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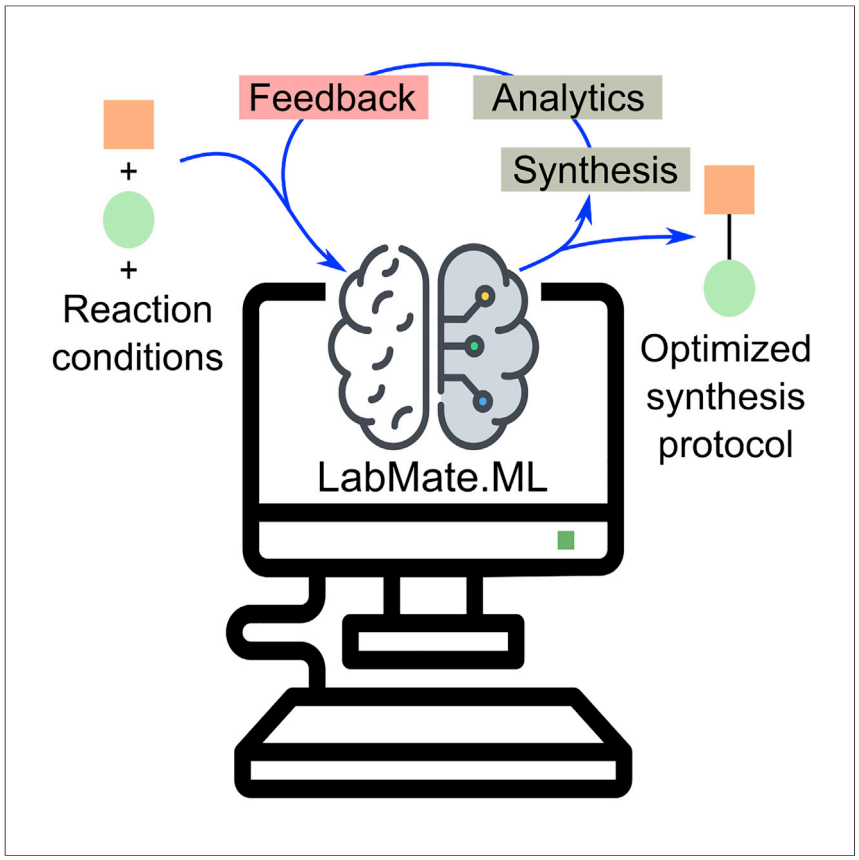

Reaction condition optimization is key for synthetic chemistry. Reker et al. implement and validate an algorithm, coalescing random search space sampling and adaptive machine intelligence for optimizing small-molecule, glyco-, and protein chemistries. They show the competitive behavior of the heuristics relative to expert chemical intuition.

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HIGHLIGHTS

Self-evolving machine learning for chemistry optimization

Small data (0.03%–0.04% of search space) for adaptive learning

Simultaneous optimization of real valued and categorical features

Augmentation of intuition in small-molecule, glyco-, and protein chemistry examples

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Adaptive Optimization of Chemical Reactions with Minimal Experimental Information

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SUMMARY

Optimizing reaction conditions depends on expert chemistry knowledge and laborious exploration of reaction parameters. To automate this task and augment chemical intuition, we here report a computational tool to navigate search spaces. Our approach (LabMate.ML) integrates random sampling of 0.03%–0.04% of all search space as input data with an interpretable, adaptive machine-learning algorithm. LabMate.ML can optimize many real-valued and categorical reaction parameters simultaneously, with minimal computational resources and time. In nine prospective proof-of-concept studies pursuing distinctive objectives, we demonstrate how LabMate.ML can identify optimal goal-oriented conditions for several different chemistries and substrates. Double-blind competitions and the conducted expert surveys reveal that its performance is competitive with that of human experts. LabMate.ML does not require specialized hardware, affords quantitative and interpretable reactivity insights, and autonomously formalizes chemical intuition, thereby providing an innovative framework for informed, automated experiment selection toward the democratization of synthetic chemistry.

INTRODUCTION

Chemistry and synthetic method development are central to successful chemical biology, drug discovery, materials science, and engineering research programs.[1,2] However, the identification of appropriate synthetic procedures requires expert chemistry knowledge[3] that may lead to suboptimal goal-oriented methods, given predisposed assumptions.[4,5] The selection of experiments toward a predefined objective (e.g., optimal reaction conditions) remains a subjective/non-deterministic task when performed by expert chemists.[6] Moreover, traditional chemometrics and full/fractional factorial design of experiments are laborious.[7,8] Thus, the development of computational technologies from minimal data can assist future discovery chemistry by streamlining the identification of optimal reaction conditions and augmenting chemical knowledge.[9,10]

Formalizing decision making in machine circuits may reshape how science is carried out,[11,12] and its application in automated laboratories is expected to accelerate drug development.[12–19] Despite being an enabling technology in chemistry,[20–22] current machine-learning implementations rely on harnessing massive datasets coupled to black-box algorithms and retrospective benchmark statistics. In addition, given the need of expert chemistry knowledge to effectively tackle non-routine tasks, most algorithms have experienced questionable applicability to organic chemistry practice.[3,23] These hurdles have kept the optimization of chemical reaction conditions toward a desired objective as a challenge with only a few significant

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reported applications.[24] For example, reaction feasibility can be predicted by classifiers,[25] and substrate scoping (i.e., determining which building blocks react under certain fixed conditions) is predictable by leveraging brute-force reaction screening data.[26,27] Similarly, the discovery of new chemical reactions has been automated,[28] using thousands of data points (entries of reaction data) to teach a machine, which is only feasible with the means for conducting/analyzing hundreds to thousands of reactions in parallel. However, these algorithm applications do not allow optimizing reaction conditions to maximize product amounts and/or yields. To that end, deep-learning architectures employing several thousand probability density functions for simulated data pre-training have been used to optimize only three reaction parameters over 40 iterations.[21] More recently, a black-box algorithm was integrated into a flow chemistry apparatus to enable fast feedback loops in reaction condition optimizations. With said algorithm, up to five reaction variables, in multiple chemical reactions, were optimized over 30–60 iterations.[24,29] While these applications highlight the computational tractability of reaction condition optimization, we hypothesized that reaction modeling routines can more efficiently navigate larger parameter spaces than current state-of-the-art methods, leverage significantly less data, and require manifold fewer optimization iterations.

