path length. Molecular fingerprints are fast and easy to calculate, making them a popular choice for representing molecules. They are established in machine learning for virtual screening³⁹ and have emerged in the prediction of reaction conditions.^{13,14} Sandfort et al.⁴⁰ have shown that two-dimensional, structure-based molecular fingerprints can achieve similar accuracy to quantum chemical descriptors in the prediction of chemical reactivity. Reactions were represented by a concatenation of multiple fingerprint features (MFFs) and were used to build random forest models to predict reaction yields and %ee.⁴⁰ Fingerprints have also been utilised in kernel-based QSAR/QSPR relationship models, using the Tanimoto or RBF kernel.²⁷⁻²⁹

Labelled molecular graphs are another two-dimensional representation that depict the connectivity of a set of nodes, labelled with atom type, by a set of edges that are labelled by the bond order. From herein, we refer to labelled molecular graphs as molecular graphs. The global molecular structure is considered, in contrast to the local environments in fingerprints. The kernel trick can be applied to molecular graphs to build machine learning models based on kernel methods, including SVMs.⁴¹ Kriege et al.²³ give a detailed overview of graph kernels and provide guidelines to aid researchers in the identification of successful kernels for different applications. The Weisfeiler-Lehman (WL)⁴² graph kernel is well-established in cheminformatics.²³ The WL graph kernel has been embedded in a neural network^{43,44} and applied to the prediction of chemical reactivity.^{12,44} Molecular graphs have been used in combination with deep learning to generate graph convolutional network models for reaction prediction,¹² retrosynthetic route design⁷ and the prediction of reaction conditions.⁴⁵

The prediction of reaction yields and enantiomeric excess are multidimensional problems as reaction outcomes depend on multiple reaction parameters, including both categorical and continuous variables. Small changes in the reaction conditions such as catalyst(s), reagent(s), solvent(s), as well as temperature and pressure can result in radically different reaction out-

comes or possibly failed reactions. Even with the chemical intuition and experience of expert synthetic chemists, chemical reactivity and reaction outcomes can be challenging to anticipate. High-throughput experimentation enables the screening of multiple discrete reaction variables (catalysts, reagents, solvents) on a nanomolar scale.^{46,47} A matrix of parallel reactions is performed on a plate at the desired temperature and pressure, with the same reaction time. The samples in each well are analysed using liquid/gas chromatography-mass spectrometry (LCMS/GCMS). There are challenges associated with such high throughput chemistry. These include the handling of very small volumes of liquid, evaporative solvent loss due to the use of volatile organics and solubility. The technique has proved useful for the optimisation of reaction conditions, as well as the discovery of new chemical reactivity in the pharmaceutical industry and academia.^{46,47} It is also a lower cost alternative for generating reaction data with which to build machine learning models.^{19,32,40,48}

An open-source combinatorial dataset, including reaction yields, was reported by Doyle et al.¹⁹ The experiments were performed on three 1536-well high-throughput plates with the use of the Mosquito robot. The dataset contains a set of Buchwald-Hartwig amination reactions between 4-methylaniline and 15 aryl halides, under varying reaction conditions (Scheme 1). The mechanism of the Buchwald-Hartwig cross-coupling reaction is well understood, including the role of the catalyst and base.⁴⁹ This type of palladium catalysed C-N cross-coupling of amines and aryl halides has attracted particular attention due to its wide application in the pharmaceutical industry.⁵⁰⁻⁵² The aromatic amine products are important building blocks for the synthesis of small drug-like molecules.⁵³ However, this key transformation can be limited if the substrates contain a five-membered ring with a heteroatom-heteroatom bond. Despite the drug-like characteristics of such heterocycles, for example isoxazoles, they are not common in approved pharmaceuticals.⁵³ Potentially inhibitory isoxazole additives were included in the Buchwald-Hartwig reactions to assess the effect of compounds containing isoxazole heterocycles on the reaction performance. Glorius developed an approach to identify catalysis inhibiting sub-structures by deliberately adding representative fragments

to the catalytic mixture.⁵⁴ This allowed assessment of the sub-structures' effect on reaction performance, without the need to synthesise and isolate isoxazole (or other) containing aryl halides as a prior step to performing the coupling reactions. Doyle et al. performed additional experiments which supported their hypothesis that electrophilic isoxazole additives undergo a competitive side reaction.¹⁹ The N-O oxidative addition of the electrophilic isoxazoles to palladium results in a lower yield of the amine products in the Buchwald-Hartwig reactions.



Scheme 1: Buchwald-Hartwig amination reaction.¹⁹

The dataset reported by Doyle et al. was used to build machine learning models to predict reaction yield.¹⁹ The reactions were represented using quantum chemical descriptors for each reaction component (aryl halide, additive, base and catalyst ligand). Datasets with combinatorial structure have an intrinsic pattern (i.e. the presence or absence of molecules) which can lead to large variations in the performance of a model depending on the train-test split of the data.⁵⁵ By splitting the data randomly, the reaction components in the test reactions will also be present in different training reactions. This type of in-sample test, where descriptors of molecules in the test reactions are already observed in training, can result in an unreliable representation of model generalisability. Models may fit the pattern of the data, rather than the relationship between chemically meaningful descriptors and the observed data. These models would therefore struggle when extrapolating to unseen chemical entities. One-hot encodings⁵⁶ can be used as a baseline to validate model performance and reveal potential patterns within the training data that may be fitted by models built on chemically meaningful descriptors. This one-hot encoding of a reaction simply denotes the presence or absence of each molecule in the form of a vector and encapsulates no information

beyond this. For a random 70-30% train-test split of the Buchwald-Hartwig data, Chuang and Keiser showed models built on one-hot encodings exhibited near identical performance to quantum chemical descriptors.⁵⁶

A more appropriate assessment of model generalisability is to test models with molecules that are not present in the training set, an out-of-sample test.⁵⁵ A set of reactions containing specific molecules (one or more reaction components) are withheld from model training and used to assess the predictive ability of the trained model. It is important to ensure models are trained on reactions that cover a broad range of chemical space and observed variables. Doyle et al.¹⁹ designed out-of-sample test sets by splitting the reactions along the high-throughput plates, where each plate contained a different set of additives. The random forest model built on quantum chemical descriptors was trained using the reactions on plate **1** and **2**, then tested using plate **3**. Chuang and Keiser identified that alternative splits of the plates resulted in a much lower performance, suggesting the random forest model built on quantum chemical descriptors was limited.⁵⁶ Splitting the data along plate lines was also not a reliable way to assess model generalisability as each plate did not cover an even spread of chemical reactivity (Figure S5). Out-of-sample test sets were therefore redesigned using activity ranking, along the additive dimension.⁵⁷ The mean yield of the reactions containing each additive were ranked from lowest to highest. The highest and lowest yielding additives were included in all training sets. Test sets were constructed from the remaining additives by taking every fourth molecule. This was repeated three more times to create a total of four test sets. Designing test sets using activity ranking ensured the model was trained on a range of reaction yields (Figure S6).⁵⁷ The quantum chemical random forest model showed good generalisability across the additive dimension, with a mean coefficient of determination (R^2) of 0.69 and root-mean-squared-error (RMSE) of 14.9% in the additive ranked test. Doyle et al. did not perform out-of-sample tests using activity ranking along the aryl halide dimension.

Support vector regression (SVR) models have been successful in the prediction of numer-

ical values²⁰ related to QSAR and chemoinformatics.⁵⁸ Although Doyle et al. reported that the random forest method outperformed SVR in an initial in-sample test,^{19,57} we investigate the application of kernel methods further in the prediction of reaction yields, with more rigorous testing. In this study, SVR models are built on quantum chemical descriptors and two types of structure-based descriptors: molecular graphs and molecular fingerprints. Structure-based descriptors are applicable to a wider range of molecules and are less computationally demanding than quantum chemical descriptors. Therefore, the extent of generalisability of the molecular descriptors, without compromising on performance, is investigated by evaluating model performance along the dimension of each reaction component. To ensure the reported generalisability of the models is reliable, test sets are designed using activity ranking and the applicability of the models was assessed. A set of prospective reactions are outlined for model validation and predictions of reaction yields are reported prior to experimentation.

Methodology

Dataset

The data used in this study were 4608 single-step reactions reported by Doyle et al.¹⁹ This open access dataset contains the reactants, products, reaction conditions and yields of a single reaction class, the Buchwald-Hartwig amination reaction (Scheme 1). The reactions varied in 23 isoxazole additives, 15 aryl/heteroaryl halides, three bases and four Buchwald ligands (Figure S1, S2 and S3). The data was generated using ultra-high-throughput experimentation in three 1536-well plates, giving a full matrix of reaction components including controls. Once the control reactions and reactions containing additive seven were removed, a total of 3955 reactions remained. Additive seven was removed as quantum chemical descriptors could not be calculated;¹⁹ see the Supporting Information for details. The names of the aryl halide, additive, base and ligand in each reaction were converted to SMILES (Simplified Molecular Input Line Entry Specification) strings.⁵⁹ This was completed using

the NCI/CADD Chemical Identifier Resolver API⁶⁰ with the exception of a few unrecognised names, which were drawn and converted to SMILES strings in ChemDraw.

