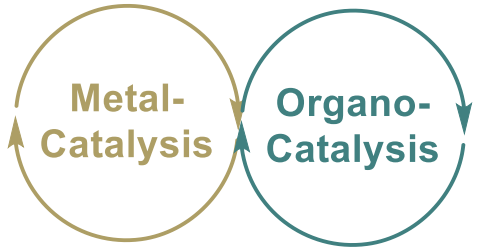
Accelerating optimization in synthetic chemistry through ML approaches

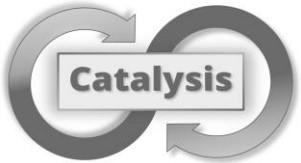
Dr Laurence Grimaud
laurence.grimaud@ens.psl.eu

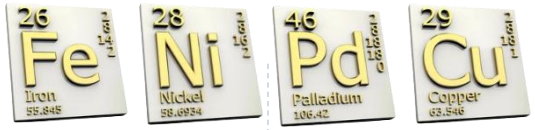
Team's research interests

Dr Maxime Vitale

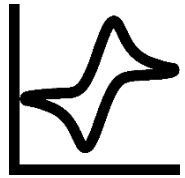
Catalysis





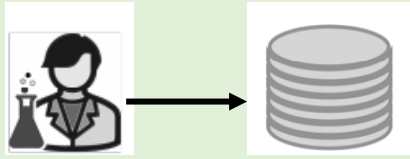


Mechanistic Studies



Isocyanides : Photocatalysis and Electrosynthesis

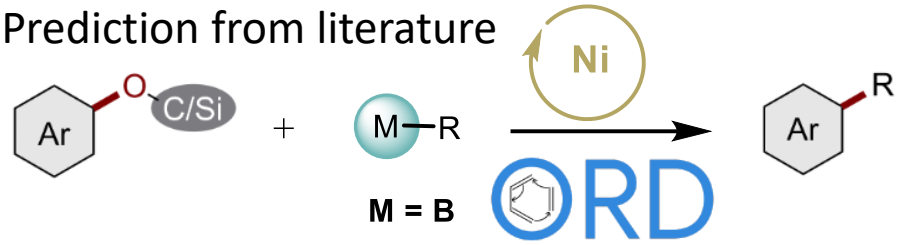
Machine Learning

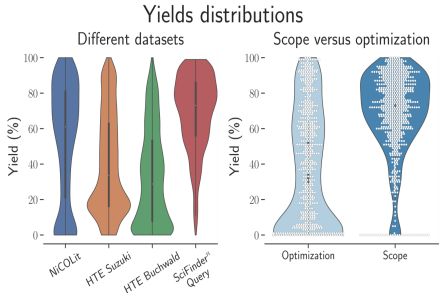


AI in our lab

Pr Rodolphe Vuilleumier (ENS)

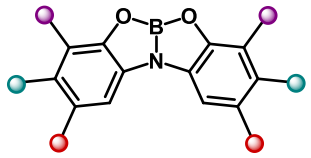
Prediction from literature

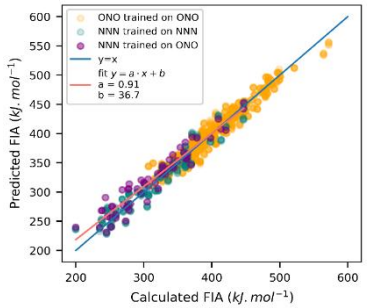


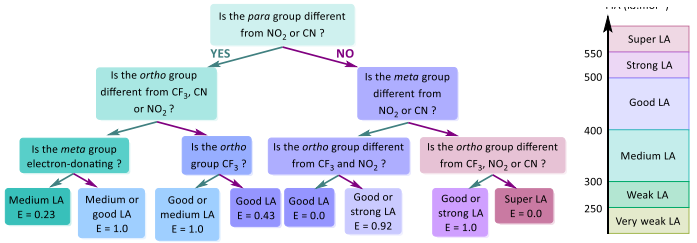


J. Am. Chem. Soc., **2022**, *144*, 14722

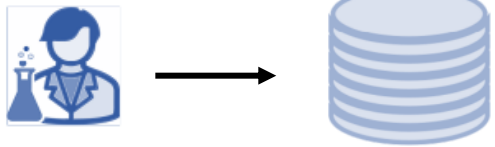
Prediction of Properties



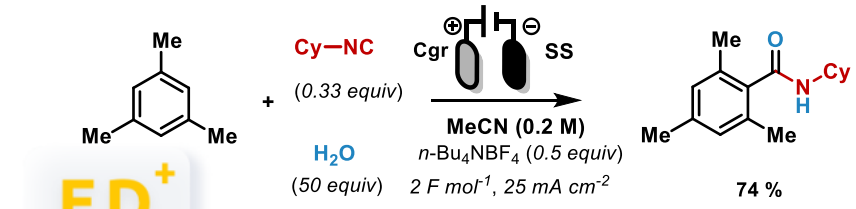


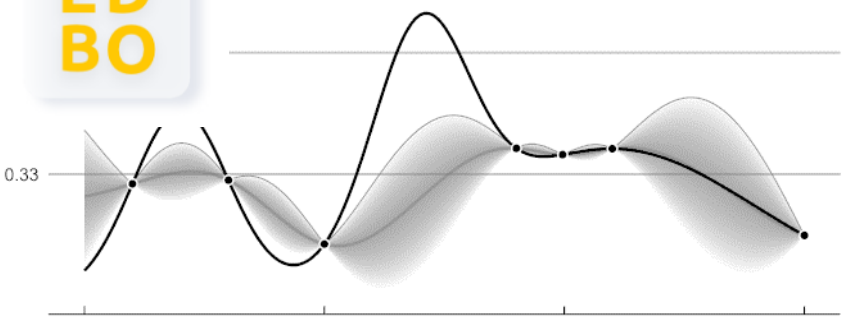


Digital Discovery **2025**, *4*, 3623



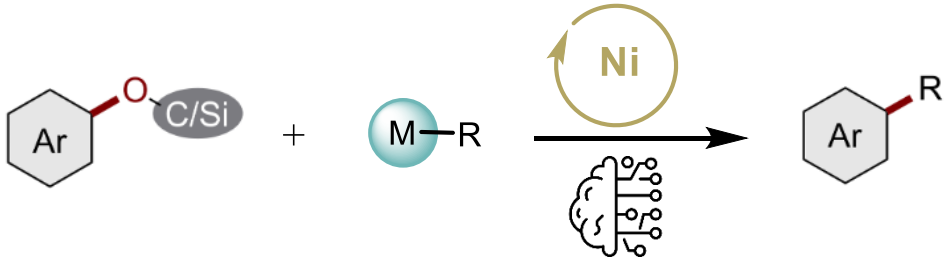
Bayesian Optimisation





C. R. Chim. **2026**, accepted. DOI: 10.5802/crchim.431

Predicting reaction yields from a literature-based reaction dataset

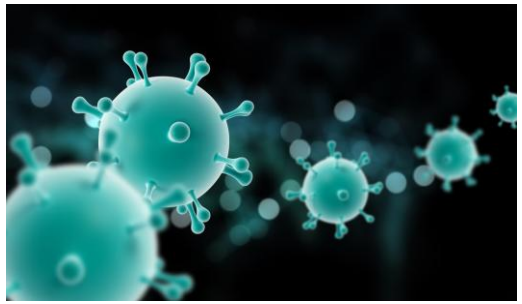


Prediction of the yield:

- ✓ Reduced cost
- ✓ Reduced time
- ✓ Reduced resources

Jules Schleinitz

Maxime Langevin

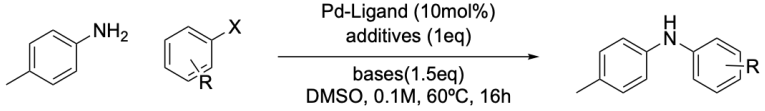


Yanis Smail & Benjamin Wehnert

Chemistry Literature for ML yield prediction ?

How to access quality data ?

HTE

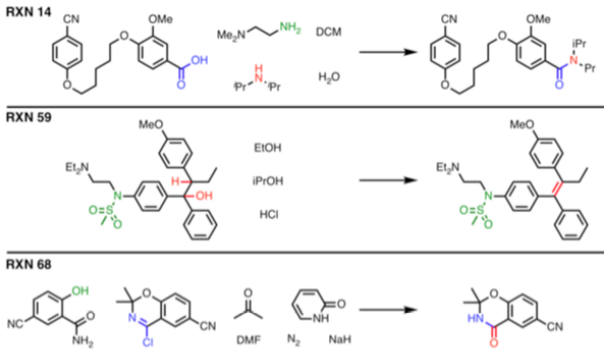


- **Very specific dataset**
  small chemical space
- **Low report bias**
- **Good ML performances**

D. Perera, J. W. Tucker, S. Brahmbhatt, C. J. Helal, A. Chong, W. Farrell, P. Richardson, N. W. Sach, *Science* 359, 429 (**2018**).

D. T. Ahneman, J. G. Estrada, S. Lin, S. D. Dreher, A. G. Doyle, *Science* 360, 186 (**2018**)

USPTO



- **Very broad dataset**
  Huge chemical space
- **High report bias towards high yields**
- **Poor ML performances**

*D. M. Lowe, Ph.D. thesis, University of Cambridge (**2012**)*

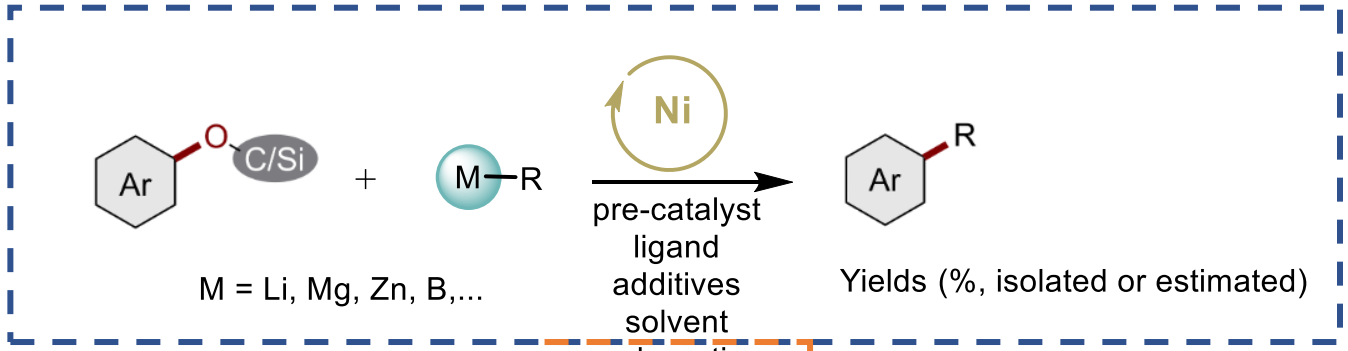
Literature data

- **Very broad dataset**
  Huge chemical space
- **High report bias**

?

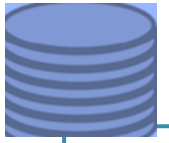
Beker, W.; Roszak, R.; Wołos, A.; Angello, N. H.; Rathore, V.; Burke, M. D.; Grzybowski, B. A. *J. Am. Chem. Soc.* **2022**, 10.1021/jacs.1c12005
Strieth-Kalthoff, F.; Sandfort, F.; Kühnemund, M.; Schäfer, F. R.; Kuchen, H.; Glorius, F *Angew. Chem. Int. Ed.* **2022**, 10.1002/anie.202204647

Manually extracted and curated database



From main text and SI

2000 reactions
45 publications



ORD

NiCOLit Database

Preprocessing (chemical rules + relevance criteria)

1400 reactions

Featurization

RDKit + OHE

RXNFP

DFT-based

Auto-QChem

*

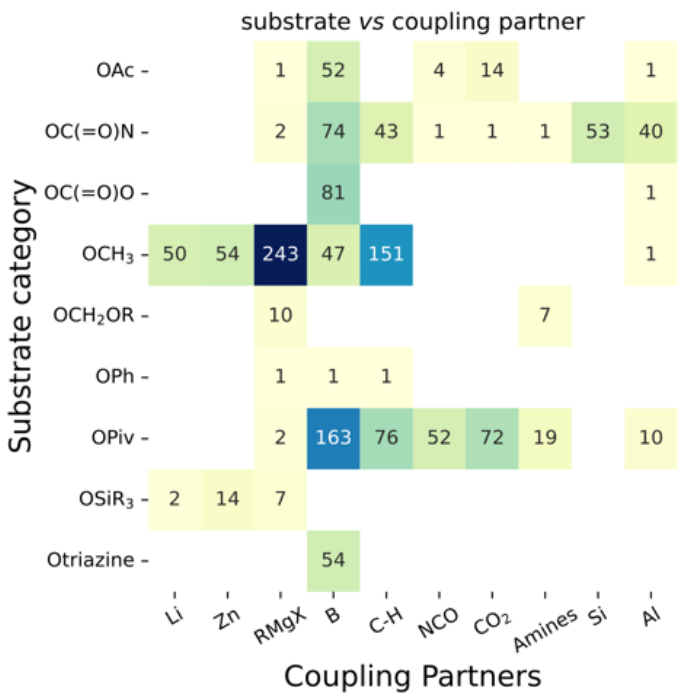
Random Forest
Regression Model

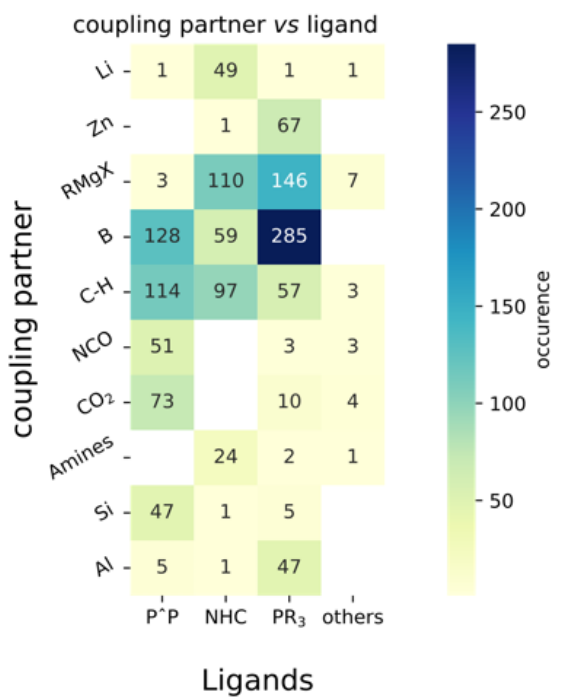
Dataset analysis
Predictive models

Kearnes, S. M.; Maser, M. R.; Wleklinski, M.; Kast, A.; Doyle, A. G.; Dreher, S. D.; Hawkins, J. M.; Jensen, K. F.; Coley, C. W. *J. Am. Chem. Soc.* **2021**, *143*, 18820.