Here, we report the development and application of a computational framework (LabMate.ML) leveraging unbiased, random experiment selection for initialization and adaptive machine learningto navigate unknown reactivity spaces. LabMate.ML models an unprecedented number of reaction condition variables to augment human chemical perception, albeit being agnostic to the identity and mechanism of the studied chemical transformation. This tool runs on a personal computer and does not require any specific computational or laboratory equipment. By optimizing distinct chemistries for a myriad of objectives, we provide validations for our computational routine. Namely, we apply LabMate.ML to multiple small-molecule, glyco-, and protein chemistries that are relevant to scaffold generation and decoration as well as late-stage functionalization. Our learning approach formalizes chemical intuition and contrasts with methods built from big data and complex algorithms.[21,26–28] Instead, the software relies on an easily accessible volume of information and a fully traceable decision tree-based algorithm. Specifically, LabMate.ML uses small data (5–10 data points; 0.03%–0.04% of search space) to navigate the reaction condition space, and optimizes up to eight condition parameters simultaneously using only 1–10 additional iterations/reactions. Our method identified optimal synthetic methods toward a specified optimization objective and unveiled new chemistry insights neglected by a panel of >40 expert chemists, endorsing the power of driverless machine learning in future organic synthesis and providing the first direct comparison of automated reaction optimization with human reasoning. These operational features provide substantial improvements and versatility over the current state-of-the-art and advocate for the use of next-generation machine learning and chemometrics tools in this space. Our data support the deployment and transferability of the here-described and related technologies for a plethora of different types of parameter optimizations, either as standalone tools for practitioners or integrated with synthesis robots.

RESULTS AND DISCUSSION

Architecture of LabMate.ML

We designed our software (Figures 1 and S1) to mitigate automated reaction optimization limitations (e.g., small data availability, large number of variables, and no specialized hardware required) by analyzing and providing a validation for its

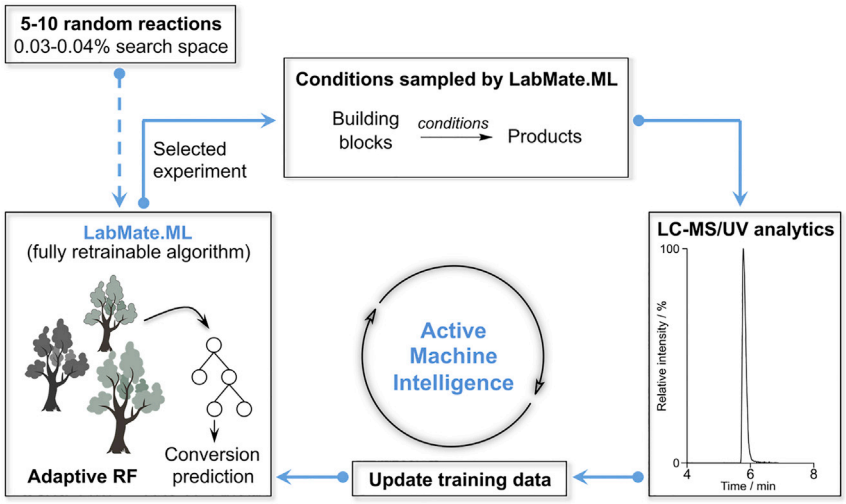


Figure 1. Workflow for Reaction Optimization

LabMate.ML selects 5–10 random reactions for initialization (module 1/Initializer). The reactions are performed and the collected data are used as an initial knowledge base. Subsequent reactions are performed with computer-suggested conditions, based on active learning heuristics (module 2/Optimizer), and assessed by liquid chromatography–mass spectrometry/ultraviolet-visible (LC-MS/UV-vis). The area under the curve (AUC) value for the required *m/z* or UV absorption peak is used as the objective target value in machine learning. Specifically, the AUC is transformed according to the objective of the optimization experiment and used as a proxy for the reaction outcome (e.g., total product amount or yield). The reaction conditions are used as features for LabMate.ML training in the Optimizer. LabMate.ML uses random forests (RFs) to generate models that rationalize the available data and suggest a new condition set. The software is autonomous and re-trainable after each iteration; with the additional data, the RF hyperparameters are optimized using cross-validation. LabMate.ML runs for 5–10 min for a full cycle of re-training and prediction on a single personal computer (e.g., Mac Pro and mid-range MacBook Pro).
See Figure S1 and Supplemental Experimental Procedures for details.

reaction optimization concept. LabMate.ML is composed of two modules that are responsible for generating small data for initialization (module 1/Initializer) and suggesting experiments based on adaptive random forest (RF) heuristics (module 2/Optimizer). Crucially, LabMate.ML requires only 5–10 data points (reaction conditions and respective outcomes) to provide the initial knowledge base—up to 400-fold less data than previous methods[28,30]—to build a crude model from which a new experiment is suggested. Neither prior assumptions nor pre-training are required. Considering that each selected reaction is informative, the model changes dynamically, as captured by changing ideal RF parameters. To adapt to new data, LabMate.ML creates the best machine learning method on its own, evolving in an autonomous and stepwise fashion. In doing so, it mimics on-the-fly learning[31] by synthetic chemists to efficiently detect patterns in small data and to obtain increasingly better statistical models and predictions. To the best of our knowledge, LabMate.ML pioneers small-data-enabled, adaptive machine learning inspired in chemistry practice for reaction optimization. We implemented different machine learning-based prioritization strategies in the Optimizer to evaluate efficiency and speed to identify optimal reaction conditions for a pre-defined objective, among commonly probed mechanism-agnostic reaction variables. In one case, the LabMate.ML Optimizer uses predictive uncertainty measures rather than random sampling to efficiently explore multidimensional search spaces; it selects reaction conditions least understood by the model, irrespective of the predicted reaction outcome. In doing so, we recognized that the random, small data gathered by the