A set of prospective combinatorial reactions was compiled to validate the SVR models. The proposed reactions will be performed experimentally using high-throughput chemistry to identify reaction yields. All possible combinations of 59 aryl halides, three bases, four catalyst ligands and two additives, formed a total of 1416 proposed reactions. Five of the aryl halides are present in the Doyle et al.¹⁹ dataset and will be used as standards. The remaining aryl halides cover ortho, meta and para substituents, with a range of electron withdrawing and electron donating groups (Figure S4). The base, DBU, and catalyst ligand, BrettPhos, were selected along with the two higher yielding bases and ligands from the Doyle et al. dataset: MTBD, BTMG, *t*-BuXPhos and *t*-BuBrettPhos (Figure S3). The prospective reactions will also be performed without a catalyst to investigate whether the reactions of the *ortho*-substituted halopyridines are proceeding via an alternative reaction pathway. As the aim of these reactions is to assess model generalisability, particularly along the aryl halide dimension, the reactions will be carried out, with and without, a single isoxazole additive: 3-methylisoxazole (Figure S1).

Molecular Descriptors and Preprocessing

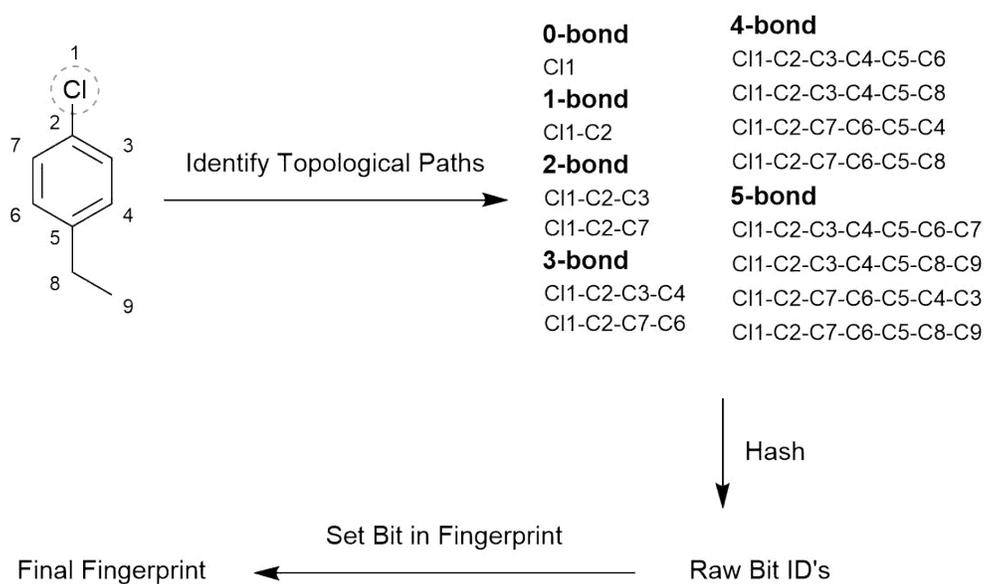
One-hot Encodings. One-hot encodings of chemical reactions are binary vectors that denote the presence or absence (1 or 0) of each molecule in the training reactions as shown in Table 1, where A_n , H_n , B_n and L_n are the number of additives, aryl halides, bases and ligands present in the training reactions. The reactions are represented without using chemically meaningful information and by construction are not able to generalise to unseen chemical entities. Building machine learning models on one-hot encodings can reveal underlying patterns in combinatorial datasets and should be used as a validation method.

Table 1: Format and Notation of the Quantum Chemical Descriptors, Fingerprints, Tanimoto Kernel Descriptors, WL Kernel Descriptors and One-hot Encodings for a Single Reaction

Descriptor	Additive			Aryl Halide			Base			Ligand		
One-hot Encodings	A_1	\dots	A_n	H_1	\dots	H_n	B_1	\dots	B_n	L_1	\dots	L_n
Quantum Chemical	$[1 \quad \dots \quad 0]$			$[1 \quad \dots \quad 0]$			$[1 \quad \dots \quad 0]$			$[1 \quad \dots \quad 0]$		
Fingerprints	$[D_1^A \quad \dots \quad D_{19}^A]$			$[D_1^H \quad \dots \quad D_{27}^H]$			$[D_1^B \quad \dots \quad D_{10}^B]$			$[D_1^L \quad \dots \quad D_{64}^L]$		
Tanimoto Kernel	$[\dots \quad 0 \quad 1 \quad \dots]$			$[\dots \quad 0 \quad 1 \quad \dots]$			$[\dots \quad 0 \quad 1 \quad \dots]$			$[\dots \quad 0 \quad 1 \quad \dots]$		
WL Kernel	$[\quad k_{TA} \quad]$			$[\quad k_{TH} \quad]$			$[\quad k_{TB} \quad]$			$[\quad k_{TL} \quad]$		
	$[\quad k_{WLA} \quad]$			$[\quad k_{WLH} \quad]$			$[\quad k_{WLB} \quad]$			$[\quad k_{WLL} \quad]$		

Quantum Chemical Descriptors. A combination of calculated molecular, atomic and vibrational properties for the additive (D^A), aryl halide (D^H), base (D^B) and ligand (D^L) formed a set of quantum chemical descriptors for each reaction (Table 1). The quantum chemical descriptors for the Doyle et al. dataset were calculated by Doyle et al.¹⁹ The molecular descriptors included molecular volume, surface area, ovality, molecular weight, E_{HOMO} , E_{LUMO} , electronegativity, hardness and dipole moment. The atomic descriptors, NMR shifts and electrostatic charge, were calculated for shared atoms in each reaction component. The common molecular vibrational modes across the set of molecules for each reagent class were identified. The vibrational frequencies and infrared transition intensities were calculated for the common modes. The Spartan '14 interface for the Q-Chem quantum chemical software package^{61,62} was used to calculate 120 descriptors per reaction (19, 27, 10 and 64 descriptors for the additive, aryl halide, base and ligand, respectively) using the density functional B3LYP with the 6-31G(d) basis set.^{63,64} The same method was used to calculate the quantum chemical descriptors for the prospective reactions; computational details can be found in the Supporting Information. The descriptors were standardised by centring the data to have zero mean and scaling to unit variance. The mean and standard deviation were calculated on the training set and used to standardise both the training and test sets.

(a)



(b)

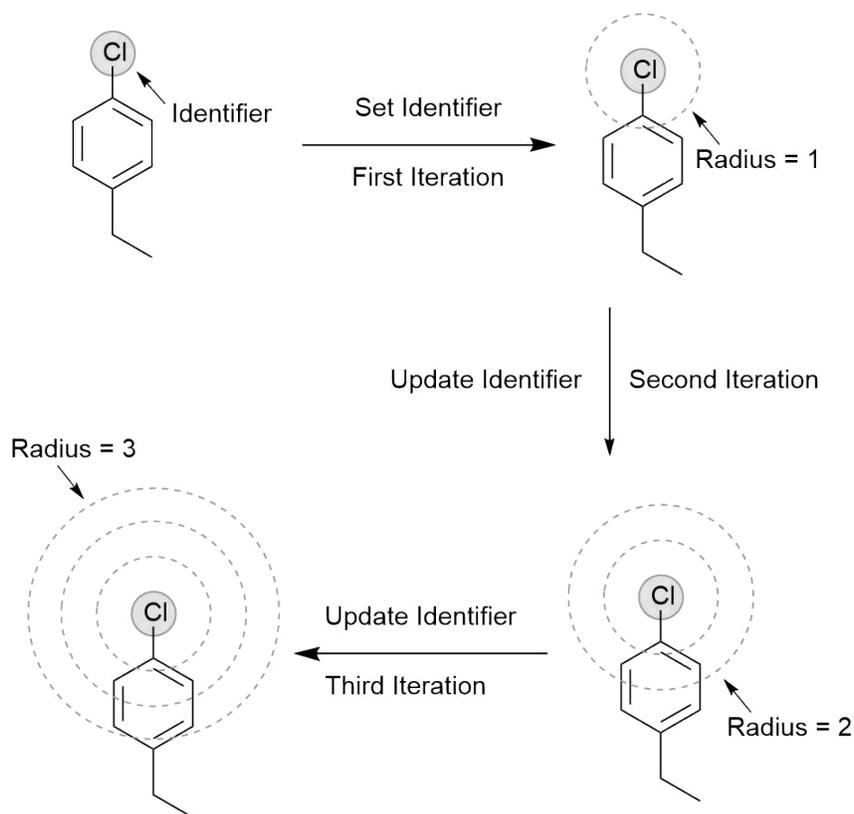


Figure 1: Schematics of how (a) RDK fingerprints and (b) Morgan fingerprints are calculated, using the chlorine atom in 1-chloro-4-ethylbenzene as an example. These processes would be repeated for each atom in the molecule.