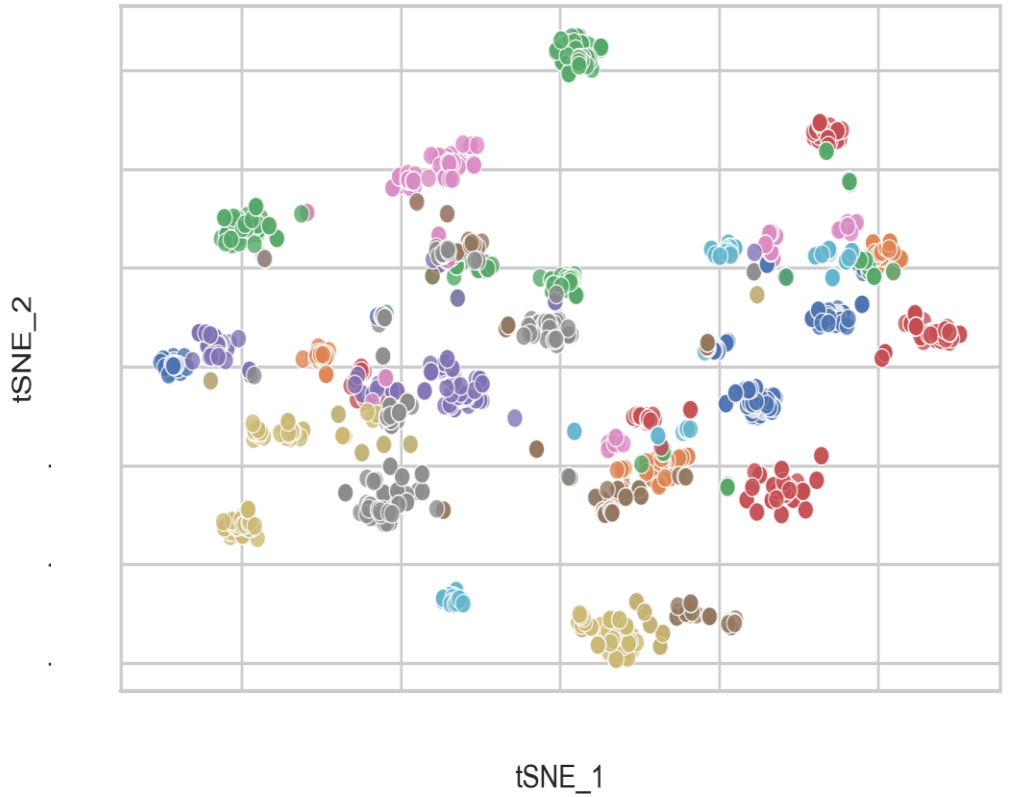
P. Schwaller, A. C. Vaucher, T. Laino, J.-L. Reymond, Machine Learning: Science and Technology **2021**, 2, 015016

Specific combinations and minimal overlap between publications

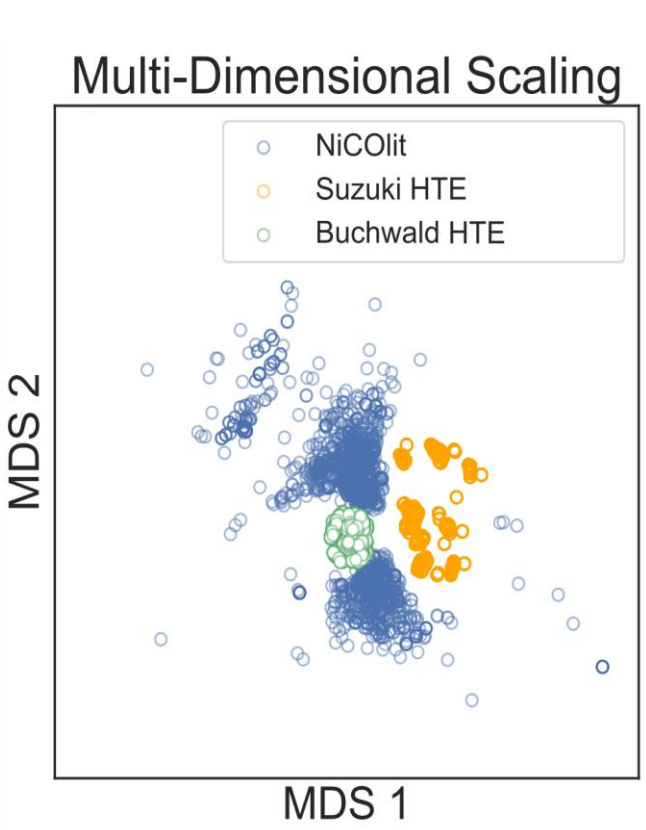




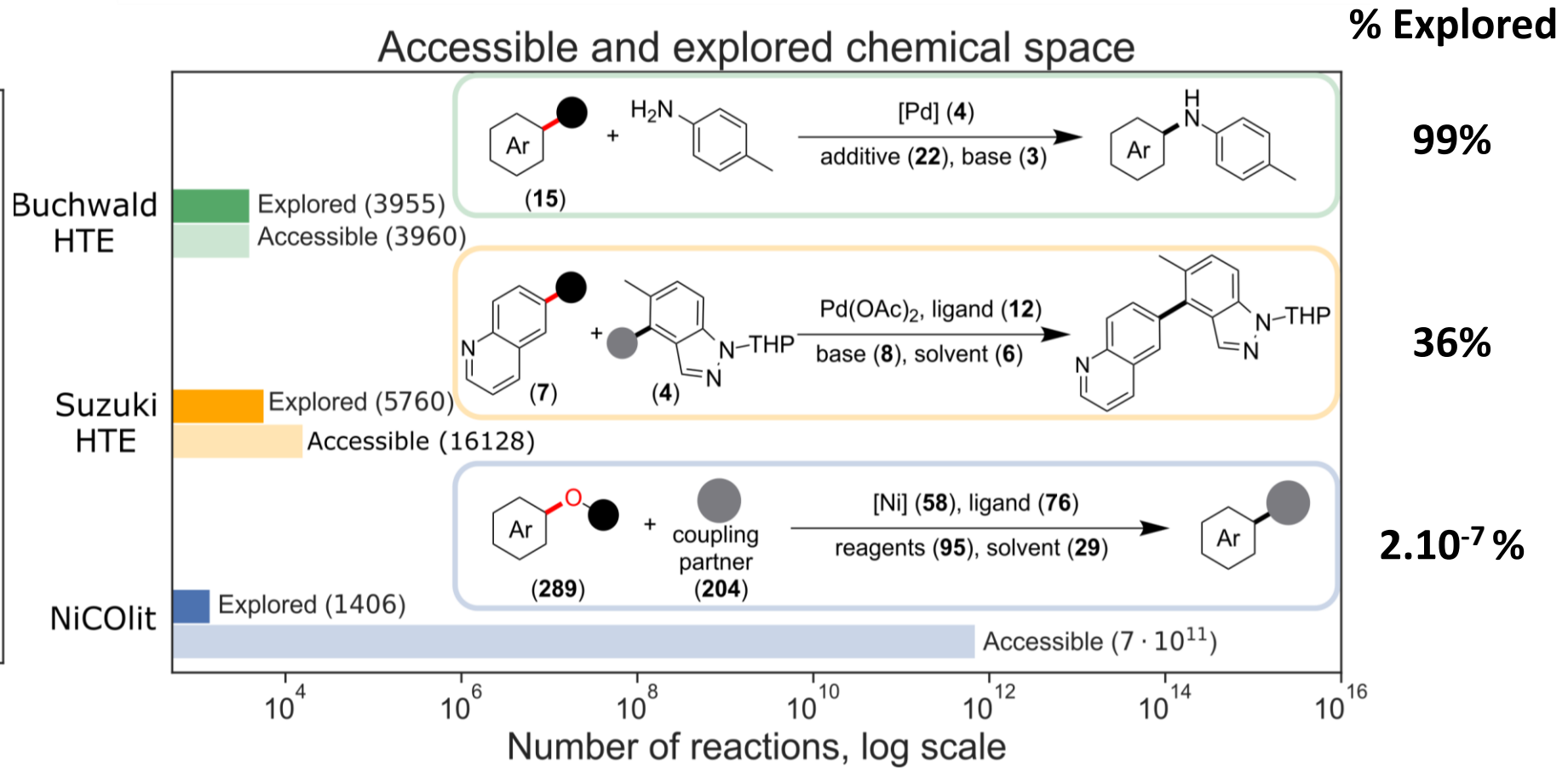
t-SNE NiCOlit coloured by publication



Comparison with HTE



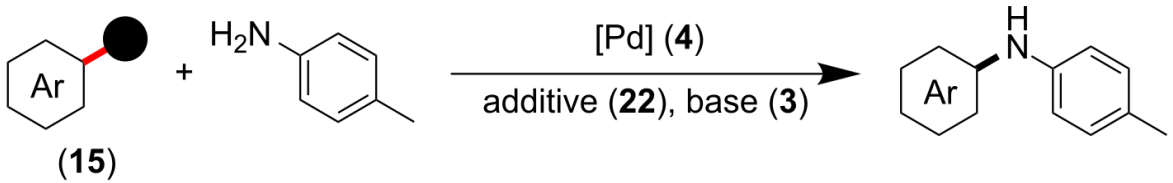
Analysis with RXNFP featurization

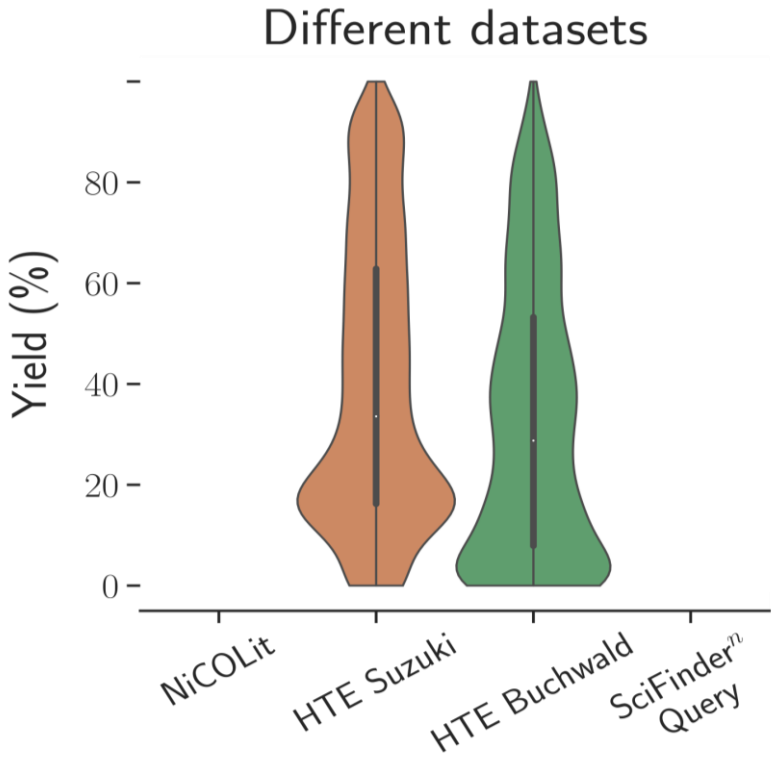


Ahneman, D.T.; Estrada, J. G.; Lin, S.; Dreher, S. D.; Doyle, A. G. *Science* **2018**, *360*, 186

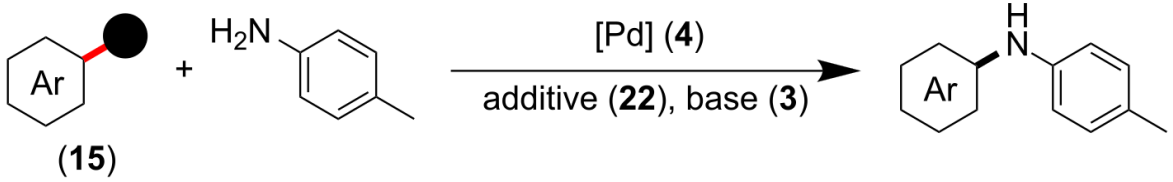
Perera, D.; Tucker, J. W.; Brahmbhatt, S.; Helal, C. J.; Chong, A.;Farrell, W.; Richardson, P.; Sach, N. W. *Science* **2018**, *359*, 429.