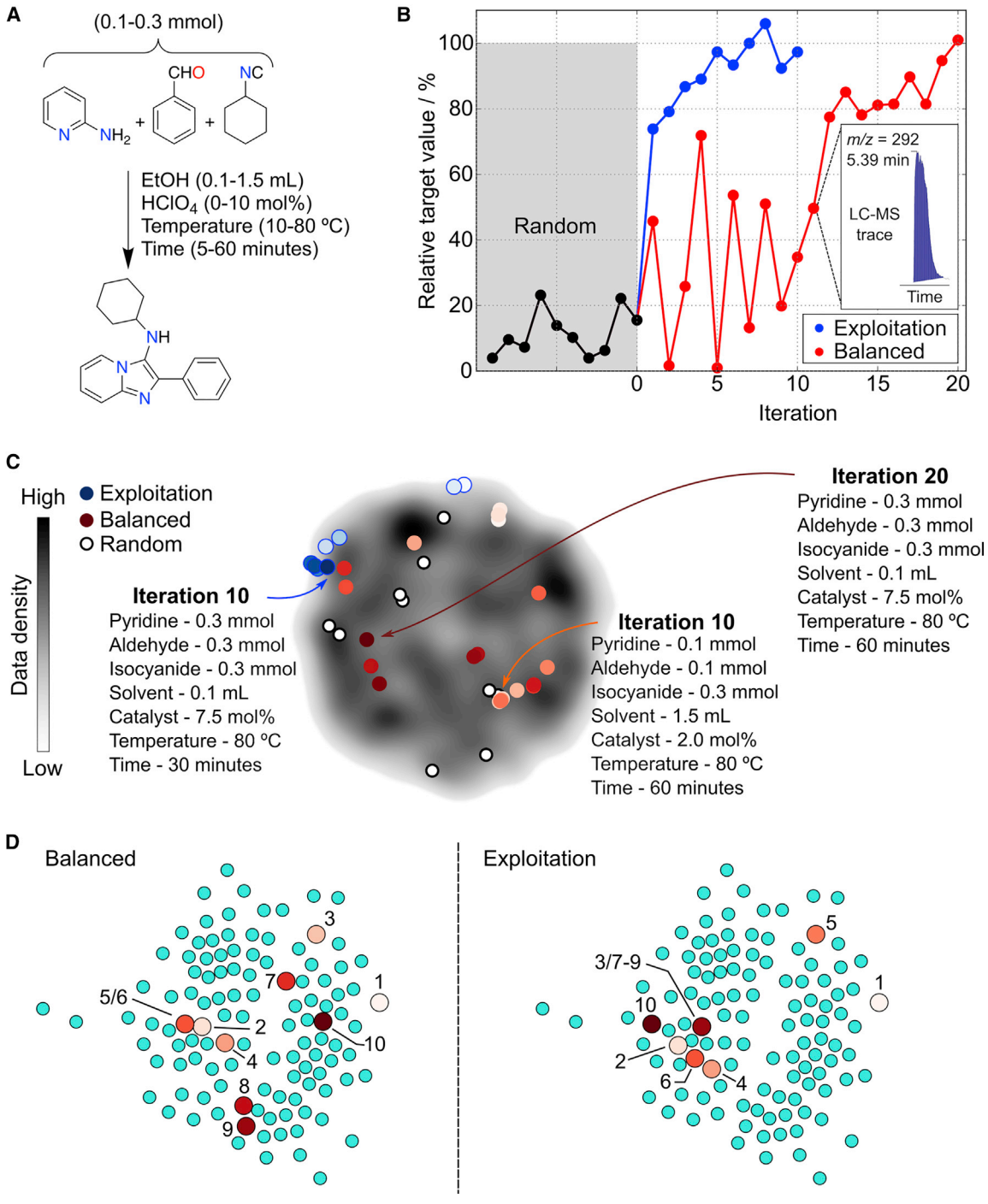


Figure 2. Adaptive Machine Learning Optimizes Ugi Chemistry

(A) Studied chemical reaction for proof-of-concept. Conditions were selected within the depicted range.

(B) LabMate.ML Initializer selected 10 random reactions, which were performed to afford an initial model. Subsequent reaction conditions were selected one at a time based on active learning heuristics, according to different criteria: (1) exploration of the reaction condition space (iterations 1–10, red), and exploitation of the most promising region (iterations 11–20, red) and (2) full exploitation (iterations 1–10, blue).

(C) Projection of the multidimensional search space using the t-distributed stochastic neighborhood embedding (t-SNE) learning algorithm. The background depicts the density of the conditions within the search space. White dots: random reactions (LabMate.ML Initializer); blue dots: exploitative

LabMate.ML Initializer could be insufficient for an acceptable understanding of chemical reactivity and identification of an optimized outcome. LabMate.ML then adopts a balanced or exploitative approach to select the least (balanced) or most confident (exploitative) of the perceived top 10 high-yielding reactions. The former approach takes into account both the exploration and exploitation of the reaction conditions' space. Conversely, another LabMate.ML routine was pursued to obtain high target values directly from the information enclosed in small data by using a "greedy"/exploitative approach (see Method Details).

Proof-of-Concept with Ugi Chemistry

As an initial proof-of-concept and validation example, we selected an Ugi 3-component reaction. This is a well-studied and tractable example that affords a privileged structure[32] in drug discovery, imidazopyridines (Figure 2A). Despite the fact that Ugi reactions have a high substrate scope and reaction-condition tolerance, obtaining good yields (>50% of limiting reagent conversion) is not straightforward,[33] given the multiple variables that must be optimized simultaneously. The area under the curve (AUC) for the required product in liquid chromatography-mass spectrometry (LC-MS) traces was used as a proxy for the reaction outcome—amount of product formed—and, therefore, as target value for LabMate.ML. As an initial training set, the LabMate.ML Initializer selected only 10 random conditions from the enumerated search space. These represent a minute amount (10/27,000, or ≈0.04%) of a vast multidimensional search space, here compressed to 27,000 discrete combinations by chemistry-based understanding of the problem at hand. This amount of training data sharply contrasts both "big data" and a recent active learning[28] study. The 10 random reactions provided a range of product amounts, yet suboptimal and mostly negative conditions for the proposed goal (Figure 2B; Tables S1 and S2) that are devoid of anthropogenic biases.[4] This underscores the complexity of finding optimal reaction conditions and that random condition selection—the initialization routine in LabMate.ML—may be impractical as the sole approach for optimizing organic synthesis protocols. Between learning iterations 1–10 (red), the LabMate.ML Optimizer informatively explored the reactivity space and selected conditions that afforded imidazopyridine in various amounts. With the generated information, LabMate.ML was then able to optimize the synthetic method in a stepwise fashion toward a set of conditions that gave a 5-fold improvement in generated product amount relative to the best randomly selected (training data) reaction. A similar outcome was obtained through an exploitative (greedy) approach (blue) with the benefit of minimizing synthetic effort (i.e., number of performed reactions relative to the more explorative software counterpart). With only five trials, similar optimal reaction conditions were achieved. The latter result is surprising because the use of LabMate.ML for out-of-sample predictions led to the swift identification of productive reactions. This was against our expectations, since we assumed that preferred reaction conditions were out of the model's domain of applicability, given the suboptimal results in the small training dataset. The result suggests that the initially provided small set of random conditions, with varying but low target values, still captures the blueprints for a successful reaction outcome. With the collected data in hand, we further analyzed the behavior of both software tools. By using dimensionality reduction to visualize the trajectory of picked conditions in the experimental space, it can be concluded that the exploitative LabMate.ML approach

approach reactions (LabMate.ML Optimizer); red dots: explorative reactions of the balanced approach (LabMate.ML Optimizer). The color gradients mirror the iteration number. The data are normalized relative to the best-performing reaction.