Fingerprints and Tanimoto Kernel Descriptors. The topology of molecules can be represented by molecular fingerprints. Three types were implemented using the RDKit package: MACCS Keys,³⁶ RDK fingerprints³⁸ and Morgan circular fingerprints.³⁷ Fingerprints are hashes (i.e. binary bit vectors) of a specified length, set to 512-bit for this study (see the Supporting Information for further discussion), except the MACCS fingerprint which is 167-bit by definition. The bits within a MACCS fingerprint define the presence or absence of predefined substructures/fragments, called MACCS Keys. A total of 166 public MACCS Keys define the substructures/fragments as SMARTS strings. Note: There are 167 bits due to zero indexing in python, to allow for the original numbering of the MACCS keys (1-166), i.e. every fingerprint begins with a zero. RDK topological fingerprints and Morgan circular fingerprints are topological descriptors that define the connectivity of molecules. For the RDK fingerprints, fragments are generated by topological paths starting from each atom up to a predefined path length (number of bonds); the default seven was used (Figure 1a). The bond order and neighbour counts of each fragment are used with a hash function to set the bits in the molecular fingerprint. Morgan circular fingerprints, also called Extended Connectivity Fingerprints (ECFPs), initially set an identifier for each atom based on the number of adjacent non-hydrogen atoms, number of bonds to "heavy" atoms, atomic number, atomic mass, number of bonds to hydrogen atoms and whether the atom is in a ring. Feature Morgan fingerprints are a variant, also known as the Functional-Class fingerprints (FCFPs), that differ in the assignment of the atom identifier by assigning a code for the atom's role instead, e.g. hydrogen-bond acceptor and donor, aromatic, halogen, basic or acidic. In both types of Morgan fingerprints, each identifier is iteratively updated to include the identifier and bond order of neighbouring atoms (Figure 1b) up to a specified radius. Each iteration includes a larger circular environment around the atoms. Once the iterations are complete, the identifiers are folded into the length of the bit vector using a hashing function. For the purpose of this study, Morgan fingerprints with a radius of one was investigated. Feature Morgan fingerprints and radii greater than one were omitted from the study, see the

Supporting Information for additional details.

The fingerprint of the aryl halide, additive, base and ligand in each reaction was calculated. The fingerprints of the reaction components were used to generate fingerprint descriptors, by concatenating to form a single reaction fingerprint (Table 1), and Tanimoto kernel descriptors. Tanimoto similarity scores were calculated between the fingerprints of molecules within the same reaction class, as implemented in RDKit. For two molecules in a single reaction class represented by molecular fingerprints (F_{m_1} and F_{m_2}), the Tanimoto similarity^{65,66} is defined as

$$k_T(F_{m_1}, F_{m_2}) = \frac{c}{a + b - c} \quad (1)$$

where a and b are the number of bits set in fingerprints F_{m_1} and F_{m_2} , and c is the number of bits set in common in F_{m_1} and F_{m_2} . Although small changes in the structure of small molecules can lead to large changes in the Tanimoto similarity, it is a very well-established measure and thus appropriate for us to consider. To calculate the Tanimoto kernel between two reactions ($R_x, R_{x'}$), the Hadamard product of the reaction component kernels was taken. This is shown in Eq. 2, where A_i, H_i, B_i, L_i are the additive, aryl halide, base and ligand in reaction i .

$$k(R_x, R_{x'}) = k(A_x, A_{x'}) k(H_x, H_{x'}) k(B_x, B_{x'}) k(L_x, L_{x'}) \quad (2)$$

The training kernel is a symmetrical matrix generated using this method between all pairs of training reactions. The test kernel matrix is generated by calculating the Tanimoto kernel between the test reactions and training reactions. For a single reaction (R_x) in the training or test set, the Tanimoto kernel (Table 1) is in the format

$$K_{R_x} = k_{A_x} k_{H_x} k_{L_x} k_{B_x} \quad (3)$$

where the Tanimoto kernel of each reaction component is

$$k_{T_{M_x}} = [k(M_x, M_1) \cdots k(M_x, M_n)]$$

M is the reaction component class and n is the number of training reactions.

Molecular Graphs and WL Kernel Descriptors. A molecular graph represents the topology of a molecule by a set of labelled nodes corresponding to the atoms, connected by a set of labelled edges corresponding to the bonds. From the SMILES string of each molecule in the dataset, the atomic symbol, the index of each atom, the bond order, the index of each bond and the adjacency matrix were obtained using RDKit.³⁸ This information was parsed to a module within GraKel to generate molecular graph representations.⁶⁷ Weisfeiler-Lehman subtree (WL) graph kernels⁴² were calculated for each reaction component using GraKel. The number of iterations, hyperparameter h (also referred to as the WL depth), was set to five (see the Supporting Information for further discussion). The Hadamard product of reaction component kernels was calculated to give the WL reaction kernel as shown in Eq. 2. The training and test kernel matrices were also generated using the same method as the Tanimoto kernel descriptors. For a single reaction, R_x , the format of the WL kernel (Table 1) is shown in Eq. 3.

Encoding missing molecules The descriptors must account for the missing molecules included in the proposed reactions. For the quantum chemical descriptors, concatenated molecular fingerprints and one-hot encodings, the bits corresponding to the missing molecules were set to zero. For the kernel-based descriptors, the missing molecules were incorporated in the calculation of the kernel of each reaction component. For example, the kernel between two molecules (m_1 and m_2) represented by molecular graphs is defined below.

$$k'(m_1, m_2) = \begin{cases} k(m_1, m_2) + 1, & \text{if } m_1 \text{ and } m_2 \text{ are both present} \\ 2, & \text{if } m_1 \text{ and } m_2 \text{ are both missing} \\ 1, & \text{otherwise} \end{cases}$$

If both molecules are present the kernel of the two molecules is the original kernel plus one, if both molecules are missing the kernel equals two, otherwise the kernel is equal to one. This method is only applied when the training or test data includes missing molecules.

Support Vector Regression Models

Machine learning models relating descriptors to reaction yield were developed using the SVR method as implemented in scikit-learn.⁶⁸ In ϵ -SVR, the aim is to find a function that deviates from the observed variables by a maximum of ϵ for each training point. The following values were considered for the ϵ hyperparameter: 1, 5 and 10. To prevent overfitting of the training data, slack variables (ξ) are introduced to allow for errors larger than ϵ . Only the points x_i that fall outside of the ϵ -insensitive tube contribute to the objective function, with their contribution being equal to ξ_i or ξ_i^* .²⁰ Eq. 4 describes the optimisation problem that is solved during the training of the SVR algorithm.

$$\begin{aligned}
 \min_{\mathbf{w}, \xi, \xi^*} \quad & \frac{1}{2} \|\mathbf{w}\|^2 + C \sum_{i=1}^n (\xi_i + \xi_i^*) \\
 \text{subject to} \quad & y_i - \mathbf{w}^T x_i \leq \epsilon + \xi_i \\
 & \mathbf{w}^T x_i - y_i \leq \epsilon + \xi_i^* \\
 & \xi_i, \xi_i^* \geq 0
 \end{aligned} \tag{4}$$

The hyperparameter, C , can be tuned to determine the toleration of points outside of ϵ . As C increases, the tolerance increases. The following values were considered for C : 1, 10, 100 and 1000.

SVR uses a kernel function to map input data to a higher-dimensional feature space where regression is performed linearly. The kernel functions (Table 2) explored were: linear, polynomial, Gaussian radial basis function (RBF) and sigmoid. The sigmoid equation is not a valid kernel but has been successfully applied, see Schölkopf⁶⁹ for further details.

The equations of these kernel functions between two data points (x and x') represented by molecular descriptors are shown in Table 2. All four kernels were applied to the quantum chemical, concatenated molecular fingerprint and one-hot encoding feature vectors, with the hyperparameters set to the values in Table S3, using scikit-learn. Although Kriege et al.²³ suggest there is little benefit in the combination of the WL kernel with non-linear kernels, we explored the WL kernel in combination with linear and non-linear kernels for completeness. Both kernel-based descriptors were used as a precomputed kernel as well as with the polynomial, RBF and sigmoid kernels applied to the individual entries of the kernel descriptor matrix. The hyperparameters of the kernels were tuned over the values in Table S3.

Table 2: Kernel Equations on two data points x and x'

Kernel Name	Equation, $k(x, x')$
Linear	$x^\top y$
Polynomial	$(\gamma_p x^\top x' + c_p)^d$
RBF	$\exp(-\gamma_r \ x - x'\ ^2)$
Sigmoid	$\tanh(\gamma_s x^\top x' + c_s)$

Model Building and Evaluation

The hyperparameters of the SVR models (ϵ and C) were optimised in scikit-learn by performing an exhaustive grid-search over the specified parameter grid (Table S2 and S3) on the training set, using five-fold cross-validation. For each train-test split of the data, the training set was shuffled and split into five groups. In turn, each of the five groups was used to test a model trained on the remaining four groups. The average performance statistics were calculated and compared to identify the best combination of hyperparameters. This grid search cross-validated and training performances are reported for each model in the out-of-sample tests and the prospective SVR models in the Supporting Information. The best combination of hyperparameters was used to build the SVR model on the training set for the particular train-test split and are reported for the prospective SVR models in the

Supporting Information.