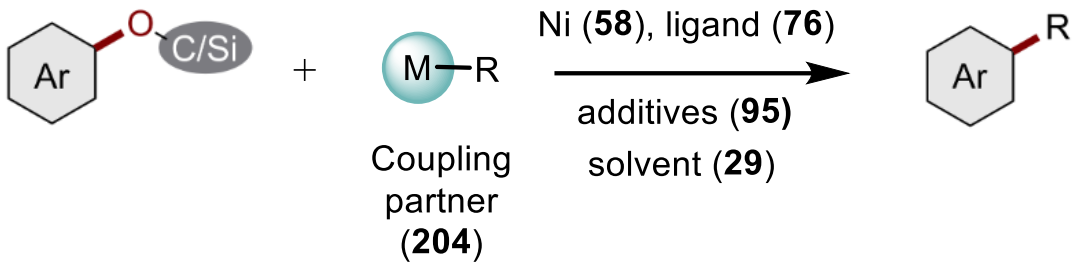
Yields distribution

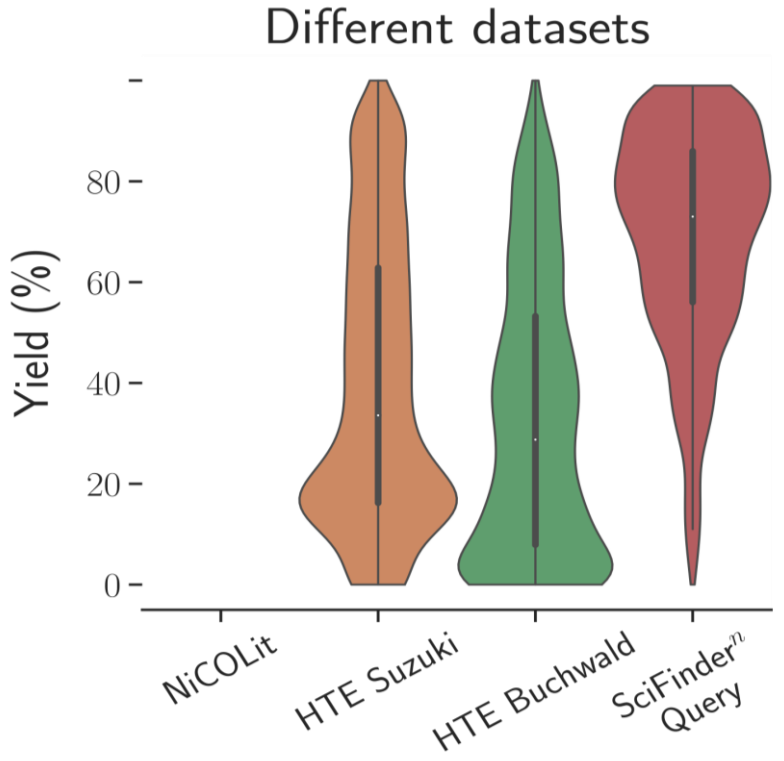




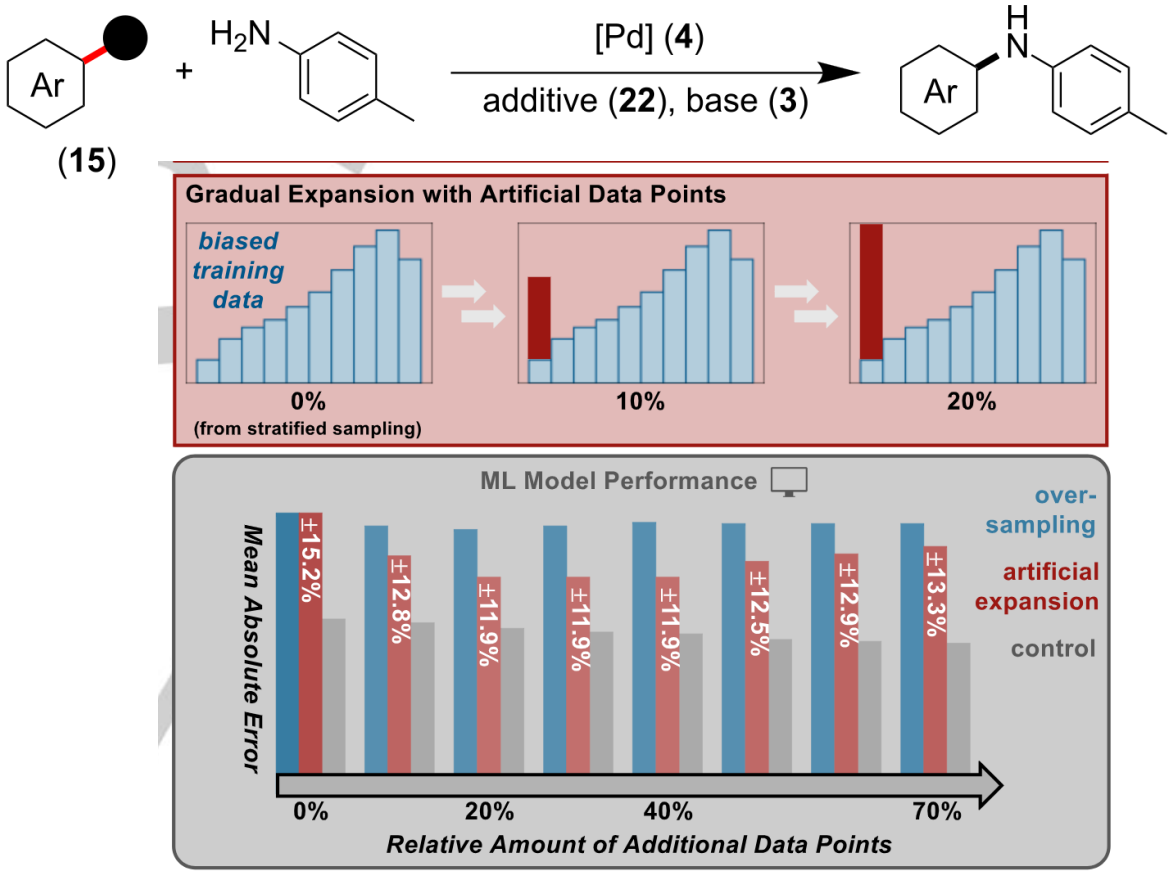
Yields distribution

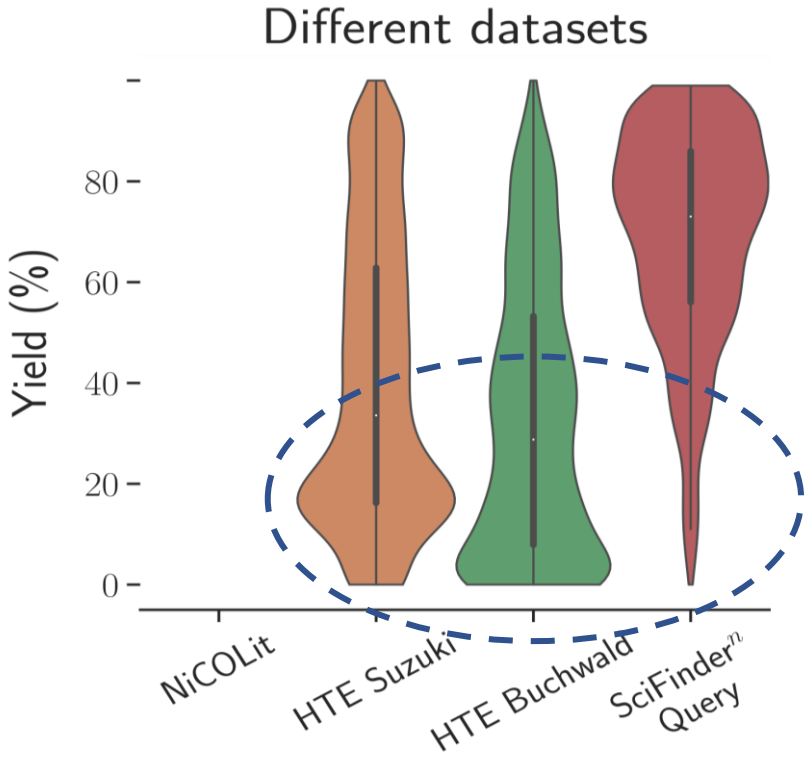






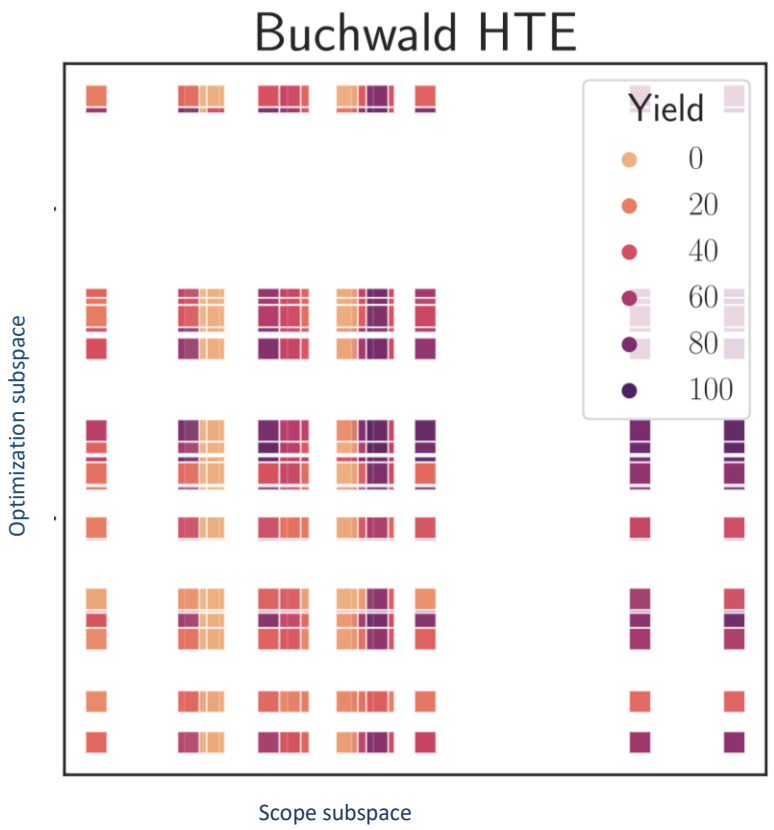
Yields distribution

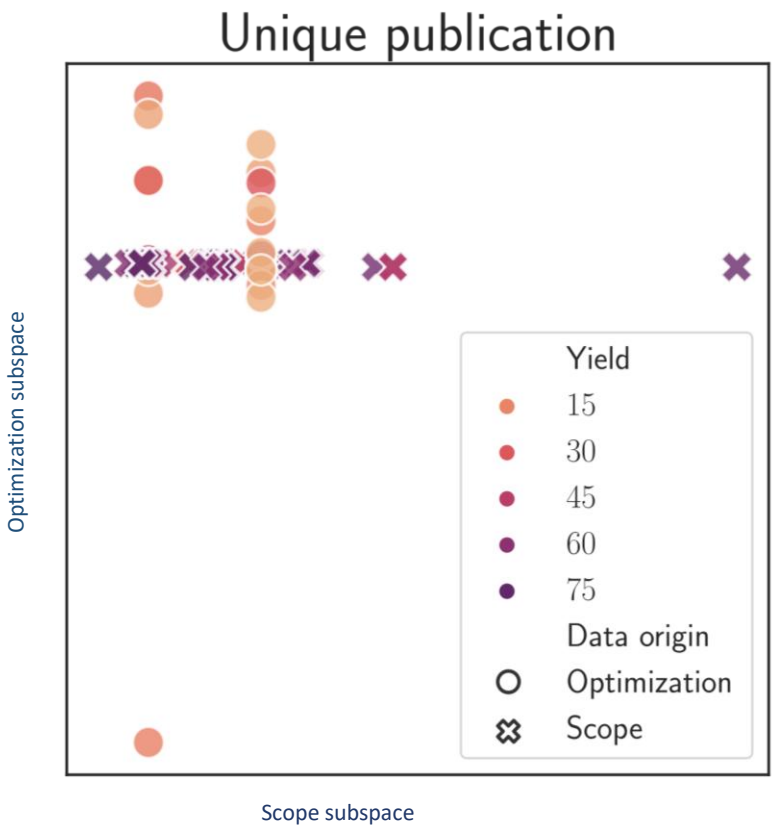




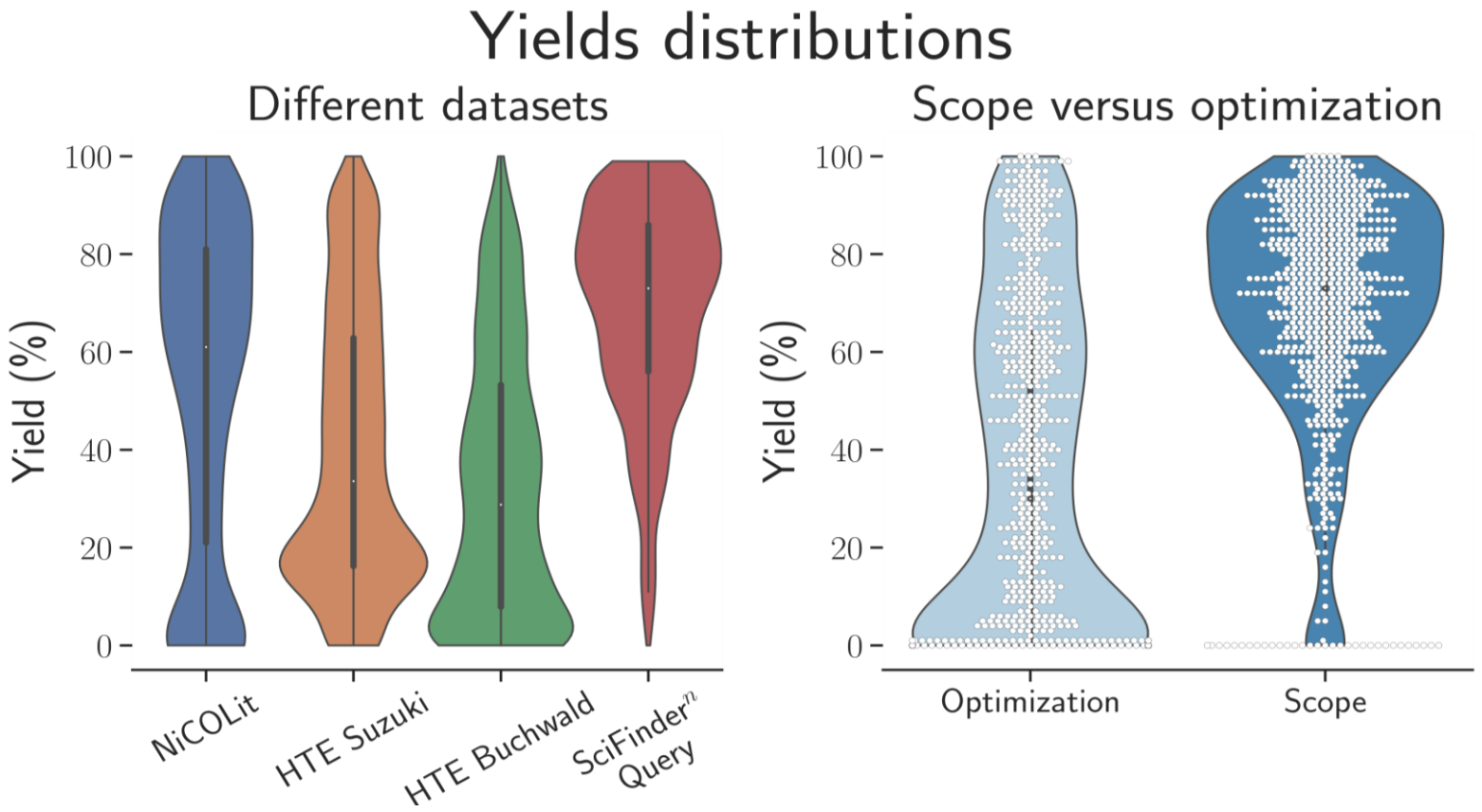
Strieth-Kalthoff, F.; Sandfort, F.; Kühnemund, M.; Schäfer, F. R.; Kuchen, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2022**, *61*, e20220467

Comparison with HTE

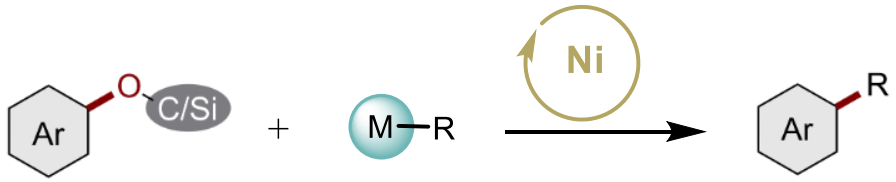




Scope and Optimization data



Performances of the model on a random split



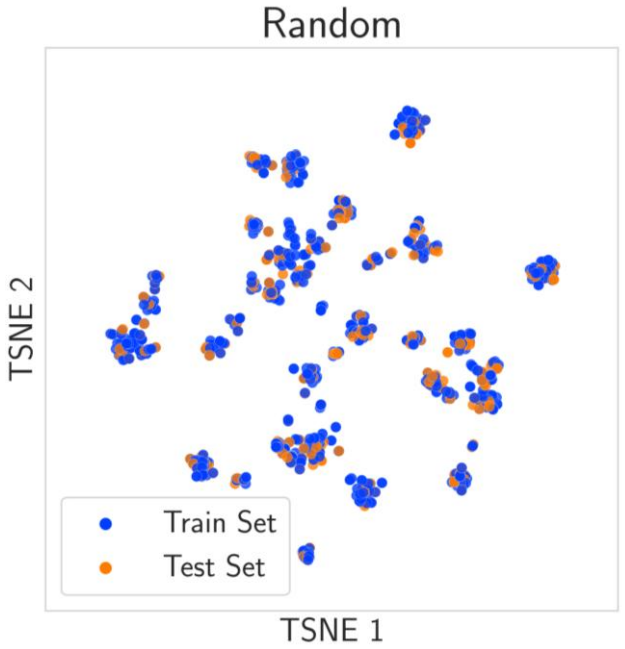
M = Li, Mg, Zn, B,...