(D) t-SNE of the optimized hyperparameters for LabMate.ML Optimizer, which is fully re-trainable to provide updated parameters and models for improved performance. The color gradient shows the unsupervised, self-evolution of LabMate.ML. The model instances are labeled.

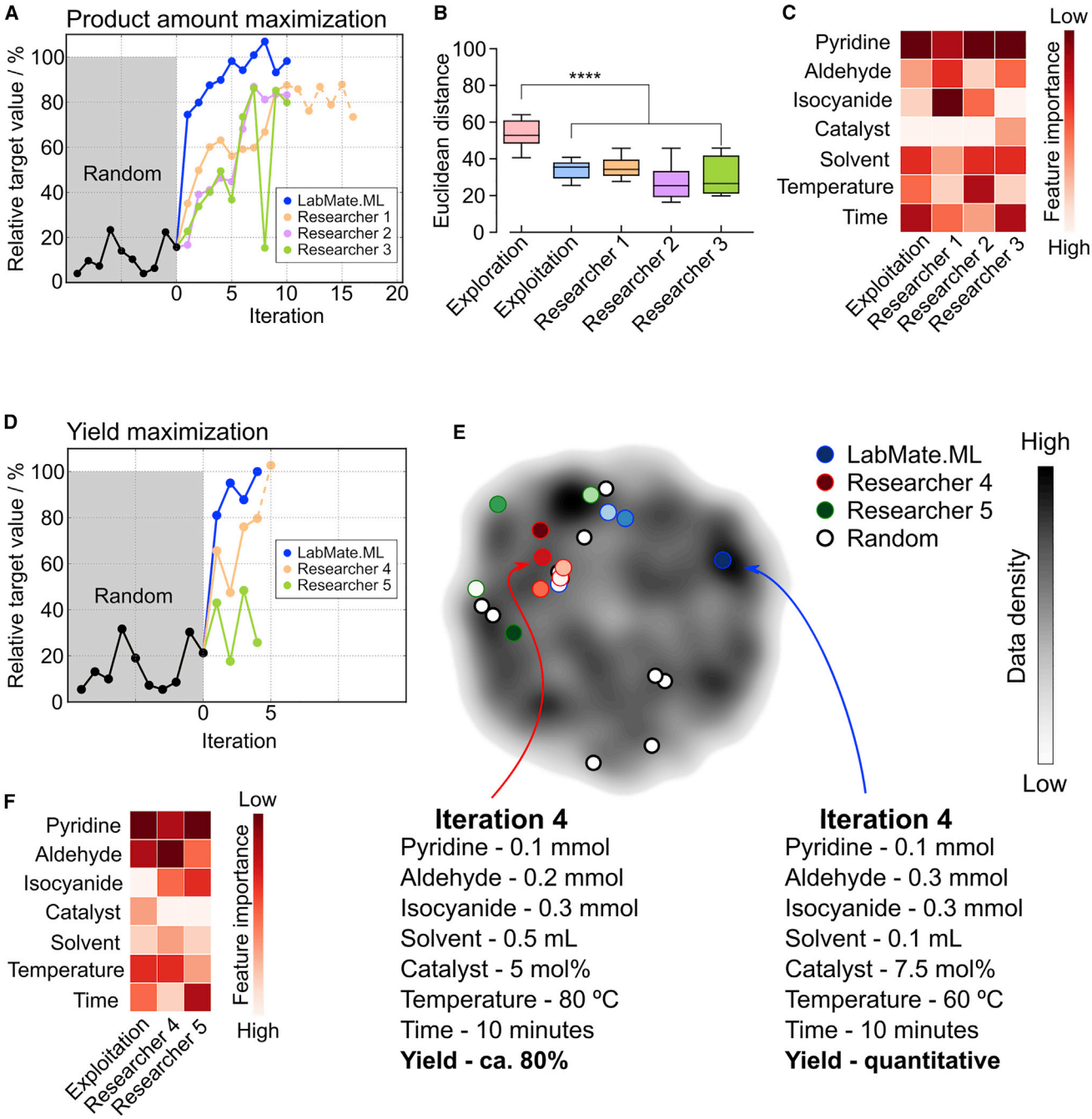


Figure 3. Active Machine Learning Is More Efficient at Optimizing Chemical Reactions Than Human Intuition

(A) Researchers with a non-identifiable descriptor vector optimize reaction conditions toward a maximized product amount in stepwise fashion, but never reach the level of optimization achieved by the algorithm. Best-performing reactions (average value ± confidence interval 95%)—LabMate.ML: 100% ± 3%, n = 5; researcher 1: 90% ± 1%, n = 3; researcher 2: 91% ± 2%, n = 3; researcher 3: 90% ± 3%, n = 3; researcher 4: 88% ± 3%. $p = 0.001$ (researcher 1), $p = 0.004$ (researcher 2), $p = 0.010$ (researcher 3), Welch's t test. Iteration 8 of LabMate.ML was not reproducible and thus considered an outlier. The data are normalized relative to the best-performing reaction. Ten reactions with random conditions are performed for initial training.

(B) Distribution of the average Euclidean distances (relative to A) calculated between a given reaction and all previous iterations. The exploitative LabMate.ML performs "condition hops" similar to the researchers ($p > 0.10$). The explorative LabMate.ML selects more dissimilar conditions. $p < 0.0001$, n = 10, unpaired 1-way ANOVA, Dunnett's test.

(C) Heatmap of feature importance (relative to A) extracted from RFs fitted to reactions selected by exploitative LabMate.ML/human intuition. Euclidean distances between exploitative LabMate.ML and researchers 1–3: 6.48 (14% match), 4.24 (43% match), and 3.16 (43% match), respectively.

exclusively selects conditions from within two islets with identical reaction outcomes. The curiosity-driven selection method probes different regions in feature space, as originally desired (Figure 2C).