Five-fold cross-validation was performed on the Doyle et al. dataset to identify the optimal values for the bit length of the molecular fingerprints and the WL depth of the WL graph kernel. Out-of-sample test sets were designed to assess model generalisability to unseen molecules along each reaction component (additive, aryl halide, base and ligand). The models were tested on a specific set of molecules that were withheld from model training. Activity ranking was used to generate the additive and aryl halide test sets, to ensure the models were trained on a range of reaction yields.⁵⁷ The mean yields of the reactions containing each additive and aryl halide were ranked from lowest to highest. The highest and lowest yielding additives and aryl halides were included in all training sets for the additive and aryl halide tests, respectively. Test sets were constructed using every n^{th} molecule where $n = 4$ for the additives (Table S34) and $n = 3$ for the aryl halides (Table S35). Due to the small number of bases (three) and ligands (four) in the dataset, two leave-one-out test were performed. In the first leave-one-out test, the dataset was split into three test sets based on the base used in the reactions, herein called the leave-one-base-out. For the second test, the dataset was split into four test sets based on the ligand used in the reactions, herein called leave-one-ligand-out. In turn, each test set was withheld from model training. The performances of the regression models were evaluated by the coefficient of determination (R^2) and RMSE for data points outside of the training set. The coefficient of determination can be negative if the mean of the data is a better fit to the observed values than the predicted values, i.e. $SS_{res} > SS_{tot}$, see Eq. 5.

$$R^2(y, \hat{y}) = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y})^2} = 1 - \frac{SS_{res}}{SS_{tot}} \quad (5)$$

where $\bar{y} = \frac{1}{n} \sum_{i=1}^n y_i$; \hat{y}_i is the predicted value of the i -th sample; y_i is the corresponding observed (experimental) value; and n is the total number of samples. The residual sum of squares, SS_{res} is the discrepancy between the observed and predicted values. The total sum

of squares, SS_{tot} is proportional to the variance of the data. All analysis was performed using scikit-learn. SVR models built on one-hot encodings were used as a baseline, for comparison.

Results and Discussion

Diversity of the Train-Test Splits

The reactions in the Doyle et al.¹⁹ dataset cover a range of yields (Figure 2), with the majority low yielding (0 to 10%) and few high yielding (90 to 100%). It is important in an assessment of model performance, to split the data into training and test sets that ensure an even spread of chemical reactivity is included in each. Chuang and Keiser have shown that splitting this dataset by high-throughput plate (where all inhibitory additives were present on a single plate) leads to an inaccurate estimation of performance due to an uneven cover of reaction yields (Figure S5a).⁵⁶ A similar conclusion is expected when assessing the models along the aryl halide dimension, if split based on halide or ring type (Figure S5). Splitting data using activity ranking ensures models are trained and tested on similar distributions of reaction yields (Figure S6). Details of the activity ranking test sets, including the calculated mean reaction yields are presented in the Supporting Information.

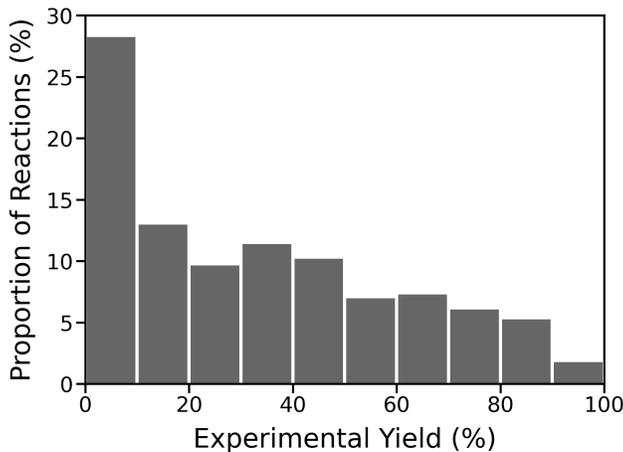


Figure 2: Distribution of experimental yields, excluding control reactions and reactions containing 5-phenyl-1,2,4-oxadiazole (additive **7**), corresponding to 3955 data points.

It is important to assess whether the reactions in the test set are within the domain of applicability. The similarity of test reactions to the training reactions was evaluated using the maximum product of pairwise Tanimoto scores, calculated using the Morgan2 fingerprint, of the reaction components. The maximum similarity to training reactions for the additive and aryl halide ranked tests range from 0.30 to 0.65 and from 0.30 to 0.55, respectively (Figure 3). The models are expected to predict instances with low maximum similarity scores less accurately than those with high maximum similarity scores.

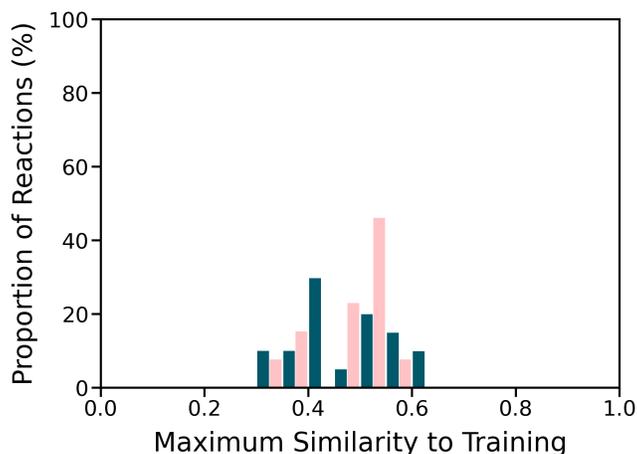


Figure 3: Distributions of maximum similarity to training reactions for the additive ranked test sets (dark blue bars) and aryl halide ranked test sets (pale pink bars). Maximum similarity to training was calculated using the maximum product of pairwise Tanimoto scores (with the Morgan2 fingerprint) of the reaction components.

Prediction of Reaction Yield

An initial five-fold cross-validated test was performed to optimise the bit length of the molecular fingerprints and the WL depth of the WL graph kernel. The cross-validated performance of the SVR models is presented and discussed in the Supporting Information. The overall best fingerprint length was 512 (Table S4 to S9, Figure S10 and S11) and the best WL depth was five (Table S10 to S12, Figure S13). To evaluate the generalisability of the models, out-of-sample tests were designed without activity ranking and with activity ranking. The performance of the yield prediction models built on quantum chemical descriptors,

fingerprints, Tanimoto kernel descriptors and WL kernel descriptors for the tests without activity ranking and with activity ranking are shown in Table 3 and 4, respectively. The performance metrics are reported as the average over the test sets for the specified split of the data. The grid search cross-validated (on the training set), training set and test set performances of the models for the individual test sets can be found in the Supporting Information. The performance of the SVR models built on one-hot encodings are reported to assess whether the models were fitting any underlying combinatorial structure in the training reactions.

Without Activity Ranking

The following tests did not take into account the distribution of reaction yields in the training and test sets: additive plate split, aryl halide ring type and halide splits. The lower average performances of these tests (Table 3) in comparison to the activity ranked splits (Table 4) underscore the importance of test set design.^{56,57} These splits of the data give a low, misrepresentative estimate of model performance, due to the uneven distribution of reaction yield across the test sets (Figure S5). The average model performances for the leave-one-base-one and leave-one-ligand-out tests were modest (Table 3). The SVR model built on the MACCS fingerprints with the polynomial kernel ($R^2 = 0.57$) and the WL kernel with the Sigmoid kernel applied ($R^2 = 0.56$) were the only models to outperform the one-hot encodings model ($R^2 = 0.53$) in the leave-one-base-out test. For the leave-one-ligand-out test, all models have a negative R^2 for the XPhos test set due to the uneven representation of yields in the training and test set (Figure S5e), which resulted in overprediction of the reaction yields. The quantum chemical model has a poor performance across all ligand test sets (Table S33). The SVR model built on the Tanimoto kernel with the polynomial kernel applied outperformed ($R^2 = 0.48$) the other models ($R^2 \leq 0.32$) in the leave-one-ligand-out test.

Table 3: Mean Performance Statistics^a for the Top Reaction Yield Prediction Models Built Using the SVR Algorithm Without Activity Ranking

Split	Descriptor	Kernel	R^2		RMSE (%)	
Additive: Plate	One-hot Encodings	Polynomial	0.47	(0.28)	18.8	(3.9)
	Quantum Chemical	Sigmoid	0.24	(0.15)	23.1	(3.2)
	Fingerprints: Morgan1	RBF	0.51	(0.35)	17.6	(5.3)
	Tanimoto: Morgan1	Polynomial	0.53	(0.30)	17.4	(4.6)
	WL	Precomputed	0.50	(0.32)	17.9	(4.5)
Aryl Halide: Ring Type	One-hot Encodings	Polynomial	-0.21	(0.29)	28.6	(1.7)
	Quantum Chemical	RBF	-0.68	(0.82)	34.4	(14.5)
	Fingerprints: MACCS	RBF	0.34	(0.17)	21.6	(6.7)
	Tanimoto: MACCS	Precomputed	0.21	(0.22)	23.5	(7.5)
	WL	Precomputed	-0.04	(0.22)	26.4	(1.9)
Aryl Halide: Halide Type	One-hot Encodings	Polynomial	-0.47	(1.11)	26.9	(7.7)
	Quantum Chemical	RBF	-0.95	(0.92)	32.3	(6.8)
	Fingerprints: MACCS	RBF	-0.29	(1.15)	24.5	(9.3)
	Tanimoto: MACCS	Polynomial	-0.20	(1.01)	23.9	(8.5)
	WL	Precomputed	-0.27	(1.08)	24.3	(9.3)
Leave-One-Base-Out	One-hot Encodings	RBF	0.53	(0.25)	17.7	(4.9)
	Quantum Chemical	Sigmoid	-0.19	(0.28)	28.8	(4.9)
	Fingerprints: MACCS	Polynomial	0.57	(0.17)	17.0	(3.3)
	Tanimoto: MACCS	Precomputed	0.45	(0.24)	19.7	(6.6)
	WL	Sigmoid	0.56	(0.20)	17.3	(5.3)
Leave-One-Ligand-Out	One-hot Encodings	Polynomial	0.32	(0.54)	18.9	(2.1)
	Quantum Chemical	RBF	-0.13	(0.23)	27.1	(6.2)
	Fingerprint: Morgan1	RBF	0.30	(0.90)	16.6	(6.4)
	Tanimoto: MACCS	Polynomial	0.48	(0.62)	14.3	(7.1)
	WL	RBF	0.42	(0.77)	14.9	(6.0)

^a R^2 and RMSE statistics are reported in the format “mean (standard deviation)” for the specified test sets. Performance statistics for the individual test sets can be found in Table S19, S23, S27, S30, S33.