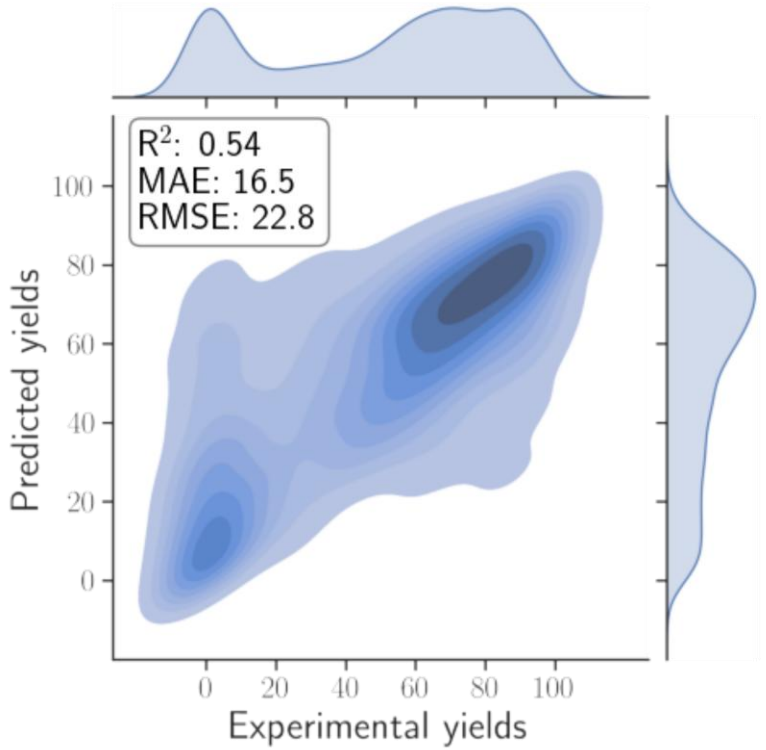
DFT featurization

Comparison to literature
HTE R^2 = 0.8
USPTO R^2 < 0.2

Training set ≈80%

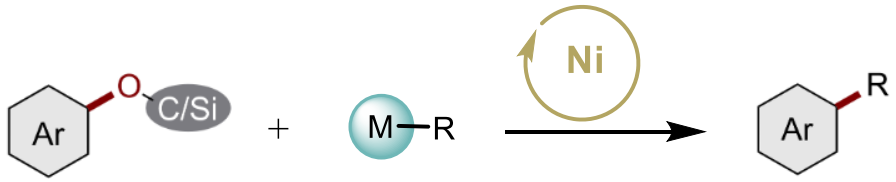
Test set ≈20%





RDKit FP and DRFP R^2 0.50
RXNFP R^2 0.37

The importance of failed experiments



M = Li, Mg, Zn, B,...

DFT featurization

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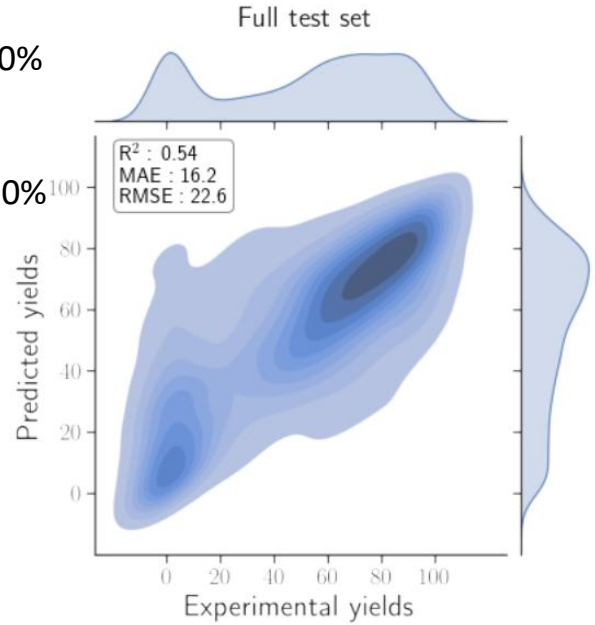
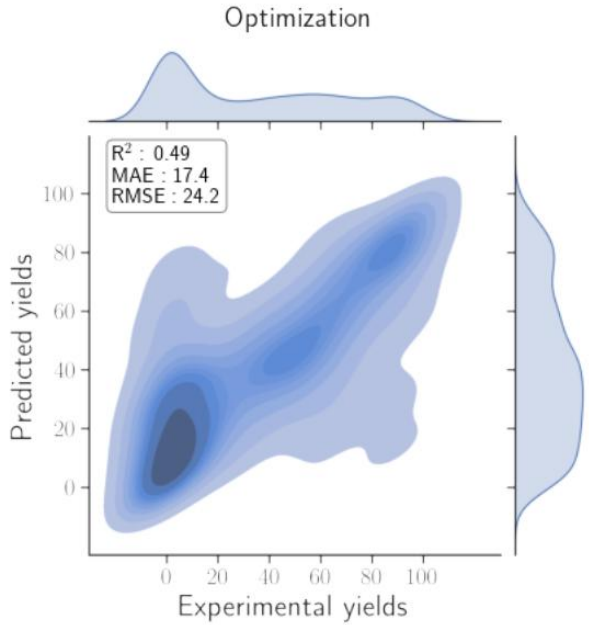
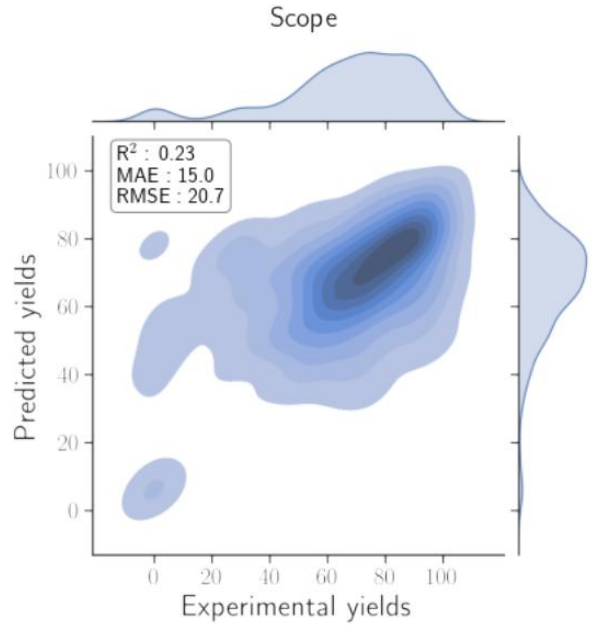
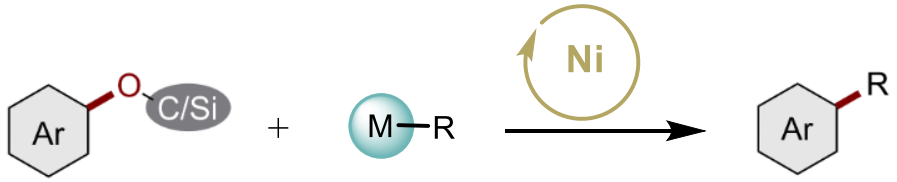






Performances for a out-of-sample publication



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DFT featurization

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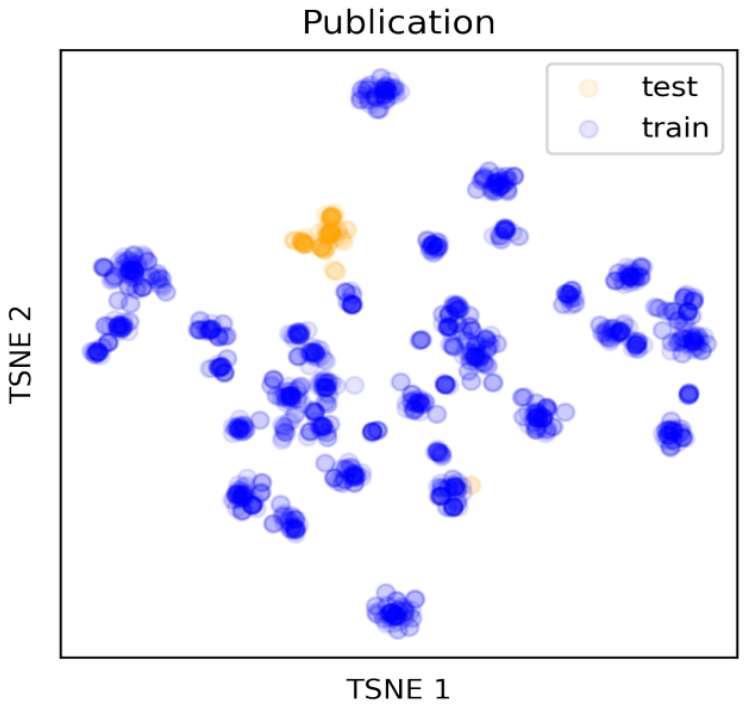
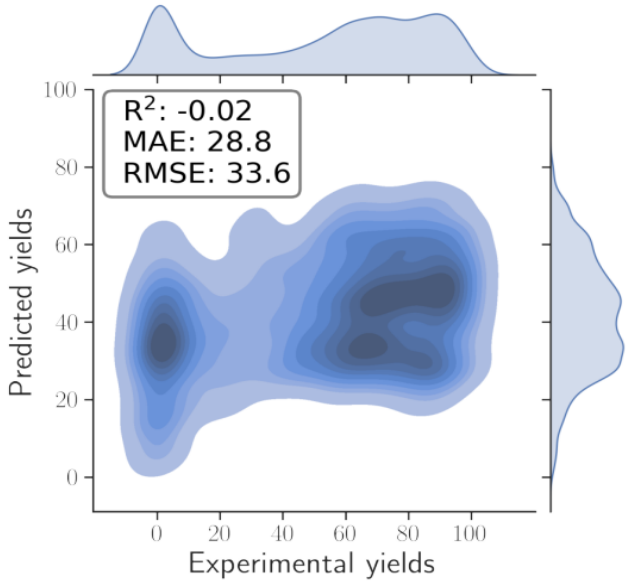
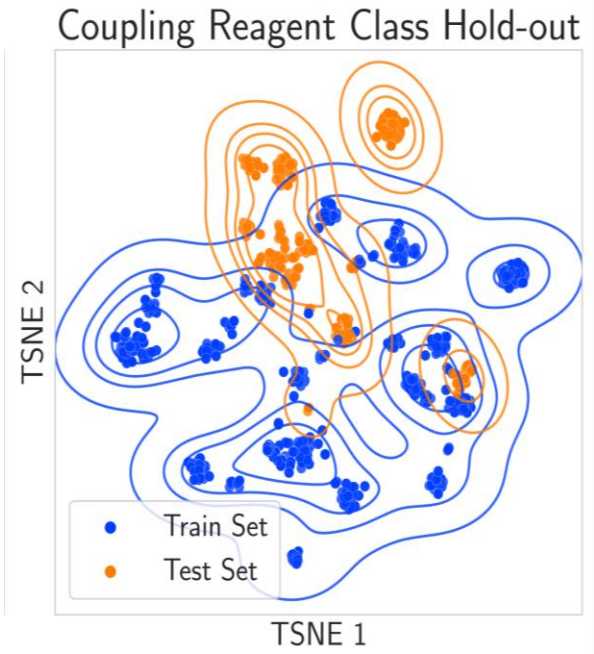
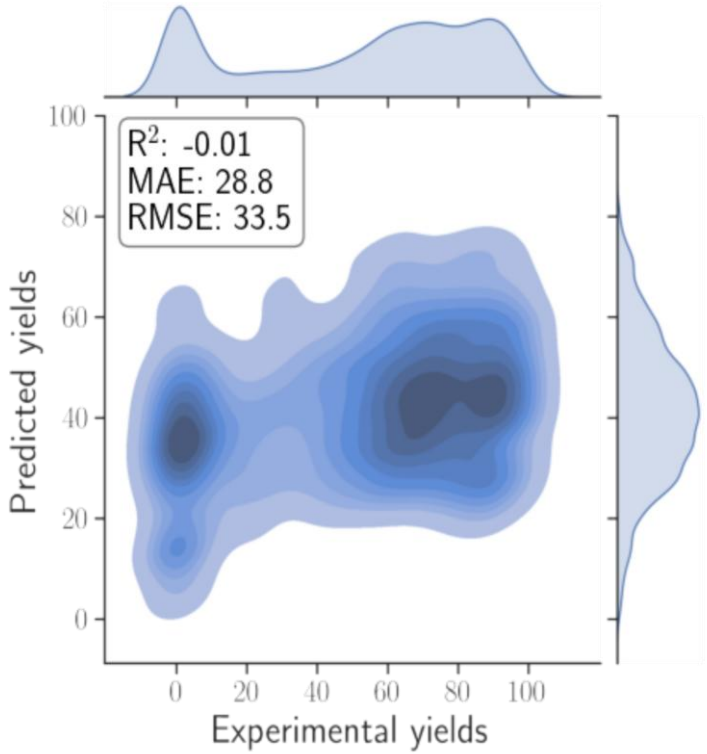




Performances for a out-of-sample coupling partner

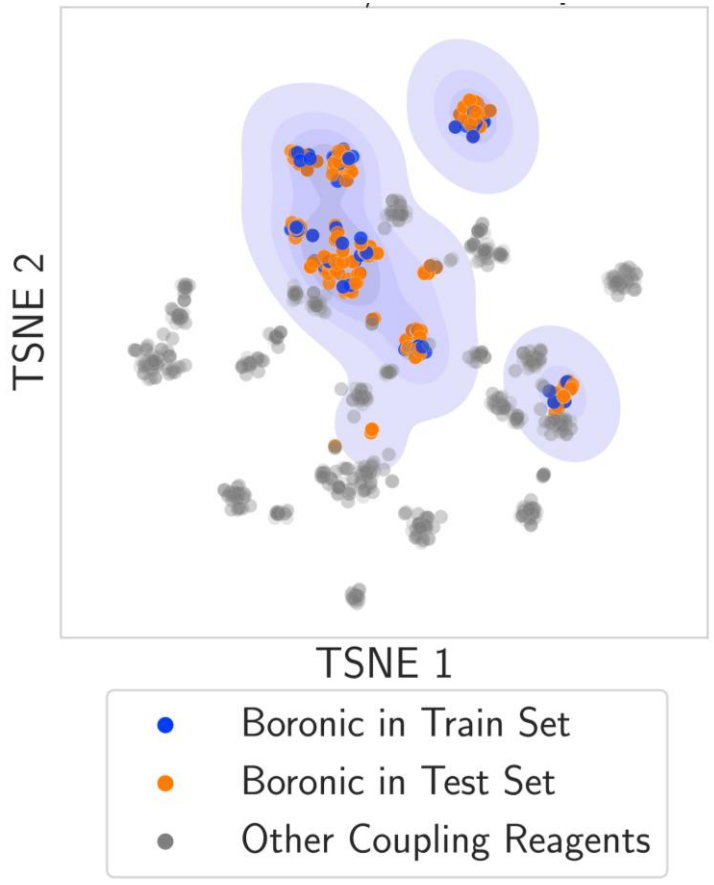
DFT featurization





Performances on a restricted dataset with similar coupling partners

DFT featurization



Coupling partner	R^2	Number of reactions	Number of publications
B	**0.47**	472	11
C-H	**0.59**	271	3
RMgX	**0.51**	266	5
CO_2	**0.52**	87	1
Zn	0.54	68	2
NCO	**0.39**	57	1
Al	0.20	53	1
Si	**0.64**	53	1