It is apparent that the diverging selection strategies affect the fate of the suggested experiments. Nonetheless, in this example, equivalent optimal conditions were obtained regardless of the conceptually different search strategies used. The difference in these search strategies is also reflected in the self-evolution of optimized RF parameters and predictive model architectures. The explorative selection method more drastically modifies the model architecture, as measured through RF feature importance changes (Tables S4 and S5). The exploitative counterpart is more conservative in its changes, possibly due to a narrower view of the reaction optimization problem (Figure 2D). We found that this can lead to a drastic difference in retrospective prediction performance; whereas the balanced method model can accurately predict reaction outcomes, the exploitative approach model is less accurate in its predictions (Figure S3). Nevertheless, our prospective data suggest that the latter method is able to correctly rank order well-performing reactions. Importantly, as a control experiment and to probe the accuracy of the method, we confirmed that conditions predicted to afford no product were indeed experimentally unable to produce the imidazopyridine (Table S3). Next, we studied whether simpler machine learning methods could have performed equally well. Irrespective of the selection approach, the predictive performance of LabMate.ML is superior to linear regression methods, as assessed by different metrics (Figure S3), which suggests that the use of adaptive random forests to chemistry optimization problems is justified. In addition, we performed Y-randomization tests to confirm that LabMate.ML does not simply overfit or memorize the training dataset, nor exploits data artifacts, but instead learns meaningful relationships between the reaction condition parameters and the obtained product amounts (Table S4, S5, and S17). Taken together, the results suggest that both selection approaches are justified, and the preference for a balanced (i.e. explorative/exploitative) or exploitative LabMate.ML depends on the goal and available data (Figure S4).

We then compared the performance of the exploitative learning approach in LabMate.ML to that of three researchers—a MSc without experience in organic synthesis, and two experienced PhD-level organic chemists—in a double-blind setup. The researchers were asked to propose conditions that would lead to large AUC values, and we subsequently performed the proposed reaction to provide feedback to the researchers for the next round of suggesting conditions (Figure S2; Tables S6–S11). Descriptors were scaled and randomized for the researchers to disable identification of the variables and thereby avoid drawing organic chemistry knowledge into play that could bias the optimization process, according to previous experience. Surprisingly, in this narrow test, the software appeared to be competitive with the three researchers at optimizing this Ugi reaction over 10 active learning iterations (Figure 3A). Not only are the curves between LabMate.ML and the

(D) LabMate.ML quickly optimizes the yield of the reaction in a competitive manner to human intuition. Best-performing reactions at comparative number of iterations (average value ± confidence interval 95%)—LabMate.ML: 100% ± 3%, n = 3; researcher 4: 79% ± 3%, n = 3; researcher 5: 43% ± 9%, n = 3; p = 0.0057 (LabMate.ML versus researcher 4), p = 0.0001 (LabMate.ML versus researcher 5), Welch's t test. LabMate.ML versus researcher 4, iteration 5: 100% ± 1%, n = 3, p = 0.59; Welch's t test. The data are normalized relative to the best-performing reaction.
(E) t-SNE of reaction condition space, showing the reactions selected by LabMate.ML, researcher 4, and researcher 5. The color gradient depicts the iteration number, with the darkest color for the last iteration.
(F) Heatmap of feature importance (relative to D) extracted from RFs fitted to reactions selected by exploitative LabMate.ML/human intuition. Euclidean distances between exploitative LabMate.ML and researchers 4 and 5: 4.47 (15% match) and 5.56 (30% match), respectively.

researchers significantly different ($p = 0.002$, $n = 4–6$, Welch's t test) but also the best-performing reaction conditions suggested by LabMate.ML afford a significantly better outcome than the optimal conditions identified by the researchers ($p = 0.001–0.010$, $n = 3–5$, Welch's t test). Moreover, when researcher 1, the best-performing human in this benchmark test, was granted additional reactions (iterations), no further progress was made toward identifying better reaction conditions. These results support the idea that optimizing reaction conditions toward any given objective is a pattern recognition problem accessible to an automated machine-learning platform. For example, researcher 1 with no in-depth chemistry education was able to find productive reaction conditions, which is in line with the above-mentioned conclusion. More important, we controlled for and disproved the possibility that the identified optimal conditions could be obtained by maximizing reaction scale, i.e. using the maximum amount of building blocks and catalyst. When performing the reaction with the highest value for each descriptor, we obtained a significantly suboptimal solution ($\approx$84% of maximum amount of product achieved by LabMate.ML: $p = 0.0001$, $n = 3–5$, Welch's t test). Apparently, LabMate.ML recognized this pattern by never suggesting a maximized parameter reaction.

To rationalize how LabMate.ML navigates the chemical reaction space, we calculated the Euclidean distances between conditions for a given iteration against the conditions of its predecessors. The results show that the "condition hop" in the human intuition-driven optimization is identical to that of the exploitative LabMate.ML approach ($p > 0.10$, $n = 10$, unpaired 1-way ANOVA with Dunnett's test; Figure 3B), whereas the explorative strategy resulted in bigger changes to the reaction conditions ($p < 0.0001$, $n = 10$, unpaired 1-way ANOVA with Dunnett's test). Thus, our data support the fact that informed decisions by learning algorithms may resemble human intuition for small-sized datasets. Also, the data-driven yet chemically naive selection by algorithms can provide an important advantage if short optimization cycles are required. For example, explorative strategies may provide the means to generate a more diverse dataset of conditions compared to human decision making. To further understand human intuition, we generated models of mental processes by fitting different learning algorithms to data generated by all of the researchers (Figure S2; Tables S6–S8) to reveal that, in most cases, machine learning can interpret the selected reactions. This is true with random forests, from which we extracted feature importance ranks in the selection process (Figure 3C). Strikingly, the catalyst amount was generally perceived and confirmed by the researchers as the most important variable for optimizing the amount of product for the Ugi reaction, whereas the pyridine amount was the least important. Interestingly, researchers 1–3 appeared to rank each feature differently, which may have affected their selected reactions (Figure S2) and hints at the subjectivity of human-guided optimization campaigns and pattern recognition capabilities. The driverless evolution of LabMate.ML was at least as competent as human intuition for the identification of patterns in small-sized datasets. Thus, in some instances, true chemical knowledge may not be strictly necessary for experiment optimization problems, but may be augmented through statistical learning.