With Activity Ranking

The performance of the yield prediction models built on quantum chemical descriptors, fingerprints, Tanimoto kernel descriptors and WL kernel descriptors for the additive and aryl halide ranked tests are shown in Table 4, Figure 4. The random forest model built on quantum chemical descriptors from Doyle et al.⁵⁷ was included for comparison. The performance of the SVR and random forest models built on one-hot encodings are reported to assess whether the models were fitting any underlying combinatorial structure in the training reactions.

A few trends in the performance of the algorithms, kernels and descriptors were present in both the additive and aryl halide ranked tests. The SVR models built on one-hot encodings had a better predictive performance than the random forest models built on the same one-hot encodings. Random forest and methods based on decision trees may not handle well the sparsity that one-hot encoding introduces into the dataset. This therefore sets a higher baseline for the SVR models (additive split: $R^2 < 0.68$, RMSE $> 15.4\%$; aryl halide split: $R^2 < 0.35$, RMSE $> 20.9\%$) than random forest, for model comparison. The one-hot encoding models in the aryl halide ranked test have a much lower performance than in the additive ranked test. This could be due to the aryl halide present in the reaction, generally having a larger effect on the reaction yield than the additive (Figure S14), base or ligand (Figure S5) present. There are only four additives that are considered reaction poisons (additives **1**, **4**, **7** and **13**) and hence have a large effect on the reaction yield. One-hot encoding models tend to fit the intrinsic pattern in the combinatorial training data (i.e. the presence/absence of each molecule). In the additive ranked test, the models learn the reactivity of the aryl halides, bases and ligands in training and are able to predict the yield of reactions in the test set to a relatively high level. However, in the aryl halide ranked test, the models struggle to extrapolate to unseen aryl halides as they have a larger effect on the reaction yield than the additives, bases and ligands that were fitted in training. This is supported by the following observation. In the aryl halide ranked test, the predicted yields (made by the one-hot encoding model) of the reactions containing the four inhibitory additives, that have a clear effect on lowering the reaction yield, are closer to experimental values than most of the other additives. If the molecules in the test set have a clear effect on the reaction yield and are also observed in training, the model can learn the reactivity of these molecules and appear to extrapolate well. The quantum chemical descriptors do not have a linear relationship to reaction yield, as the linear SVR model predictions show no statistical correlation. Non-linear kernels (polynomial, RBF and sigmoid) were considered, to transform the input data into higher dimensional feature space where regression could be performed

linearly. For the one-hot, quantum chemical and concatenated fingerprint descriptors, the performance of the SVR models implementing the polynomial and RBF kernels are generally better than the linear and sigmoid kernels. The application of non-linear kernels to the WL and Tanimoto kernel descriptors did not substantially improve the performance of the SVR models and therefore are not considered nor discussed further. The SVR algorithm performs better with the structure-based descriptors compared to the quantum chemical descriptors. It is encouraging that the Morgan fingerprints capture enough chemical information that they out-perform the quantum chemical descriptors which were adopted by Doyle et al.¹⁹

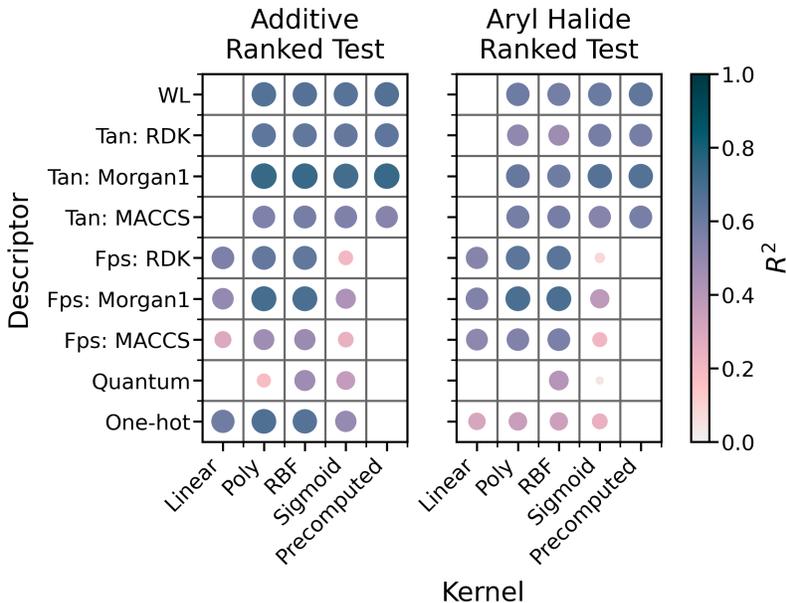


Figure 4: Predictive accuracy (coefficient of determination) comparison of the SVR models built on one-hot encoding, quantum chemical, fingerprint, Tanimoto kernel and WL kernel descriptors with a range of kernels, in the activity ranked tests. Marker size is proportional to R^2 . Numeric values can be found in Table 4.

The best descriptor-kernel combinations for the additive ranked split were One-hot-Polynomial, Quantum-RBF, Fingerprints: Morgan1-Polynomial, Tanimoto: Morgan1-Precomputed and WL-Precomputed, with R^2 in the range 0.47 to 0.73 and RMSE 19.6% to 13.8% (Table 4). The top two highest performing models, built on fingerprints and Tanimoto kernel descriptors have an R^2 of 0.70 and 0.73 and RMSE of 14.7% and 13.8%. These two models

Table 4: Mean Performance Statistics^b for the Reaction Yield Prediction Models Built Using the SVR Algorithm and Baseline Random Forest Models in the Activity Ranked Tests

Descriptor	SVR Kernel	Additive Ranked Test				Aryl Halide Ranked Test			
		R^2		RMSE (%)		R^2		RMSE (%)	
One-hot	Linear	0.59	(0.05)	17.4	(1.5)	0.31	(0.05)	21.6	(0.5)
	Polynomial	0.68	(0.05)	15.4	(1.5)	0.35	(0.04)	20.9	(0.5)
	RBF	0.66	(0.06)	15.9	(1.8)	0.34	(0.09)	21.0	(0.9)
	Sigmoid	0.49	(0.03)	19.4	(1.0)	0.24	(0.03)	22.6	(0.4)
Quantum Chemical	Linear	-0.56	(1.23)	32.2	(12.7)	-505.21	(875.86)	336.4	(549.2)
	Polynomial	0.18	(0.39)	24.0	(6.1)	-4.34	(7.85)	47.3	(41.0)
	RBF	0.47	(0.16)	19.6	(3.4)	0.41	(0.14)	19.9	(2.6)
	Sigmoid	0.37	(0.03)	21.7	(0.9)	0.04	(0.26)	25.2	(2.3)
Fingerprints: MACCS	Linear	0.29	(0.18)	22.8	(2.4)	0.52	(0.01)	18.1	(0.8)
	Polynomial	0.47	(0.18)	19.6	(3.2)	0.55	(0.17)	17.2	(3.7)
	RBF	0.48	(0.15)	19.4	(2.7)	0.56	(0.16)	17.1	(3.5)
	Sigmoid	0.24	(0.06)	23.7	(1.1)	0.21	(0.08)	23.0	(0.9)
Fingerprints: Morgan1	Linear	0.50	(0.13)	19.2	(2.7)	0.55	(0.05)	17.5	(1.5)
	Polynomial	0.70	(0.13)	14.7	(3.3)	0.69	(0.05)	14.6	(1.7)
	RBF	0.69	(0.14)	14.9	(3.6)	0.68	(0.05)	14.6	(1.6)
	Sigmoid	0.43	(0.06)	20.6	(1.3)	0.39	(0.07)	20.4	(1.4)
Fingerprints: RDK	Linear	0.56	(0.06)	18.0	(1.3)	0.54	(0.05)	17.7	(1.3)
	Polynomial	0.62	(0.09)	16.6	(1.8)	0.64	(0.11)	15.4	(2.4)
	RBF	0.63	(0.07)	16.5	(1.6)	0.65	(0.11)	15.4	(2.5)
	Sigmoid	0.20	(0.10)	24.3	(2.1)	0.09	(0.06)	24.9	(1.6)
Tanimoto: MACCS	Polynomial	0.56	(0.17)	17.8	(3.4)	0.58	(0.05)	16.8	(1.2)
	RBF	0.58	(0.16)	17.5	(3.4)	0.58	(0.04)	16.9	(0.7)
	Sigmoid	0.56	(0.11)	18.0	(2.4)	0.54	(0.10)	17.6	(1.9)
	Precomputed	0.54	(0.17)	18.3	(3.3)	0.57	(0.13)	16.9	(2.9)
Tanimoto: Morgan1	Polynomial	0.74	(0.11)	13.8	(3.1)	0.62	(0.06)	16.0	(1.1)
	RBF	0.73	(0.10)	13.9	(2.9)	0.59	(0.06)	16.5	(1.1)
	Sigmoid	0.70	(0.13)	14.6	(3.5)	0.66	(0.06)	15.1	(1.5)
	Precomputed	0.73	(0.13)	13.8	(3.5)	0.67	(0.06)	15.0	(1.4)
Tanimoto: RDK	Polynomial	0.64	(0.05)	16.4	(1.3)	0.50	(0.13)	18.2	(2.3)
	RBF	0.63	(0.05)	16.5	(1.3)	0.47	(0.13)	18.8	(2.1)
	Sigmoid	0.62	(0.05)	16.7	(1.1)	0.58	(0.12)	16.8	(2.4)
	Precomputed	0.64	(0.05)	16.3	(1.3)	0.57	(0.13)	16.8	(2.4)
WL	Polynomial	0.67	(0.17)	15.4	(4.0)	0.60	(0.05)	16.4	(0.9)
	RBF	0.66	(0.16)	15.6	(3.8)	0.58	(0.05)	16.8	(0.8)
	Sigmoid	0.65	(0.14)	15.8	(3.3)	0.61	(0.06)	16.2	(1.1)
	Precomputed	0.67	(0.18)	15.3	(4.2)	0.63	(0.06)	15.7	(1.2)
Baseline Random Forest Models:									
One-hot		0.59	(0.11)	17.4	(2.8)	-0.04	(0.33)	26.2	(3.3)
Quantum Chemical		0.68	(0.11)	15.3	(3.0)	0.20	(0.17)	23.2	(1.5)