Similar to the prediction on the whole NiCOlit database

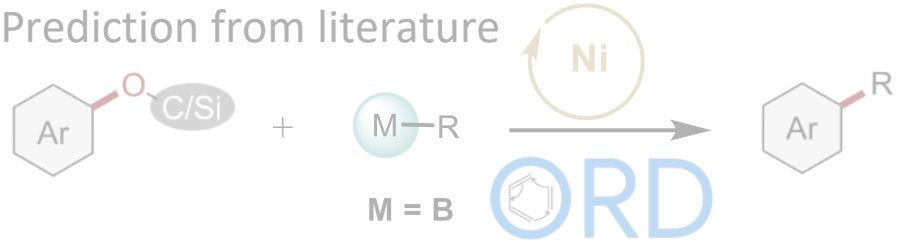
on Buchwald HTE data: R^2 = 0.59 for 98 data points

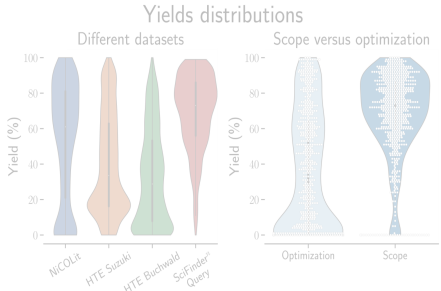
J. Am. Chem. Soc., **2022**, *144*, 14722

AI in our lab

Pr Rodolphe Vuilleumier (ENS)

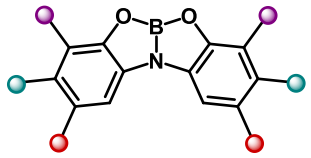
Prediction from literature

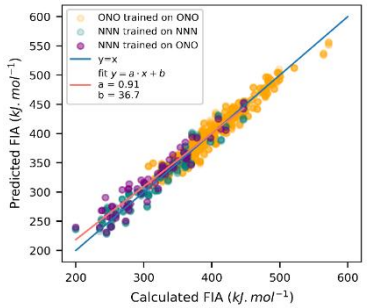


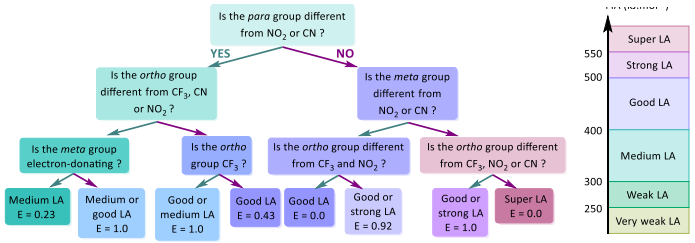


J. Am. Chem. Soc., **2022**, *144*, 14722

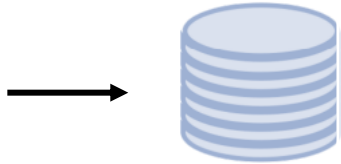
Prediction of Properties



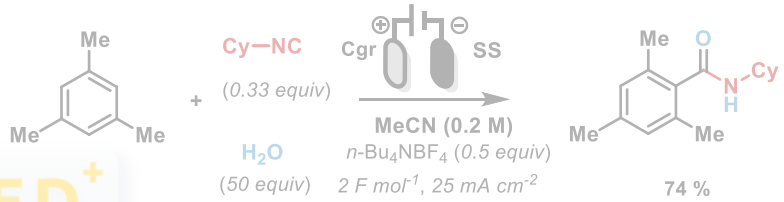


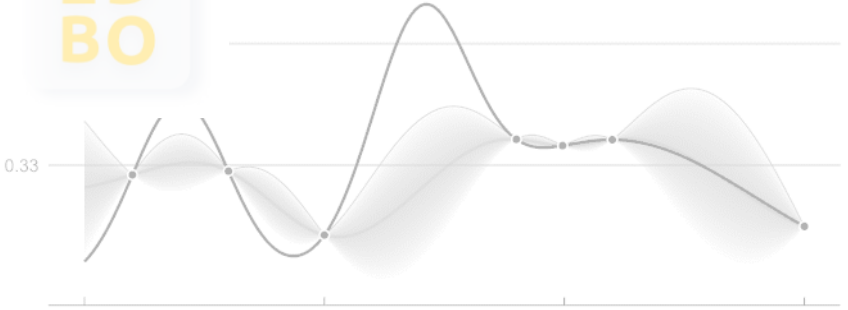


Digital Discovery **2025**, *4*, 3623



Bayesian Optimisation



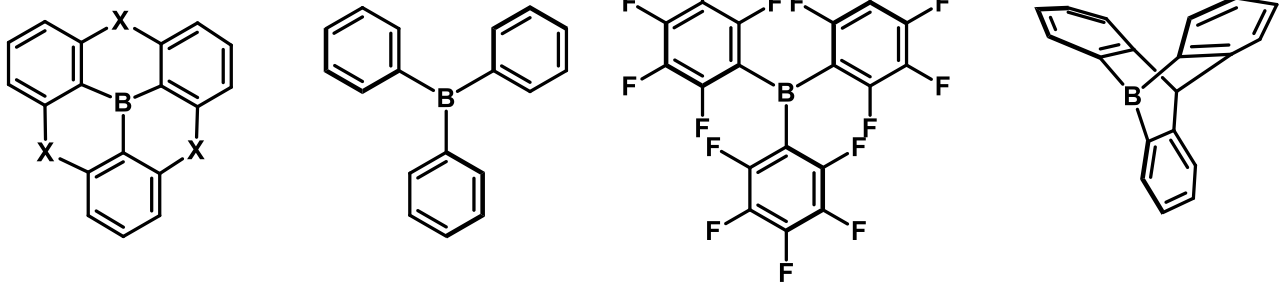


C. R. Chim. **2026**, accepted. DOI: 10.5802/crchim.431

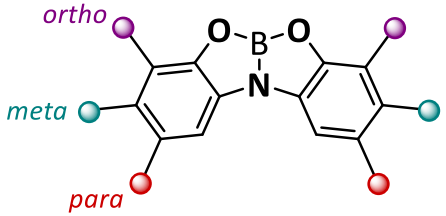
Predicting properties in low data regime: Lewis acidity

Juliette Fenogli

Boron-based Lewis acids



Using ML in low data regime



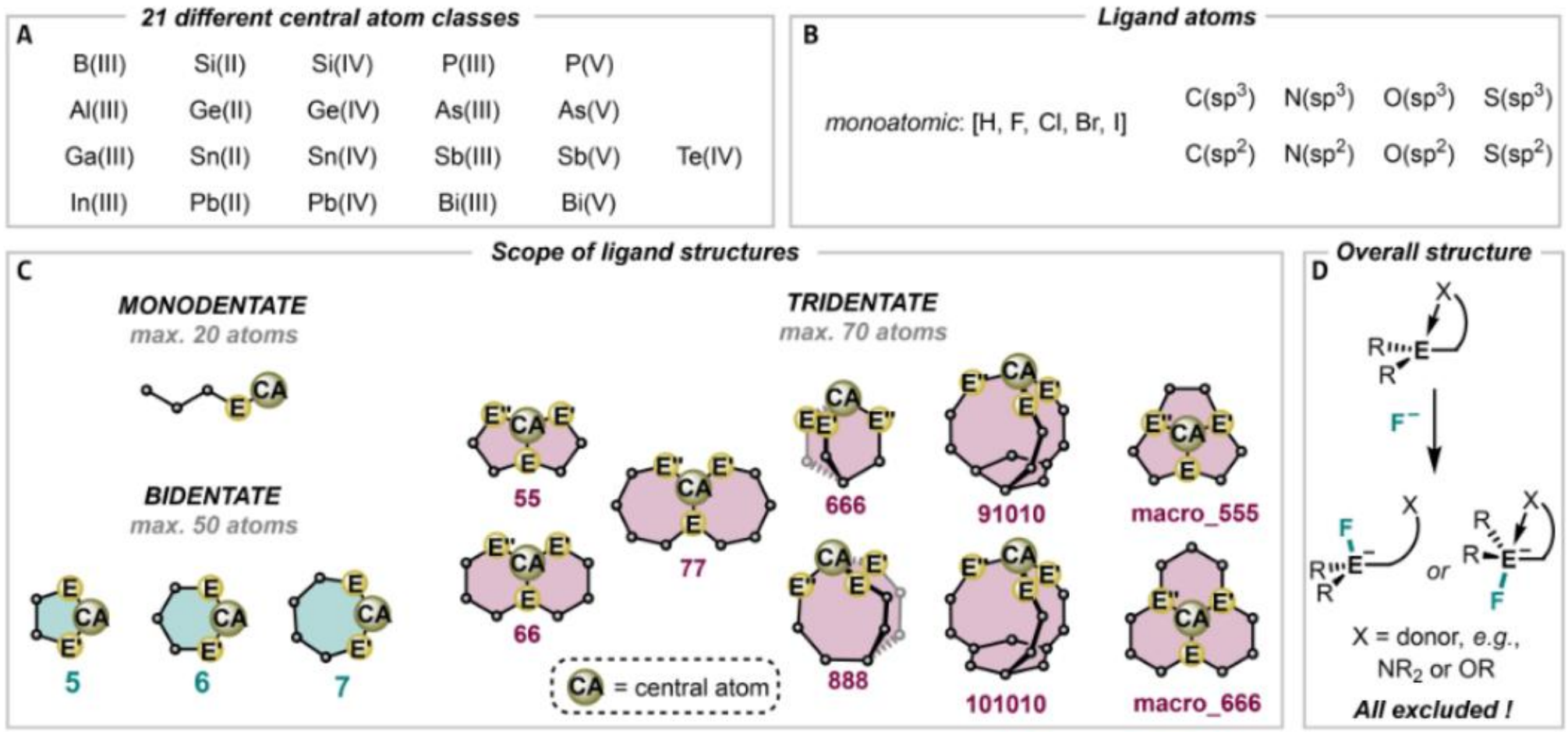
With models close to statistical analysis to perform XIA

- To get more insights into the qualitative concept of LA
- To design new LA

Massey, A. G. ; Park, A. J. *J. Organomet. Chem.*, 1964, **2** , 245
Alharbi, M. M.; Van Ingen, Y.; Roldan, A.; Kaehler, T.; Melen, R. L. Dalton Trans. 2023, 52, 1820
Ben Saida, A. ; Chardon, A. ; Osi, A. ; Tumanov, N. ; Wouters, J. ; Adjieufack, A. I. ; Champagne, B. ; Berionni, G. *Angew. Chem. Int. Ed.* **2019**, *131*, 17045
Huang, K.; Dutton, J. L.; Martin, C. D. *Chem. Eur. J.* **2017**, *23*, 10532

ML for predicting Lewis acidity

Predicting FIA using graph neural network

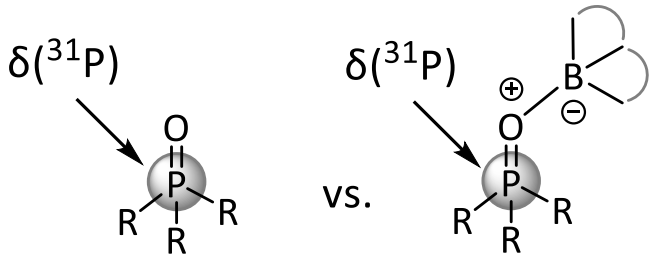


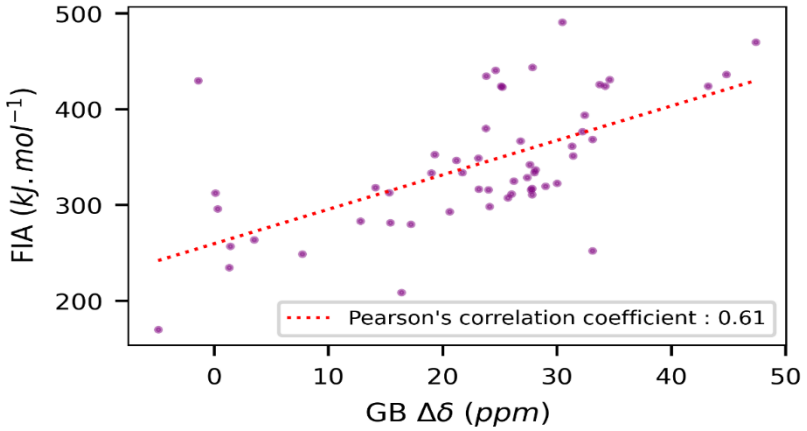
49 000 molecules !

Sigmund, L. M.; S., S. S.; Albers, A.; Erdmann, P.; Paton, R. S.; Greb, L. *Angew. Chem. Int. Ed.* **2024**, e202401084.

Lewis acidity determination

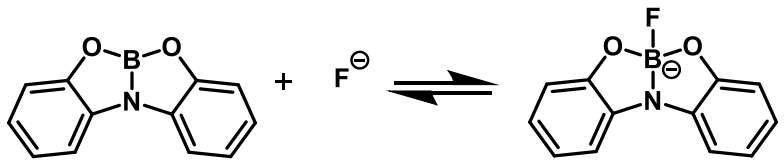
Experimental determination: Gutmann-Beckett NMR displacement



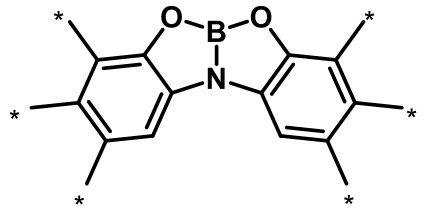


Theoretical determination: Fluoride ion affinity

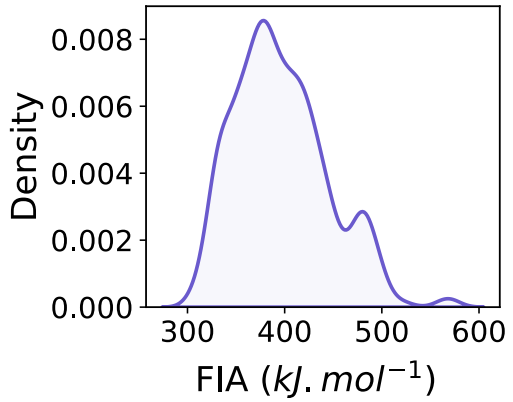
For a reliable database based on
DFT calculations (M062X/6-31G(d))