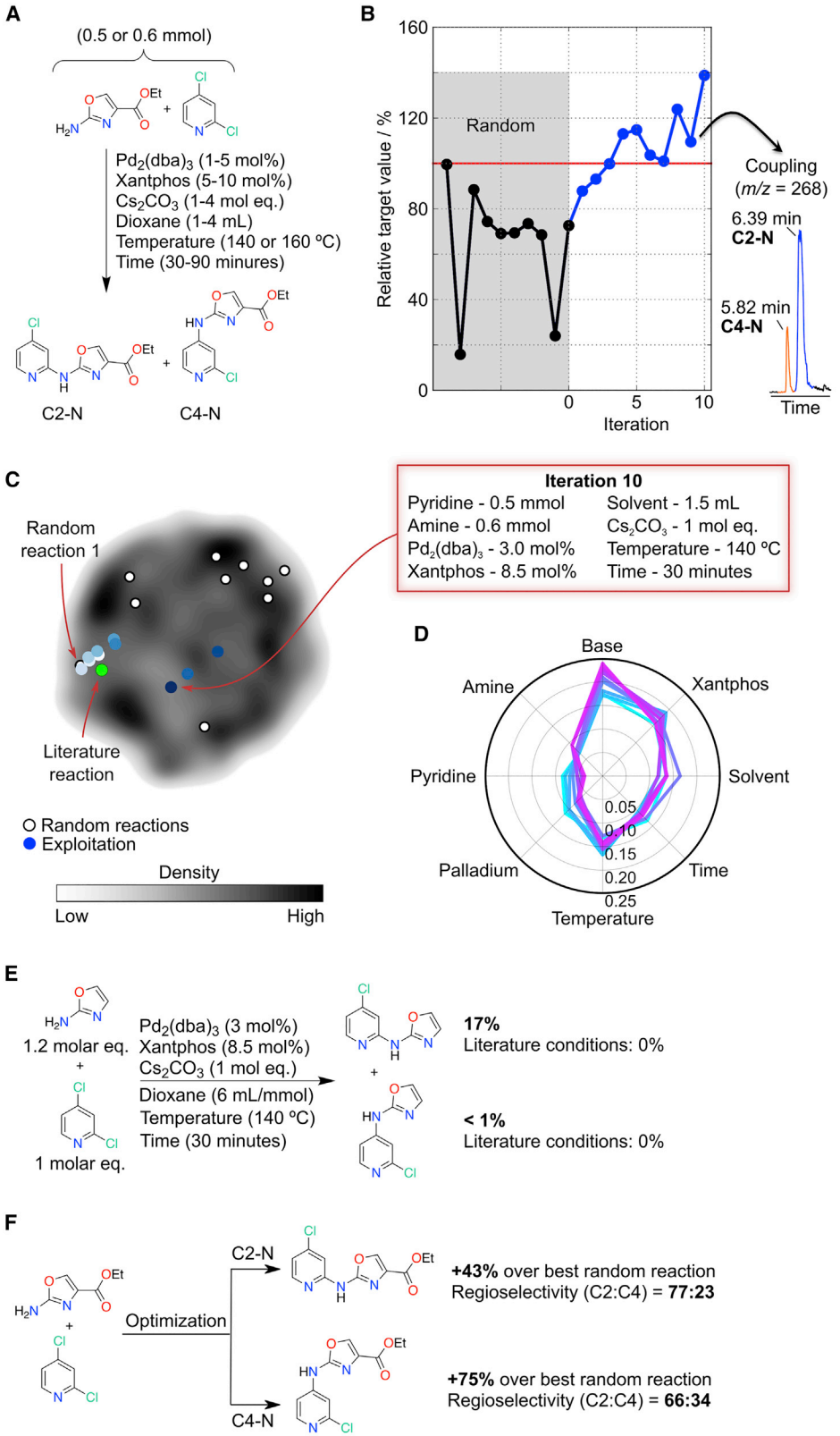
Although in this experiment we confirmed that optimization is possible on uncorrected AUC values, we recognized that maximizing reaction yields (i.e., scale-corrected reaction outcomes) may be a more realistic use case for our software suite. Therefore, we used the exploitative LabMate.ML approach in another optimization campaign toward the same imidazopyridine. This time, we corrected the measured target values from the training data according to the reaction scale (limiting reagent

amount), thereby optimizing the yield (see Method Details). All of the iterative measurements followed the same correction. Starting from the first iteration, the Optimizer suggested a distinct optimization path (different selected conditions) relative to what the algorithm had previously requested when optimizing for product amounts (uncorrected AUC values, Tables S2 and S12). This indicates that the algorithm changes the optimization campaign with respect to the desired objective and is not simply driven by target-agnostic parameter exploration. Nevertheless, it took only four iterations to identify a set of conditions that afforded complete conversion of the limiting reagent (100% yield; Figure 3D) to the required imidazopyridine. Apparently, the software is efficient at optimizing chemistry toward different objectives by devising appropriate reaction scoring functions that fit the needs of the project. This is achieved by including regularizers to minimize costs, reduce side products, and improve atom economy.

We then set out to contextualize the performance of the machine-learning algorithm in LabMate.ML. Two additional human controls (researchers 4 and 5, both with PhD-level experience in chemistry; Tables S15 and S16) had access to the same knowledge base—this time, however, with fully identified descriptors and real valued (i.e., non-normalized) reaction condition variables. Relative to this real-world comparison, LabMate.ML is at a disadvantage because it has no prior chemical knowledge, so poorer performance for our chemical intuition formalization algorithm was expected. Surprisingly, after the same number of optimization iterations (4), LabMate.ML was able to more efficiently extract knowledge toward optimal reaction conditions ($p = 0.001–0.0006$, $n = 3$, Welch's t test; Figure 3D) than either researcher (Tables S15 and S16). Interestingly, researcher 4 found a distinct local optimum in the search space ($p = 0.59$, $n = 3$, Welch's t test; Figure 3D; Table S15) but required an additional reaction for its discovery. This implies the competitiveness of our solution and that a different optimization strategy was used, which we confirmed by projecting the reaction optimization trajectories onto the search space (Figure 3E). Even though the conservative strategy for prioritizing condition changes, LabMate.ML does not appear to focus solely on one region of the search space. Conversely, researchers 4 and 5 were more or less explorative, which suggests again that the LabMate.ML performance is not exclusively a function of more or less diverse sampling of conditions. The better performance of the algorithm may be due to the difficulty for humans to identify subtle, yet desirable patterns in mostly "negative" training data. This corroborates our previous findings. The difference between human and machine-driven optimization campaigns is also supported by the diverging feature importance ranks between LabMate.ML and researchers (≈15%–30% match) that ultimately led to the obtained data (Figure 3F). Despite the highly encouraging results in these chemical intuition benchmarking tests, further evaluation with larger sets of human experts are required to statistically validate such trends.