^a R^2 and RMSE statistics are reported in the format “mean (standard deviation)” for the specified test. Performance statistics for the individual test sets can be found in Table S38 and S41. For each type of descriptor, the models with the best performance are highlighted in **bold**.

are not significantly different to one another, according to the χ^2 test (with a p -value of 0.06), under the null hypothesis that the distributions of the residual yield (Figure S15a) are the same. The rest of the models are significantly different to one another with p -values $< 10^{-7}$ (Table S42). The best one-hot and quantum chemical SVR models (One-hot-Polynomial, Quantum-RBF) have a wider distribution of residual yields than the other highest performing SVR models (Figure S15a), meaning larger associated errors. The random forest algorithm learns more from the quantum chemical descriptors ($R^2 = 0.68$, RMSE = 15.3%) than the SVR algorithm ($R^2 \leq 0.47$, RMSE $\geq 19.6\%$).

Model performances along the aryl halide dimension were significantly lower than along the additive dimension for the baseline and quantum chemical models (Table 4, Figure 4). Models built on structure-based descriptors had a similar performance to those in the additive ranked test. The best descriptor-kernel combinations for the aryl halide ranked test were the same as the additive ranked test: One-hot-Polynomial, Quantum-RBF, Fingerprints: Morgan1-Polynomial, Tanimoto: Morgan1-Precomputed and WL-Precomputed. There is a large difference in performance between the structure-based descriptors, with an R^2 of 0.63 to 0.69, compared to the Quantum-RBF (0.41) and One-hot-Polynomial (0.35) models. The low performance of the quantum chemical and one-hot encoding models suggests that they may only be fitting the intrinsic pattern in the training set and therefore, struggle to extrapolate to the unseen aryl halides. In general, there is an even distribution of residual yields around 0% for the best descriptor-kernel combinations (Figure S15b). However, the models have a tendency to underpredict the reaction yields of the unseen aryl halides as shown by the smaller, secondary peaks (between 12.5% to 37.5%) in the distribution of residual yield (Figure S15b). This is partially due to the under-representation of higher reaction yields, resulting in poorer model performances (Figure S16b). This issue is also observed in the additive ranked test to a lesser extent (Figure S16a).

Prediction Performance by Similarity to Training Data

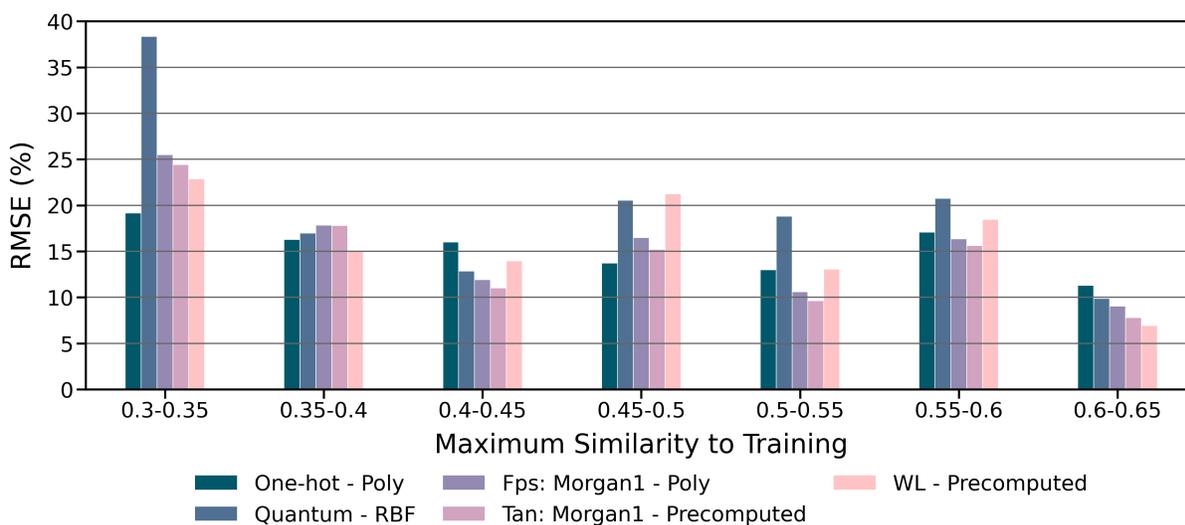
Assessing model performance with respect to maximum similarity to training reactions helps to identify molecules that may be outside the domain of applicability. Maximum similarity to training is defined as the maximum product of pairwise Tanimoto scores (between molecules in the training and test sets) of the reaction components. If all combinations of the additives, aryl halides, bases and ligands are in the dataset (this is not always the case as reactions with missing yield data were removed), the maximum similarity to training is dependent upon the unseen molecules in the test sets (i.e. the additives in the additive ranked test and the aryl halides in the aryl halide ranked test). For example, if the reaction $R_1 = (A_1, H_1, B_1, L_1)$ is in the training set and the reaction $R_2 = (A_2, H_1, B_1, L_1)$ is in the test set (where A_n is the n^{th} additive, H_n is the n^{th} aryl halide, B_n is the n^{th} base and L_n is the n^{th} ligand), then the similarity score would only be dependent on the additives in the reactions as shown in Eq. 6. The maximum similarity to training scores of the additives and aryl halides for both activity ranked tests can be found in Table S43.

$$\begin{aligned} T(R_1, R_2) &= T(A_1, A_2) T(H_1, H_1) T(B_1, B_1) T(L_1, L_1) \\ &= T(A_1, A_2) \cdot 1 \cdot 1 \cdot 1 \\ &= T(A_1, A_2) \end{aligned} \tag{6}$$

In the additive ranked test, the models performed poorly for reactions in the lowest maximum similarity to training interval, 0.30 to 0.35 (Figure 5a, S17a). These reactions contain the additives: benzo[*c*]isoxazole (additive **10**) and benzo[*d*]isoxazole (additive **15**). The performance of the models, considering the additives individually, are generally good for additive **15** (Figure S18d) but very poor for additive **10** (Figure S18a). The models overpredict the yield of reactions containing the inhibitory additive **10** and result in negative R^2 and high RMSE scores. These reactions may therefore be outside the domain of applicability. Generally, the performance of the models improves with maximum similarity

to training (Figure 5a, S17a), as expected. The models have a high RMSE ($> 15\%$) for the reactions in the maximum similarity to training intervals 0.35 to 0.40 (additives **1**, **3**, **5**, **14**) and 0.55 to 0.60 (additives **4**, **6**, **9**). This is mainly due to the underprediction of high yielding reactions, which is a result of the under-representation of higher reaction yields (Figure 2, S16a). The structure-based SVR models demonstrate good prediction statistics for reactions with a maximum similarity to training greater than 0.35.