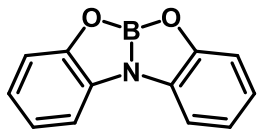
$$\Delta_r H° = -\,\mathrm{FIA}$$



-H, –F, –OH, –NH_3, –Cl, –Br, –CH_3,
–OMe, –$N(Me)_2$, –CN, –*t*Bu,
–CF_3, –NO_2



Molecular descriptors



SMILES : c12c(OB3Oc4c(N32)cccc4)cccc1

Molecular representation

Molecular descriptors

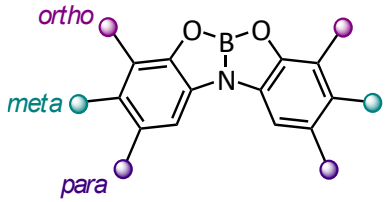
Training data

Chemoinformatics

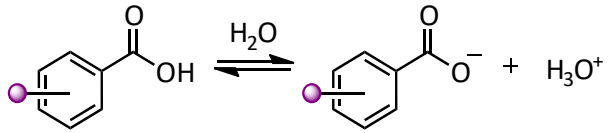
DFT-calculated

Method : M06-2X/6-31g

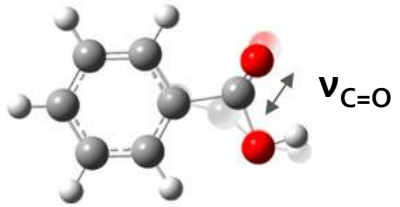
Hammett-extended

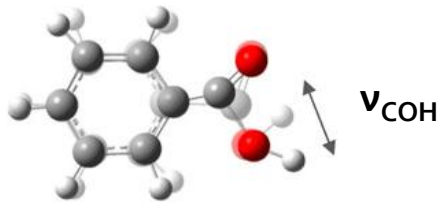


Global parameters	Dipolar moment, frontier orbitals energies, absolute electronegativity…
Atomic parameters for B	Charge, valence, buried volume…



Hammett σ constants	σ_m, σ_p
Steric parameters	Sterimol **B1**, **B5** and **L** for *o*, *m* & *p* Torsional angle : $\theta_{tor,o}$
IR parameters	$\nu_{C=O}$, ν_{COH}, $I_{C=O}$, I_{COH} for *o*, *m* & *p*
NBO charges	NBO_C, $NBO_{=O}$, NBO_O, NBO_H for *o*, *m* & *p*



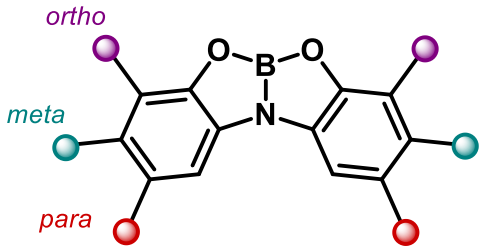


⟹ 244 concatenated features

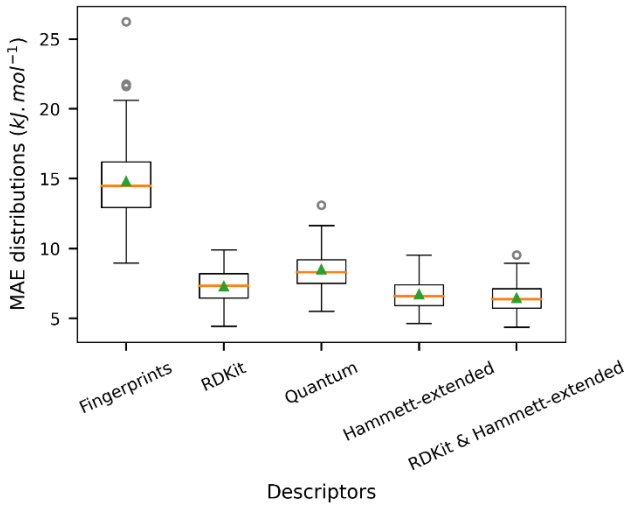
Żurański, & Doyle, *React. Chem. Eng.* **2022**, *7*, 1276

Santiago, C. B.; Milo, A.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, 138, 13424

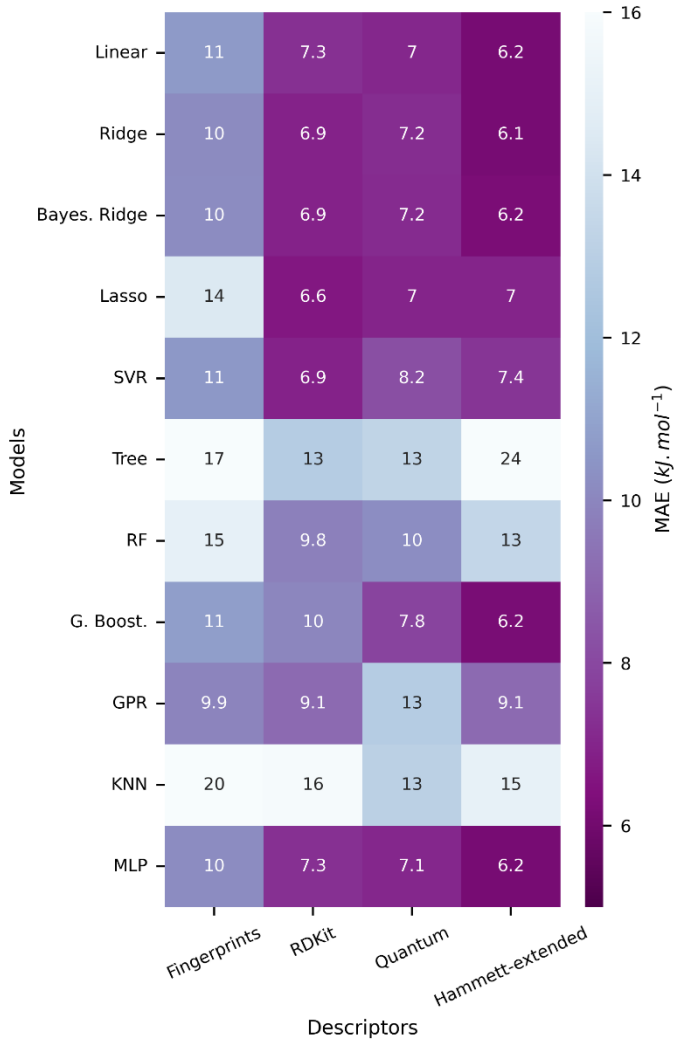
Model construction



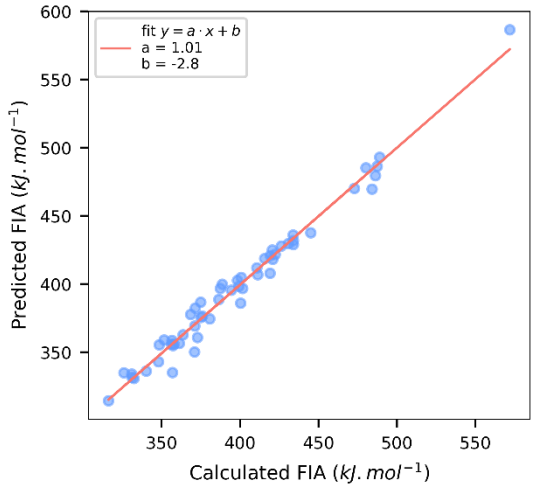
Descriptors evaluation



Test set



Optimized model: Linear Regression



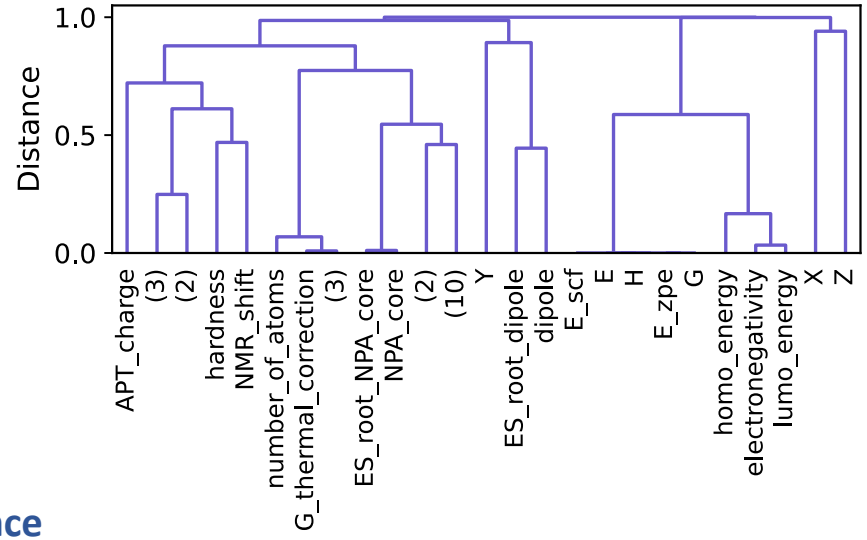
MAE about 5 kJ.mol^{-1}

⇨ Regression models offer an optimal balance between interpretability and prediction accuracy

Interpretability: finding the key feature of LA

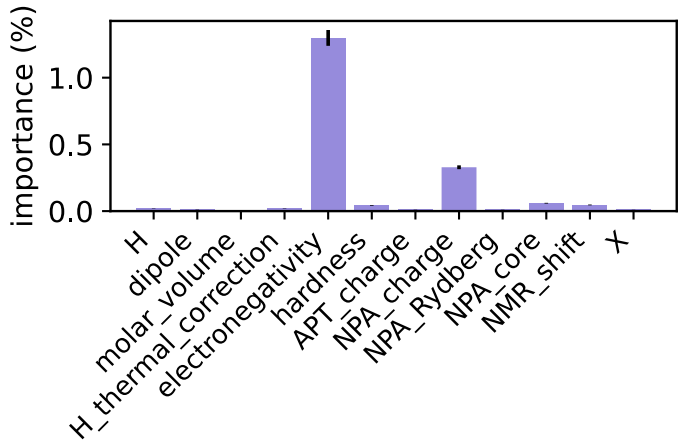
Hierachical clustering

12 uncorrelated features



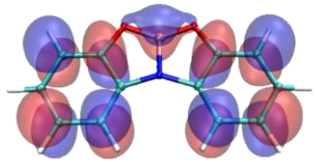
With DFT descriptors

Permutation importance



Absolute electronegativity

$$\chi = {}^{-1}/_{2}\,(E_{HOMO} + E_{LUMO})$$

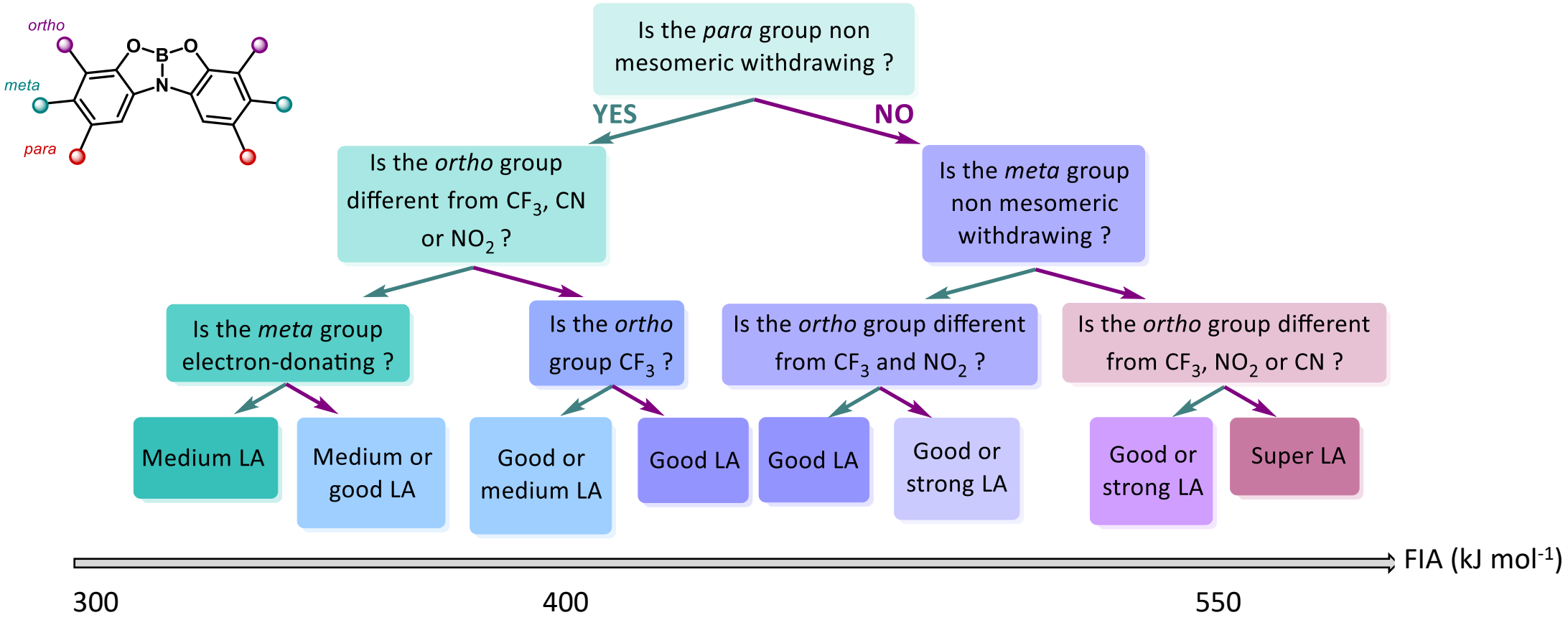


⇨ Unexpectedly Lewis Acidity is more influenced by MO interactions than by Coulombic interactions (Hard acidity)

A classification to help design

Decision tree with 3 questions

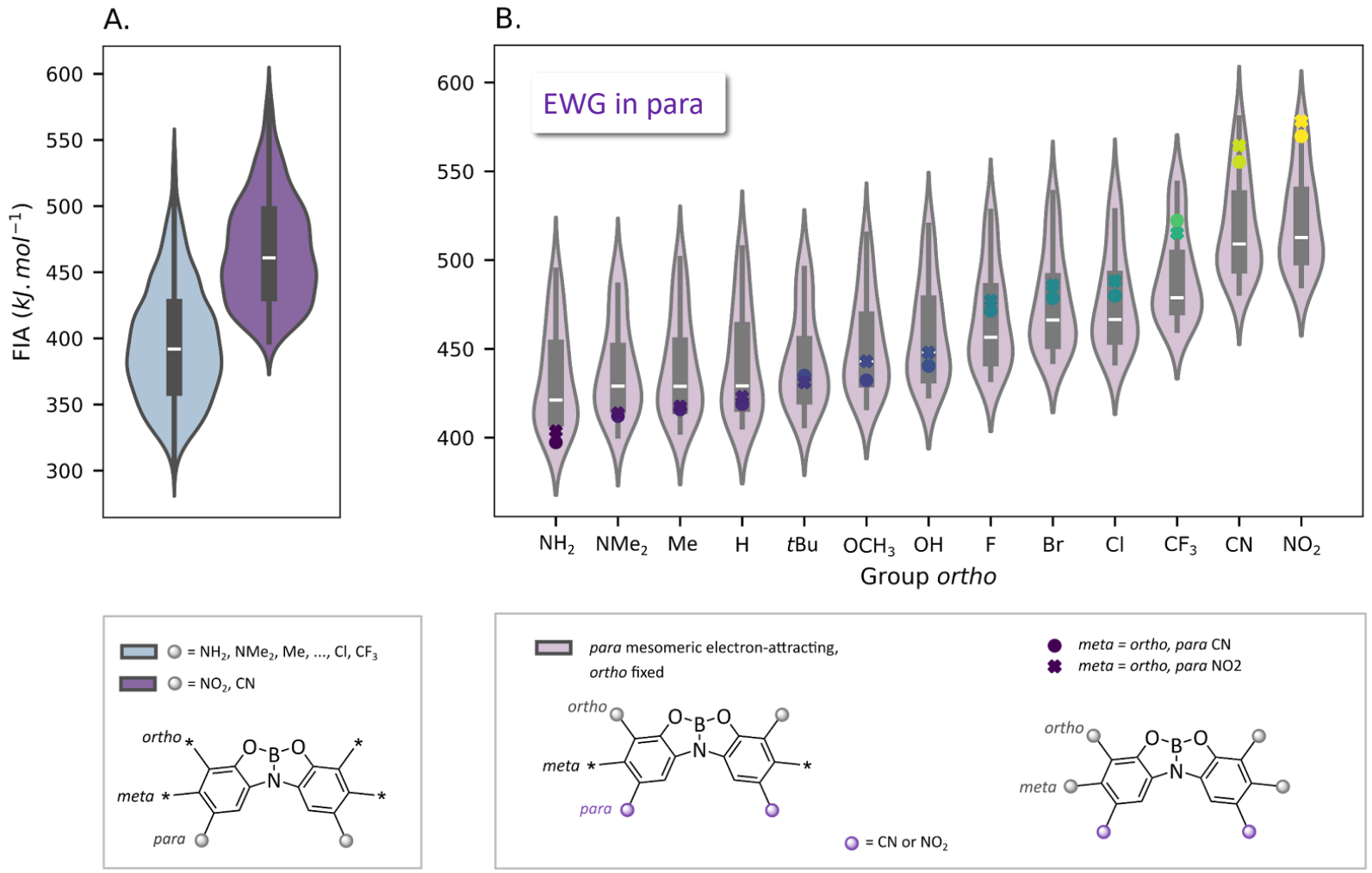
With Hammett-extended descriptors



⇨ In low-data regime, ML models can accurately and interpretably predict Lewis acidity, bridging the gap between advanced ML techniques and traditional chemical intuition