LabMate.ML Affords Insight into a C–N Cross-Coupling Reaction

As an additional validation test, we applied exploitative LabMate.ML to optimize the yield of a C–N (Buchwald-Hartwig) cross-coupling reaction (Figure 4A),[34] a relevant transformation that was previously identified as a valuable but challenging reaction in drug discovery.[35] Here, we consider a reaction as "challenging" if it has undergone extensive optimization but still provides a poor yield, due to limitations in substrate scope, irrespective of having a more or less well-studied mechanism. Replicates of the literature reaction conditions consistently afforded a mixture of regioisomers (C2–N and C4–N cross-couplings), as reported.[34] These results served as positive control (benchmarked as 100%; Figure 4B). Using the LabMate.ML Initializer


A
(0.5 or 0.6 mmol)
Pd2(dba)3 (1-5 mol%)
Xantphos (5-10 mol%)
Cs2CO3 (1-4 mol eq.)
Dioxane (1-4 mL)
Temperature (140 or 160 °C)
Time (30-90 minures)
C2-N
C4-N
B
Relative target value / %
Random
Iteration
Coupling
(m/z = 268)
6.39 min
C2-N
5.82 min
C4-N
Time
C
Random
reaction 1
Literature
reaction
Random reactions
Exploitation
Density
Low
High
Iteration 10
Pyridine - 0.5 mmol
Amine - 0.6 mmol
Pd2(dba)3 - 3.0 mol%
Xantphos - 8.5 mol%
Solvent - 1.5 mL
Cs2CO3 - 1 mol eq.
Temperature - 140 °C
Time - 30 minutes
D
Base
Xantphos
Solvent
Time
Temperature
Palladium
Pyridine
Amine
0.05
0.10
0.15
0.20
0.25
E
1.2 molar eq.
1 molar eq.
Pd2(dba)3 (3 mol%)
Xantphos (8.5 mol%)
Cs2CO3 (1 mol eq.)
Dioxane (6 mL/mmol)
Temperature (140 °C)
Time (30 minutes)
17%
Literature conditions: 0%
< 1%
Literature conditions: 0%
F
Optimization
C2-N
C4-N
+43% over best random reaction
Regioselectivity (C2:C4) = 77:23
+75% over best random reaction
Regioselectivity (C2:C4) = 66:34

to randomly sample only 10 reactions (0.03% of the reaction condition space; Figures 4A and 4B) offered a sparse dataset for training (Figure 4C). Conversion rates were on average low for those reactions conditions (60% control), with two of them yielding almost no product and one affording the required C2–N product with conversion identical to that of the previously published conditions (100%). Using these data, the software was again able to gradually optimize the cross-coupling reaction by building relevant models (Tables S18–S20). At its peak, the algorithm suggested a protocol that provided an improved conversion (an additional 40% yield) relative to the best literature reaction ($p = 0.0008$, $n = 3$; Welch's t test; Figures 4B and 4C). These results could be replicated by an independent contract-research organization (Figures S8–S11), which provides external validation for the reproducibility of the reaction suggested by LabMate.ML. Moreover, the computer-optimized protocol was twice as base and time economical compared to the reported conditions for the control protocol. As previously observed for the Ugi chemistry, LabMate.ML evolved with each reaction (Figure 4D). The analysis of the feature/parameter importance over the whole iterative experimentation and optimization revealed that the base amount steadily grew as the most important feature for building predictive decision trees. Conversely, reaction time and palladium catalyst amount were less informative in distinguishing good- from poor-yielding reactions. More important, some parameters such as solvent amount and reaction temperature dynamically changed during model evolution, with some experiments assigning increasing or decreasing importance to these parameters. A similar dynamic had been reported[30] and highlights the adaptive character of iterative learning.

Intrigued by this result, which opposed our personal understanding of the most important parameters for this type of chemical transformation, we surveyed 38 independent organic chemistry experts from universities and industry in Europe and the United States. We asked them to assign an importance rank for each of the features/parameters of this reaction (e.g., temperature, solvent amount) based on their chemical intuition. The results clearly show that LabMate.ML has an orthogonal vantage point to all of the surveyed scientists in regard to the most important feature (amount of Cs_2CO_3). This highlights the value of interpretable machine learning, wherein the algorithm can identify data relationships that are currently unexpected. At the same time, the algorithm's and the experts' opinions are in large agreement with respect to the importance of xantphos, chloropyridine, and amine amounts (Figure S28). This indicates that our method can rapidly reproduce established guidelines in organic synthesis. The algorithm indirectly learned that an increased formation of $Pd(xantphos)_2$ is detrimental for the reaction conversion rate, potentially due to its low activity as a pre-catalyst and high insolubility in dioxane.[36] A head-to-head pairing of the subjects' answers to the LabMate.ML feature ranks shows a $\leq$50% match

Figure 4. LabMate.ML Optimizes a C–N Cross-Coupling Reaction

(A) Reaction optimized by LabMate.ML. The conditions were sampled within the depicted range. The median values correspond to literature conditions.

(B) Optimization by exploitative LabMate.ML. The horizontal red line shows the conversion rate for the reaction as described in the literature.[34] Reactions were assessed in relation to the average conversion for the literature protocol (average value $\pm$ confidence interval 95%: 100% $\pm$ 6%, $n = 4$). The best suggested reaction affords a conversion rate that is significantly higher than the optimized literature protocol. Only the major product (C2–N coupling) was taken into account for data analyses. $p = 0.0008$, Welch's t test, $n = 3$–4. The data are normalized relative to the literature reaction.

(C) t-SNE of reaction condition space, which shows the focused selection of reactions by LabMate.ML. The color gradient depicts the iteration number, with the darkest color corresponding to iteration 20.

(D) Spider plot showing adaptive feature importance as LabMate.ML evolves. Cyan: iteration 1; purple: iteration 10.

(E) Reaction protocol suggested by LabMate.ML is transferrable to other starting material combinations and lead to the requested product. The literature values were obtained by reproducing the reported reaction conditions for the indicated building blocks.

(F) LabMate.ML can efficiently optimize the formation of different regioisomers from a self-suggested small training set. The optimization of reactions conditions toward different products results in varying regioselectivities.

in 89% of the cases. Also, calculating Manhattan distances, a vector comparison metric, between the assigned reaction importance ranks and subsequently performing hierarchical clustering revealed LabMate.ML to be the "outlier" in this dataset and underscores its distinct interpretation of the condition space relative to the human experts who were consulted (Figure S28). The observed general disagreement between the surveyed experts with distinct clusters of chemical intuition reiterates how subjective reaction troubleshooting routines can be. Conversely, LabMate.ML offers a robust solution to make reaction optimization processes reproducible/deterministic in the learning process while adding its unique chemical creativity and innovation to problem solving. In this particular case, LabMate.ML advocates for higher importance being assigned to the base amount for optimization of this C2–N cross-coupling product, a realization that was ancillary to the expert chemists (for whom 0% of answers included the base amount among the top two most important features), but allowed for substantially improved reaction yields.