(a)



(b)

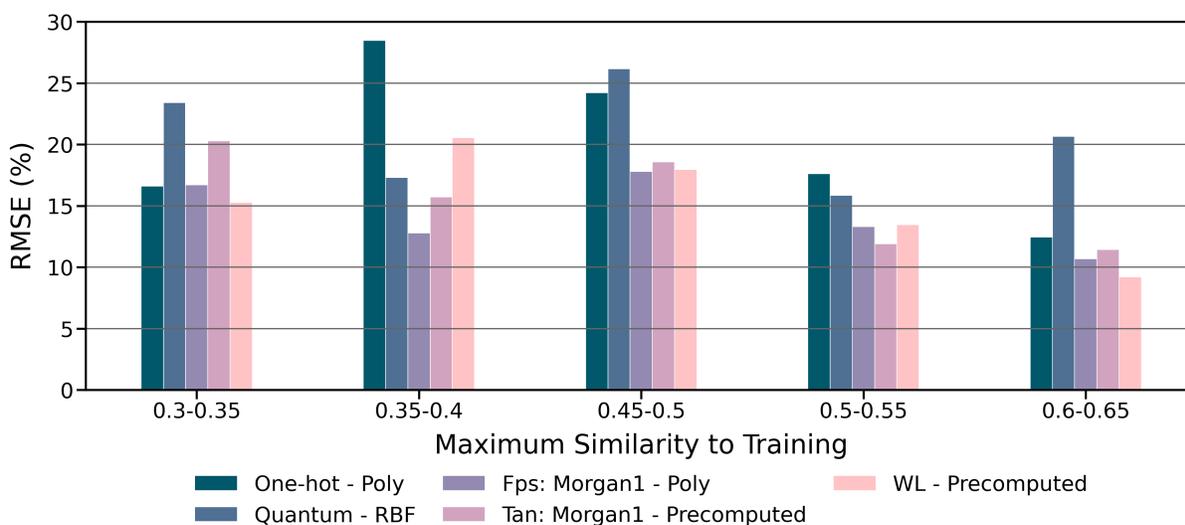


Figure 5: RMSE against maximum similarity to training for (a) the additive ranked test and (b) the aryl halide ranked test.

For the aryl halide ranked test, there is a slight improvement in the performance statistics as maximum similarity to training increases (Figure 5b, S17b). The higher yielding reactions containing ethyl substituted aryl halides (0.30 to 0.40) and halopyridines (0.45 to 0.50) are underpredicted by the models (Figure S19), due to the under-representation of higher reaction yields (Figure 2, S16b). Reactions containing the trifluoromethyl and methoxy substituted aryl halides (0.50 to 0.55) are generally predicted well by the models. It is important to consider the coefficient of determination (R^2) and RMSE together, when assessing goodness of fit.⁷⁰ This is demonstrated in the model performance of reactions containing 1-chloro-4-ethylbenzene (aryl halide **7**) and 1-chloro-4-(trifluoromethyl)benzene (aryl halide **1**). These reactions are low yielding and therefore only cover a small range of reaction yields. While this leads to low R^2 scores across all models (Figure S19), the RMSE scores are good ($\leq 15\%$) for at least half of the models.

Predictions of Prospective Reactions

A set of combinatorial reactions was compiled to validate the generalisability of the SVR models, particularly along the aryl halide dimension. Here, we present predicted yields of these reactions prior to experimentation. The SVR model with the best predictive performance for each descriptor in the aryl halide ranked test was employed: Quantum-RBF, Fingerprints: Morgan1-Polynomial, Tanimoto: Morgan1-Precomputed, WL-Precomputed and the One-hot-Polynomial baseline. The aryl halides in the prospective reactions cover a range of maximum similarity to training scores between 0.15 to 0.60 (Figure 6). This excludes the five aryl halides that are present in the Doyle et al. training set, where the maximum similarity to training was 1.00. In the aryl halide ranked test, the models predicted the yield of reactions containing the aryl halide with the lowest maximum similarity to training score (0.30 to 0.35) reasonably well (Figure 5b). The models may however, struggle to extrapolate to the aryl halides in the prospective reactions with maximum similarity scores lower than 0.30 (over half of the unseen aryl halides). These models in the base and ligand leave-one-out

tests generally showed comparable correlation to the best kernel-descriptor combinations in these tests (Table S30 and S33). The poor performance of the quantum chemical model in these tests indicates that the model is limited and may be unable to extrapolate to unseen bases and ligands.

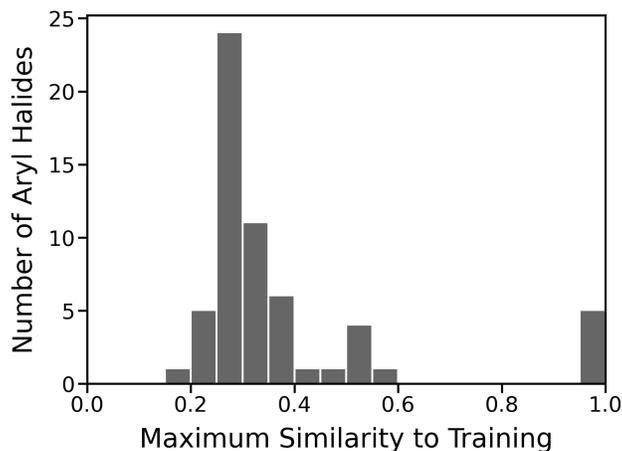


Figure 6: Distributions of maximum similarity to training for all prospective reactions. Maximum similarity to training was calculated using the maximum pairwise Tanimoto scores (using the Morgan2 fingerprint) of the aryl halides in the training and test set.

Two tests were designed to investigate the predictive ability of the SVR models identified as the top descriptor-kernel combinations in the aryl halide ranked test. The first test considered all 1416 proposed reactions for the comparison of the structure-based descriptors and one-hot encodings. These descriptors can be applied to any molecule and are quick and easy to calculate. In this test, the Fingerprints: Morgan1-Polynomial, Tanimoto: Morgan1-Precomputed, WL-Precomputed and the One-hot-Polynomial models were trained on the Doyle et al. dataset, including additive control reactions (i.e. no additive present); a total of 4135 reactions. The second test only considered a subset of the proposed reactions to compare the quantum chemical descriptors with the structure-based descriptors. The quantum chemical descriptors have a limited application range as they require predefined, key shared atoms to be present for each reaction component. The subset excluded any molecules where quantum chemical descriptors could not be calculated; this included aryl iodides (see the

Supporting Information for further details). This prospective test set contained a total of 882 reactions, a combination of 49 aryl halides, two additives, three bases and three ligands. The SVR models were trained on a subset of 2757 reactions from the Doyle et al. dataset, including additive control reactions. The predicted yields of each reaction, calculated in both tests, are shown in Figure S22 and S23.

The models built on chemically meaningful descriptors predicted the yield of test reactions that are also present in the training reactions accurately, with $R^2 \geq 0.98$ and $\text{RMSE} \leq 4.4\%$ (Figure S20 and S21). In both tests, the one-hot encodings model predicted an arbitrary number irrespective of the aryl halide present in the reaction. The predictions were primarily dependent on the type of base and ligand in the reaction (Figure S25 and S27). The reaction containing the base DBU and the reactions performed without a catalyst ligand contribute the most towards the broad peak at approximately 35% in the distribution of predicted yield for the subset of proposed reactions (Figure 7). The base MTBD and catalyst ligand t-BuXPhos have broader range of higher yields contributing to the peak around 50%. The same trend was observed when all prospective reactions were considered (Figure S26 and S28). There is minimal difference in the distributions of predicted yield of the reactions containing each base for the chemically meaningful SVR models. The baseline one-hot encodings model was unable to extrapolate to unseen aryl halides from fitting the underlying pattern in the training data. Therefore, it is anticipated that the models built on quantum chemical and structure-based descriptors were learning from chemically meaningful information.

Reactions performed without a catalyst were included in the prospective reactions to evaluate the following synthetic hypothesis; the reactions containing *ortho*-substituted halopyridines are proceeding via an alternative reaction pathway, leading to higher reaction yields. No examples of these reactions were provided in training and therefore, may be beyond the limits of the models. The Quantum SVR model predicted the yield of reactions without the presence of a catalyst to be a negative arbitrary number (-0.64%), irrespective of the aryl halide or additive present in the reactions. Predictions of this negative number suggest

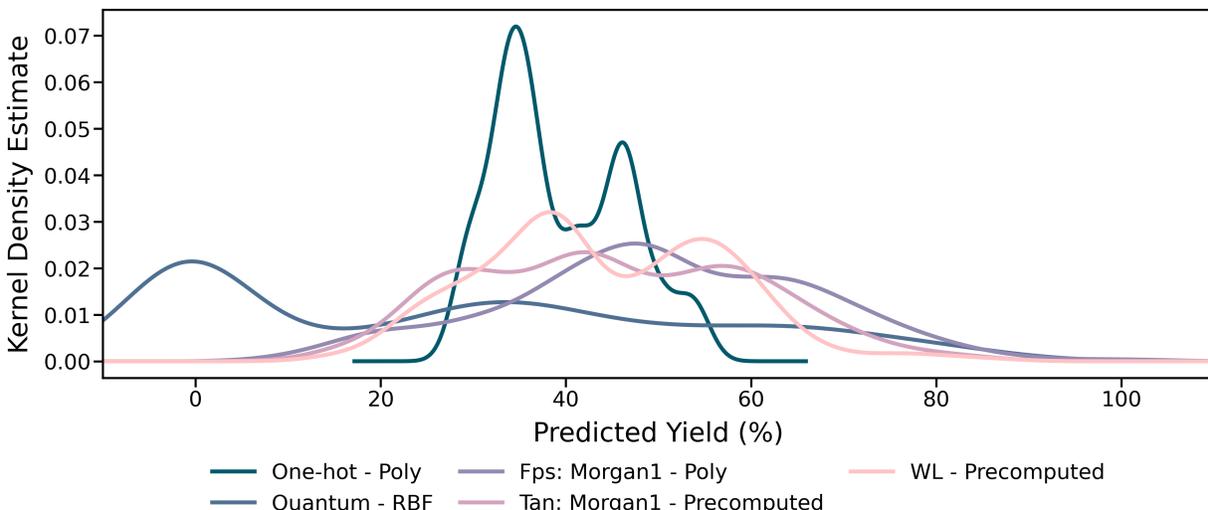


Figure 7: Distributions of predicted reaction yield for the subset (882) of validation reactions.