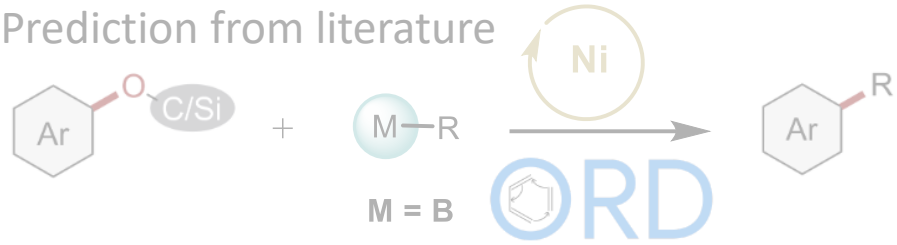
Digital Discovery **2025**, *4*, 3623

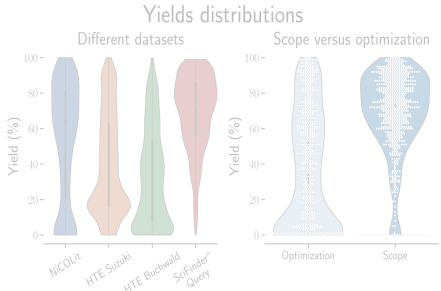
Screening and Analysing the database



AI in our lab

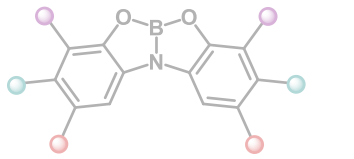
Prediction from literature

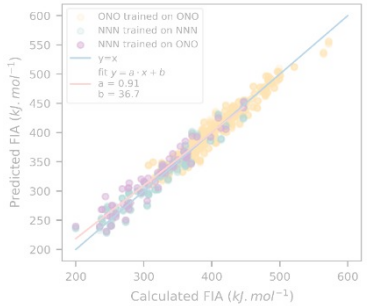


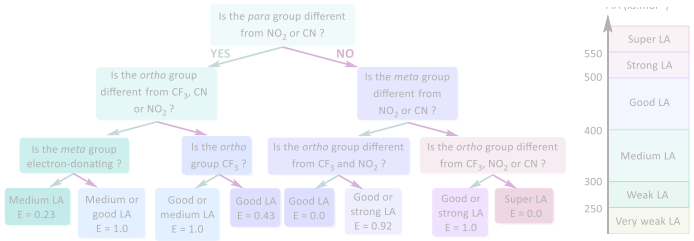


J. Am. Chem. Soc., **2022**, *144*, 14722

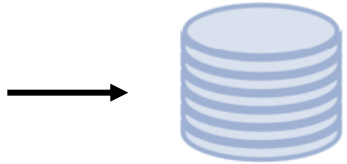
Prediction of Properties



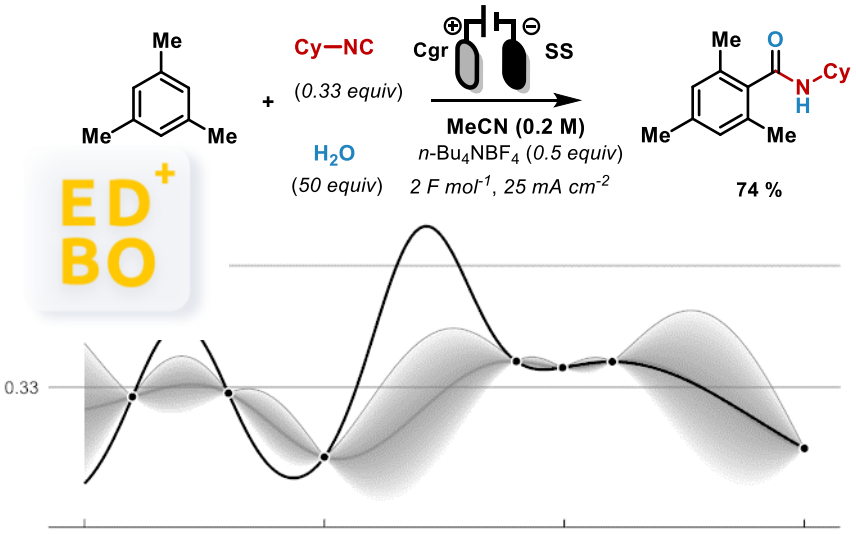




Digital Discovery **2025**, *4*, 3623



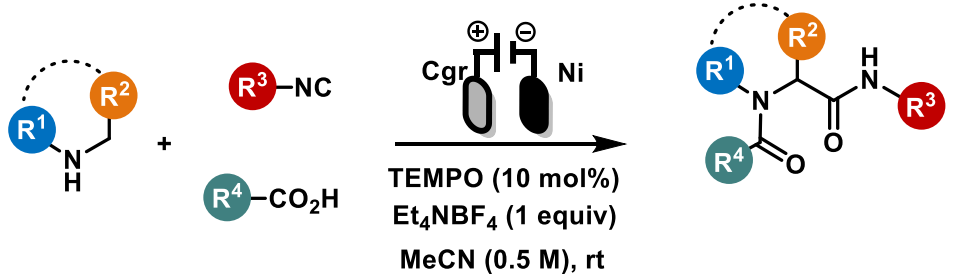
Bayesian Optimisation



C. R. Chim. **2026**, accepted. DOI: 10.5802/crchim.431

Electrosynthesis and IMCRs

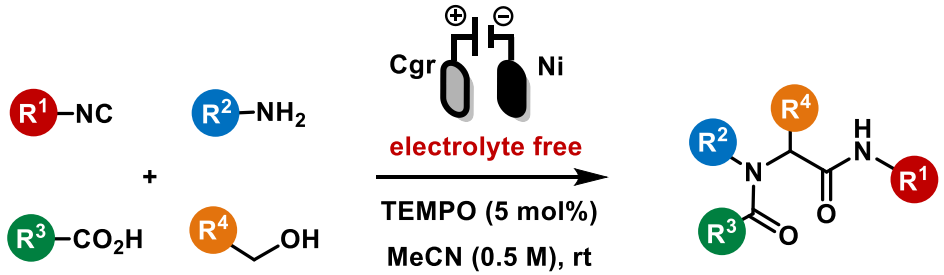
Electro-induced Ugi-Joullié coupling



Pan, N.; Ling, J.; Zapata, R.; Pulicani, J.-P.; Grimaud, L.; Vitale, M. R. *Green Chem.* **2019**, *21*, 6194

Undivided cell

Electro-oxidative Ugi Reaction

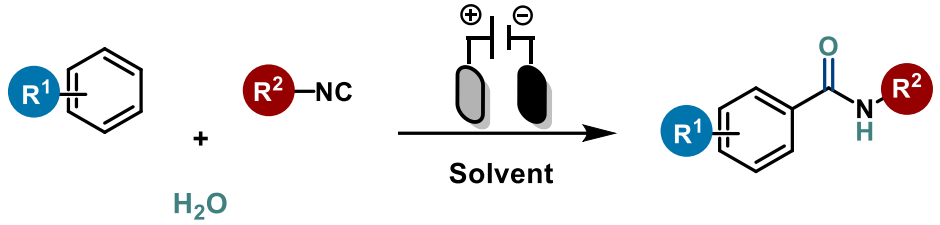


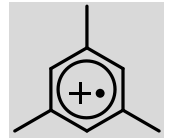
Pan, N.; Xinen Lee, M.; Bunel, L.; Grimaud, L.; Vitale, M. R. *ACS Org. Inorg. Au* **2021**, *1*, 21

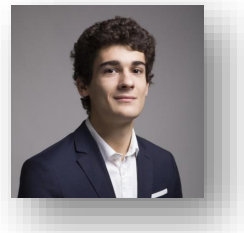
For the electro-Passerini, see: Simon, A.; Bachollet, S. P. J. T.; Pan, N.; Grimaud, L.; Vitale, M. R. *Synlett* **2024**, *35*, A-E

New electrophiles in IMCRs

Carbocations







Virgile Rouffeteau

For cation-pool: Yoshida *J. Am. Chem. Soc.* **2013**, *135*, 5000

For previous cyanation: Gooßen *Chem. Eur. J.* **2018**, *24*, 11288

Dr Maximilian Fleck

Experimental conditions

Substrates' substituants

Stoichiometry

Concentration

Solvent(s)

Temperature

etc…

+

Electrosynthesis

Electrodes materials

Supporting electrolyte

(nature/quantity)

mA or Volt

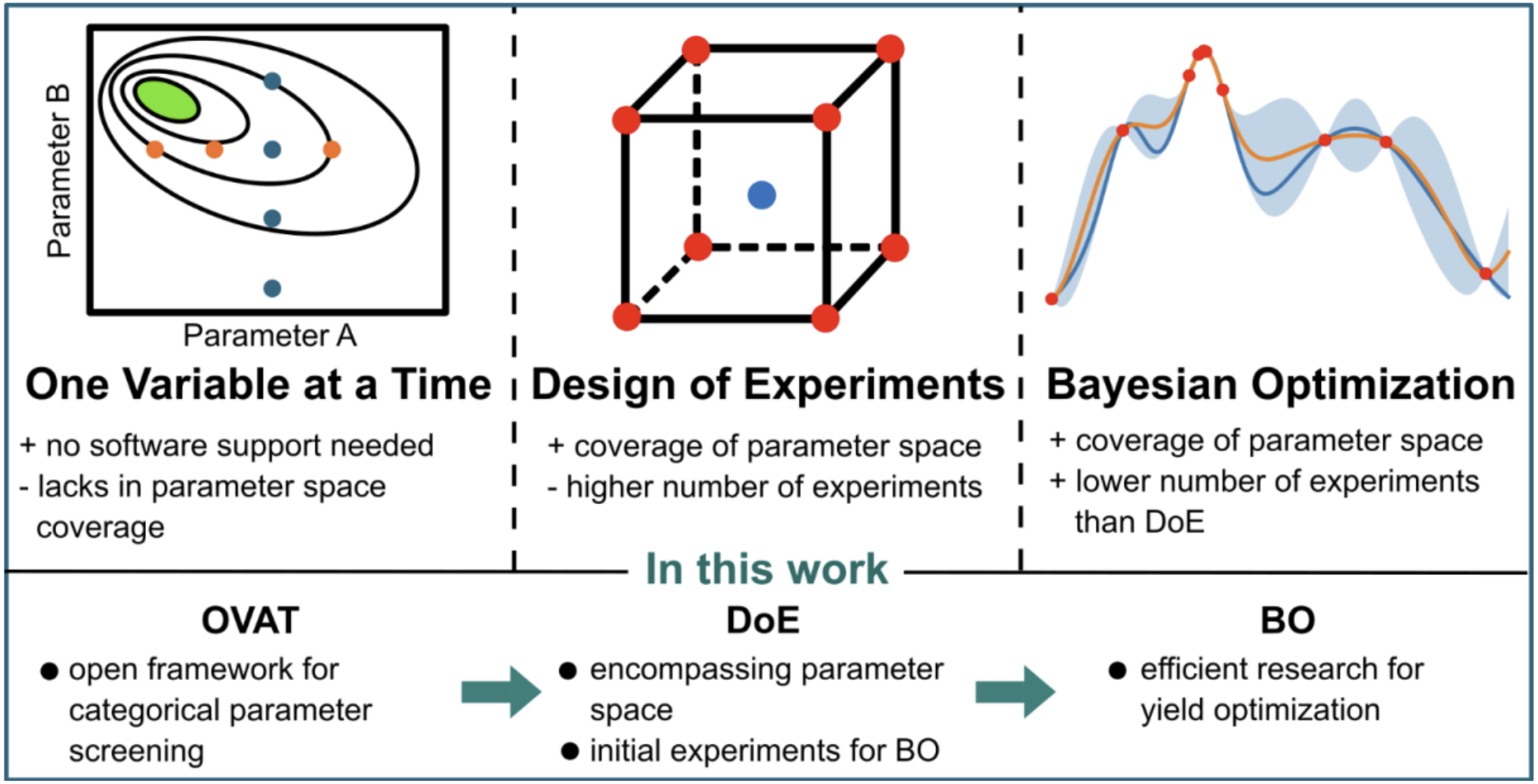
Charge (e^- injected per substrate)

etc…

> 14 parameters

> 10^9 possible combinations

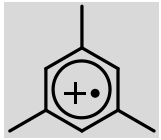
Different optimization methods

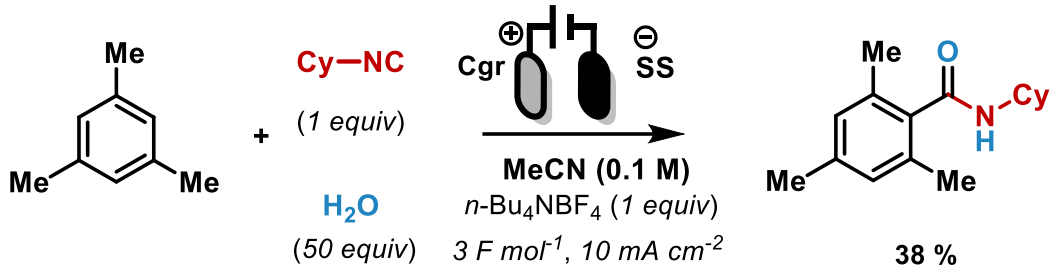


Alán Aspuru-Guzik,[b, c, e, g, h, i, j, k, l] and Siegfried R. Waldvogel ChemRXIV 2026 10.26434/chemrxiv-2026-8rd5c