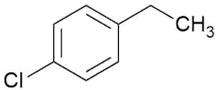
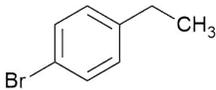
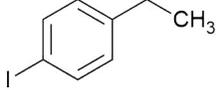
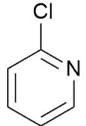
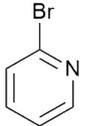
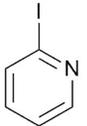
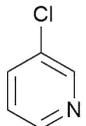
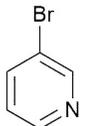
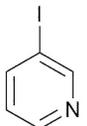
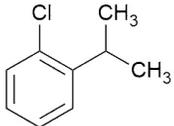
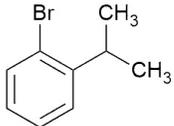
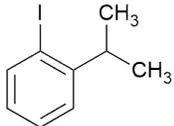
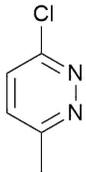
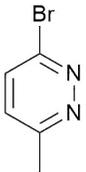
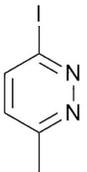
these reactions are outside the domain of applicability for the Quantum SVR model. These predictions largely contributed to the distinct peak in the distribution of predicted yield around 0% (Figure 7). The structure-based models predicted a smaller range of yields for reactions performed without a catalyst ($\sim 30\%$) compared to the reactions containing a catalyst ($\gtrsim 60\%$, Figure S27 and S28). This could indicate a potential limitation in the ability of the structure-based models to predict reactions without a catalyst. The chemically meaningful models predicted similar trends in the reactivity of the catalyst ligands (Figure S27 and S28), following the order: BrettPhos (where applicable) < no catalyst < *t*-BuBrettPhos < *t*-BuXPhos.

The prospective reactions were designed to validate the applicability of the SVR models to unseen aryl halides that are not present in the training set. The models built on chemically meaningful descriptors predicted higher yields for reactions containing aryl bromides and aryl iodides (where applicable) compared to reactions containing aryl chlorides (Figure S29 and S30). Using the reactions containing the *ortho*-halo-substituted isopropylbenzene and *para*-halo-substituted methylpyridazine molecules as examples, there is an increase in mean predicted yield from the chloride to bromide to iodide (Table 5). This trend is plausible, as it follows the trend in the training reactions (Figure S5c). Comparing the mean yield

of reactions containing 1-chloro-4-isopropylbenzene ($\sim 30\%$ to 45%) with a similar alkyl-substituted aryl halide used in training (1-chloro-4-ethylbenzene, $\sim 4\%$), suggests the models may have overpredicted these reaction yields. Aryl halides with substituents at the ortho position are sterically hindered which could potentially lower the reactivity. As there are no reactions containing *ortho*-substituted aryl halides in the training set, it is possible that the predictions were influenced by the higher yielding *ortho*-substituted pyridines (Table 5). The pyridazine molecules contain a nitrogen atom at both the ortho and meta positions. It is interesting that the structure-based models again appear to make predictions based on the higher yielding *ortho*-substituted pyridines, whereas the quantum chemical model predicts reactivity closer to the lower yielding *meta*-substituted pyridines (Table 5).

Despite the similar trends between the quantum chemical model and the structure-based models, the predictions are only slightly correlated (Pearson correlation coefficient of < 0.67 , Figure S31). The structure-based models are expected to be more robust than the quantum chemical models for extrapolating to unseen chemical entities. The predictions of the structure-based models are well correlated and have a Pearson correlation coefficient of > 0.83 (Figure S31 and S32).

Table 5: Mean Experiment Yields of Aryl Halides in the Training Set (Top) and Mean Predicted Yields of Aryl Halides in the Prospective Reactions (Bottom)^c

Mean Experimental Yields (%) of Aryl Halides in the Training Set						
						
3.9 (3.8)	43.5 (24.6)	52.6 (24.2)				
						
44.1 (26.8)	53.3 (26.5)	59.3 (26.6)				
						
14.9 (16.2)	43.9 (29.1)	52.3 (29.0)				
Mean Predicted Yields (%) of Aryl Halides in the Prospective Reactions						
						
	Subset	All	Subset	All	Subset	All
One-hot - Poly	42.4 (6.7)	47.0 (7.7)	42.4 (6.7)	47.0 (7.7)	N/A	47.0 (7.7)
Quantum-RBF	29.6 (4.4)	N/A	73.3 (4.7)	N/A	N/A	N/A
Fps: Morgan1-Poly	36.0 (4.2)	33.4 (8.6)	67.0 (4.1)	55.3 (10.6)	N/A	63.2 (8.9)
Tan: Morgan1-Precomputed	35.0 (3.7)	34.9 (7.0)	56.1 (3.8)	53.1 (9.3)	N/A	59.4 (8.0)
WL-Precomputed	41.8 (3.8)	42.8 (8.2)	55.4 (3.7)	55.0 (10.3)	N/A	56.6 (9.0)
						
	Subset	All	Subset	All	Subset	All
One-hot - Poly	42.4 (6.7)	47.0 (7.7)	42.4 (6.7)	47.0 (7.7)	N/A	47.0 (7.7)
Quantum-RBF	-4.9 (3.6)	N/A	13.7 (2.2)	N/A	N/A	N/A
Fps: Morgan1-Poly	45.3 (4.4)	39.8 (12.4)	61.2 (4.1)	57.2 (9.7)	N/A	63.2 (7.3)
Tan: Morgan1-Precomputed	41.0 (3.7)	39.0 (8.6)	58.3 (3.8)	55.0 (9.1)	N/A	60.7 (7.6)
WL-Precomputed	49.8 (4.2)	48.9 (10.2)	57.3 (4.0)	56.2 (10.5)	N/A	57.6 (9.6)

^c Experimental and predicted yields are reported in the format “mean (standard deviation)”. Reactions performed without a ligand were excluded.

Conclusions

SVR models built on structure-based and quantum chemical descriptors, for the prediction of reaction yield, were compared. The models were applied to a set of Buchwald-Hartwig reactions and the performance was assessed along the dimension of each reaction component. The models built on structure-based descriptors (molecular fingerprints and graphs) demonstrated good prediction statistics and outperformed the quantum chemical SVR models, along the dimension of each reaction component. The models built on molecular fingerprints consistently surpassed the other descriptors in each test, proving fingerprints to be robust descriptors. The moderate performances of the SVR models in the base and ligand leave-one-out tests, suggest they may benefit from including a larger variety of bases and ligands in training. The applicability, ease and quickness of calculating molecular fingerprints makes them particularly attractive (Table 6).

Table 6: Comparison of the Molecular Descriptors used in this Study^d

Descriptor	Speed	Applicability to molecules	Generalisability	
			Additive	Aryl Halide
Quantum Chemical Fingerprints	+	Subset	+	+
Tanimoto Kernel	+++	All	++++	++++
WL Kernel	++	All	++++	++++
One-hot Encodings	++	All	+++	+++
	++++	All	++	++

^d Speed and generalisability are ranked from poor (+) to good (++++). The ranking of generalisability refers to the performance of the top SVR model for each descriptor.

Predictions of reaction yield for the proposed reactions, not present in the Doyle et al. dataset, were reported prior to experimentation. Similar trends in the reactivity of the molecules along each reaction component were observed across the chemically meaningful models. The reaction yields predicted by the structure-based models are reasonably correlated. Based on the performance of the models in the preceding tests and the analysis of the predicted yields of the proposed reactions, it is anticipated that the structure-based models will extrapolate better than the quantum chemical model. The reaction yields of the proposed reactions will be attained using high-throughput experimentation, and used to

validate and assess the limits of the SVR models.

The results presented show the promising applicability of computationally less demanding, structure-based descriptors in the prediction of reaction yield, where quantum chemical descriptors have typically been preferred. The prospective prediction models and some instructions on their use are available on GitHub (https://github.com/alexehaywood/yield_prediction) to predict the yield of Buchwald-Hartwig reactions. The domain of applicability for any unseen reactions should be calculated prior to making any predictions, to assess the confidence of the model. The one-hot encodings model was only used as a baseline and cannot make any valid predictions. The chemically meaningful models should be used with caution and may struggle to extrapolate to unseen aryl halides with a similarity to training score less than 0.30, as well as to reactions that do not contain a catalyst. Further analysis of the prospective predictions is required once experimental data have been collected. The machine learning models learnt from a relatively small (a few thousand instances) combinatorial dataset, proving their use in facilitating the optimisation of reaction conditions for the synthesis of novel molecules. In the future, it would be interesting to explore the transferability of the structure-based SVR models to different reaction types or other regression related problems. The framework presented could also be applied to larger datasets when they become publicly available.

Software and Data Availability

The data and code used in this study is available online at https://github.com/alexehaywood/yield_prediction.

Supporting Information Available

Additional dataset, descriptor and model details; cross-validated, training set, grid search cross-validated and test set performances; prospective reactions and corresponding predic-

tions of reaction yield.

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Notes

The authors declare the following competing financial interest(s): A.T., A.B. and A.M. are shareholders in GSK.

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