Chemical Space for Bayesian Optimization

Electro-carbamoylation of electron-rich arenes using Bayesian optimisation





- Output Yield (based on limiting Substrate)
- Definition of space

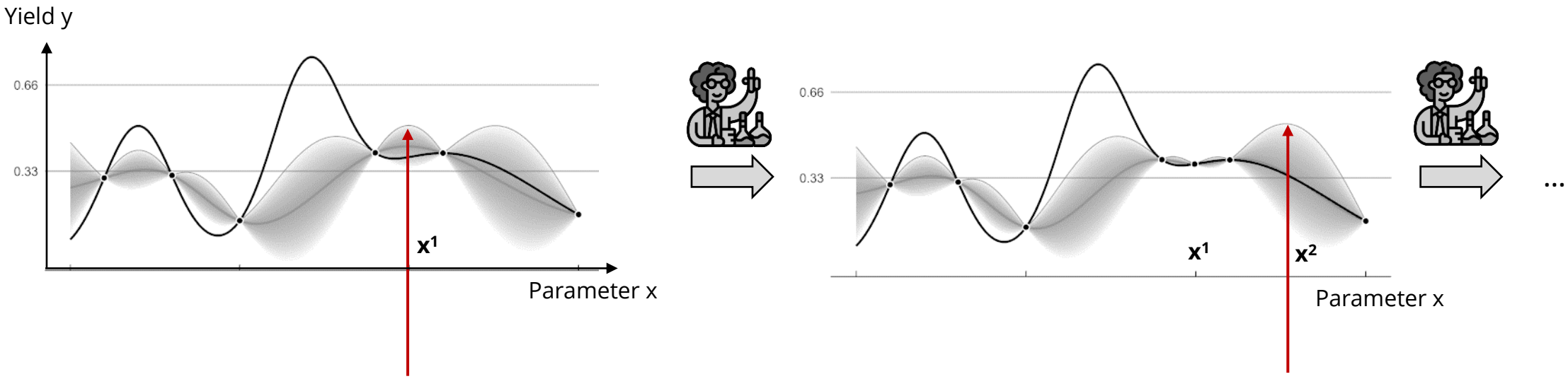
6 Parameters	Values						
Cy-NC equivalent(s)	0.33	0.5	0.75	1	1.5	2	3
Water equivalent(s) %limiting	1	5	10	25	50		
Salt equivalent(s) %limiting	0.5	1	2				
Current Density (mA.cm^{-2})	5	10	15	20	25		
Limiting Reagents' Concentration(M)	0.05	0.1	0.15	0.2			
Faraday per mole of arene	2	3	4	5	6		

- Evaluation of the efficiency (NMR with ext. Std)
- Algorithm: EDBO+

10 500 combinations !

Doyle, A., *et al*. *Nature*, **2021**, 89

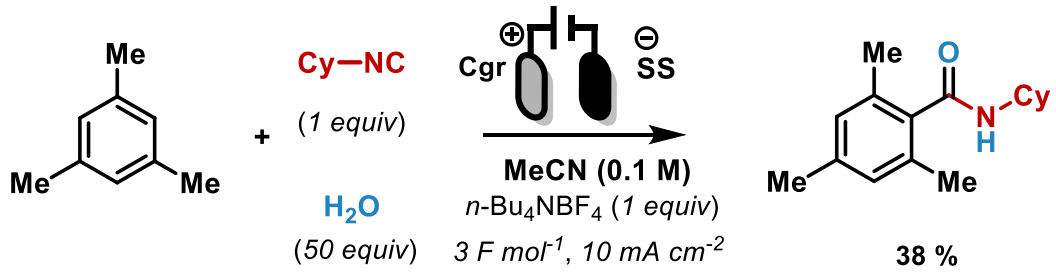
Bayesian Optimization

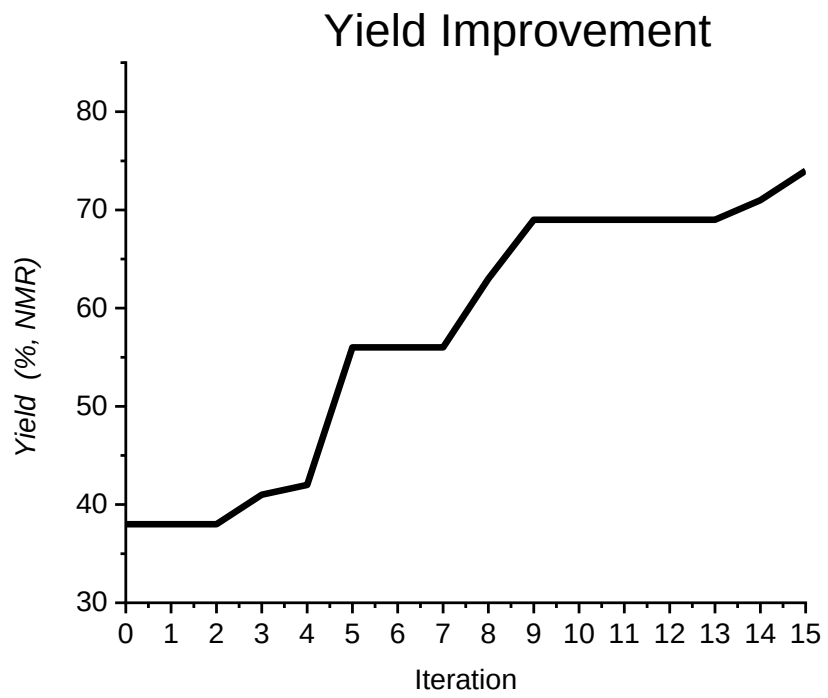


Highest peak at x^1,
new theroretical highest yield $y^{1\prime}$

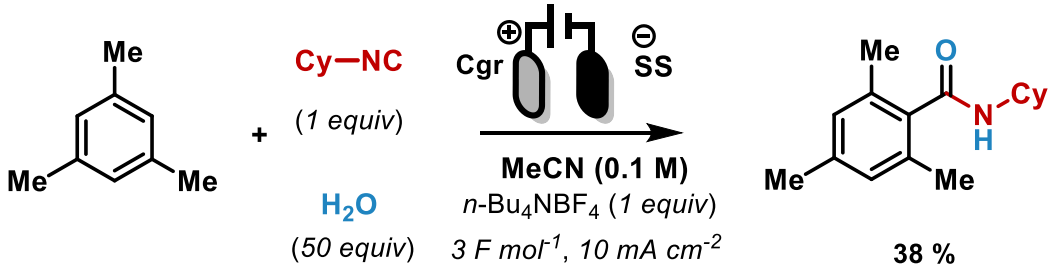
New highest peak at x^2,
new theoretical highest yield $y^{2\prime}$

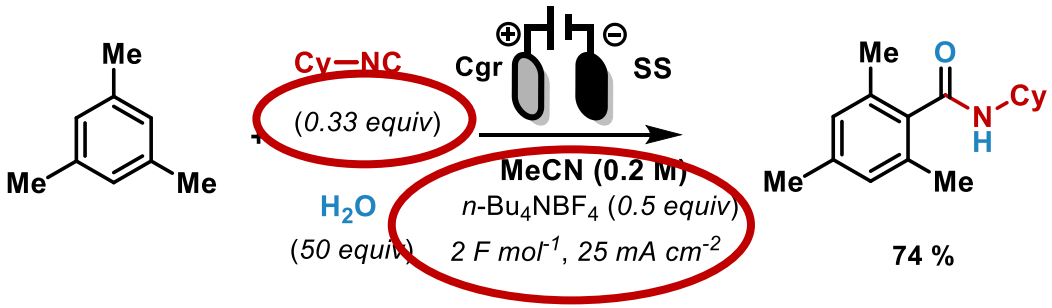
Bayesian Optimization for electrosynthesis





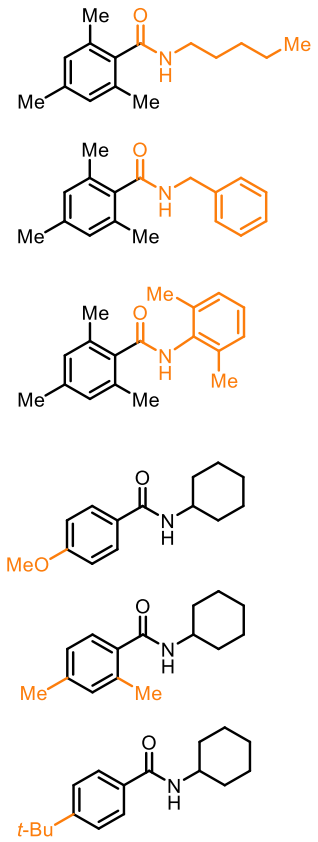
Optimized conditions



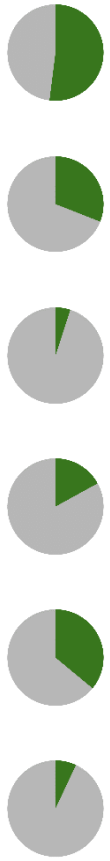


High faradic efficiency

Product



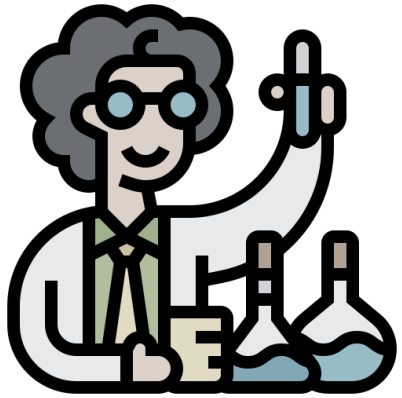
EDBO

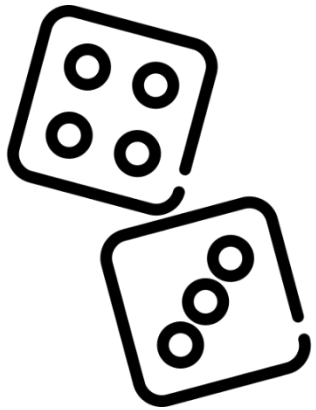


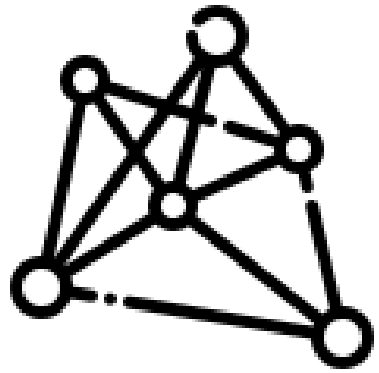
C. R. Chim. **2026**, accepted. DOI: 10.5802/crchim.431

Training Dataset Design

Precedents







- Intuitive sampling

Majority of the literature

- Random sampling

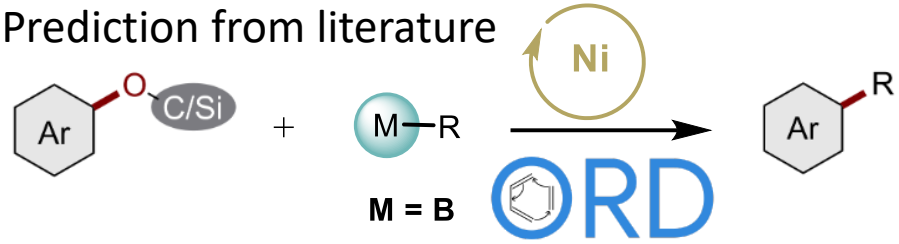
Doyle *et coll*, *Nature*, **2021**, *590*, 89.

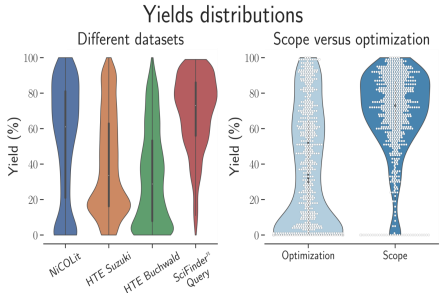
- Orthogonal sampling

Felpin *et coll*, *Org. Process Res. Dev.* **2024**, *28*, 1597.

AI in our lab

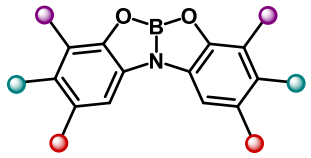
Prediction from literature

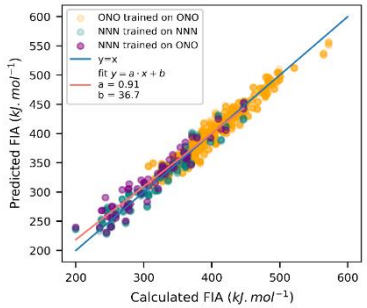


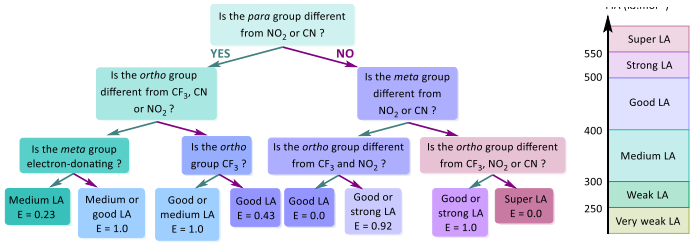


J. Am. Chem. Soc., **2022**, *144*, 14722

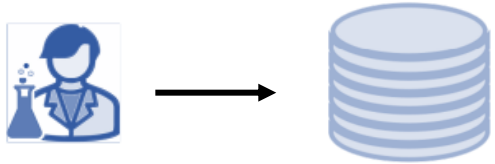
Prediction of Properties



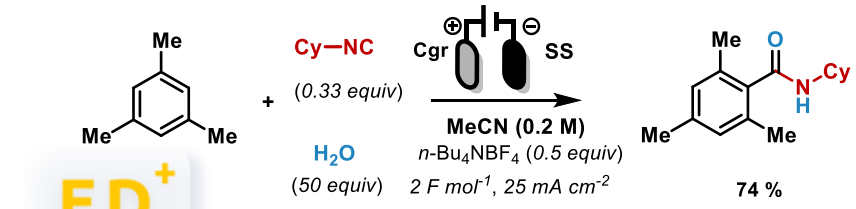


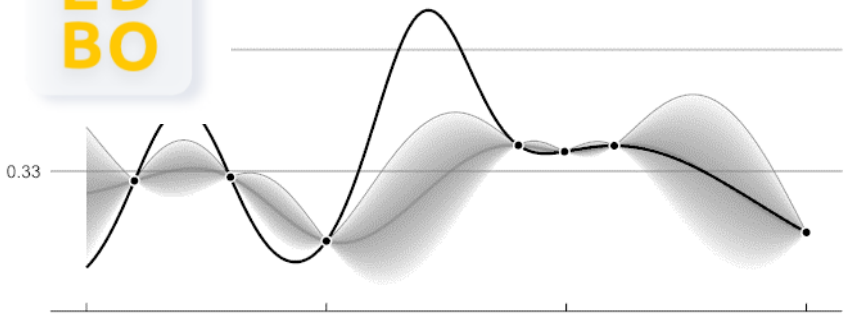


Digital Discovery **2025**, *4*, 3623



Bayesian Optimisation





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