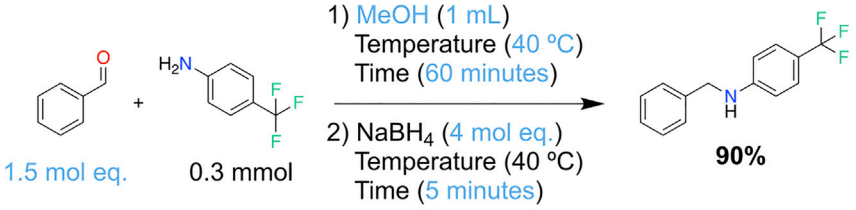
We wondered whether the identified conditions were specific to the investigated reaction (ethyl 2-aminooxazole-4-carboxylate and 2,4-dichloropyridine) or could be transferred to other educts. We confirmed the transferability of the machine-designed synthesis protocol by readily obtaining both the C2–N and C4–N cross-coupling products that result from reaction of 2-aminooxazole with 2,4-dichloropyridine (Figure 4E). Despite being originally perceived as an out-of-scope reaction,[34] the method proposed by LabMate.ML afforded the required C2–N molecule in higher yield than the trace amount previously described (17% versus 0% yield; Figures S16 and S17). This effectively supports the utility of LabMate.ML for delving search spaces for challenging chemistry.

Observing that formation of the C4–N cross-coupling product resulting from reaction of ethyl 2-aminooxazole-4-carboxylate and 2,4-dichloropyridine did not vary linearly with that of the C2–N adduct, we next deployed LabMate.ML to identify conditions that promoted the formation of the former using the same condition search space. Starting from the same unbiased training dataset, our computational routine was able to identify reaction conditions that promoted the formation of the C4–N cross-coupling product in just four iterations by diminishing the regioselectivity of the reaction (Figure 4F; Tables S21–S23). Remarkably, feature importance ranks obtained in this optimization campaign were highly disparate from those in the C2–N cross-coupling optimization example. The mapping of model architectures through feature ranks resulted in 60% of the maximum Euclidean or Manhattan distances possible between each isomer optimization campaign. This clearly shows that different determinants govern the formation of each isomer and that their correct identification is equally tractable to LabMate.ML, which successfully tuned the reaction conditions to promote one or the other product.

LabMate.ML Has Wide Applicability to a Broad Range of Different Chemistries

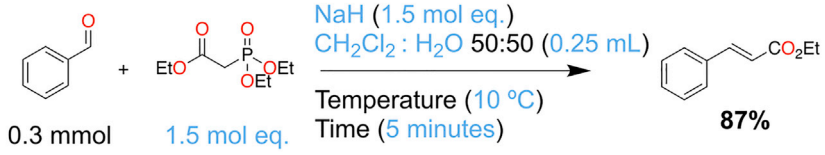
Finally, to further challenge the scope of our technology, we optimized five additional, diverse chemistries of current interest in discovery chemistry, encompassing different substrates, such as small molecules, glycosides, and proteins. The selected chemistries—reductive amination, Horner-Wadsworth-Emmons olefination, photocatalytic C–H arylation,[37] phenolic *O*-glycosylation,[38] and aza-Michael ligation on proteins [39]—presented different challenges to LabMate.ML. In addition, all of the reaction types have been either widely used[40,41] or recently developed[37–39] for the construction/decoration of scaffolds and late-stage functionalization (Figure 5). Here, we expanded the breadth of our computational routine by introducing categorical features as optimizable reaction parameters (e.g., identity of solvent, base

Reductive amination



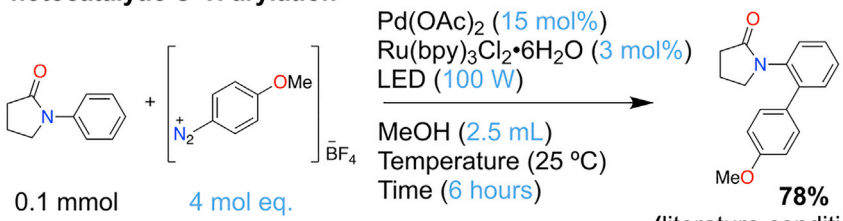
7 reaction variables optimized
3 iterations

HWE olefination



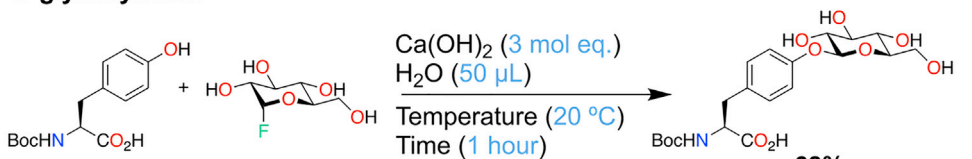
7 reaction variables optimized
7 iterations

Photocatalytic C–H arylation



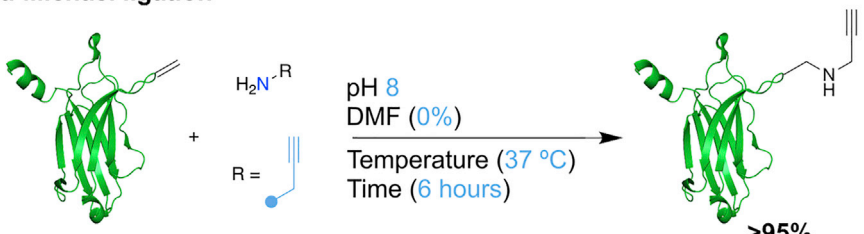
6 reaction variables optimized
9 iterations

***O*-glycosylation**



5 reaction variables optimized
7 iterations

Aza-Michael ligation



7 reaction variables optimized
7 iterations

and/or reactant type), which were one-hot encoded for machine learning. Moreover, up to seven reaction variables were modeled and target values were extracted from either LC-UV-vis (ultraviolet-visible) or ESI^+ traces. While we took literature precedents to define the search space in the case of the photocatalytic C–H arylation, phenolic *O*-glycosylation, and aza-Michael ligation reactions, for the remaining examples the search space was defined based on our chemical intuition. LabMate.ML was able to efficiently generate valid models from only 5–10 self-suggested, random reactions (≈0.03% of search space; Tables S24–S38) and identify productive conditions over 3–9 iterations in all of the cases. These results corroborate our previous observations and strongly support the wide utility of LabMate.ML as a complement to human perception, both for augmenting it and/or assisting in unraveling the unknown. The identified synthesis protocols were at least as efficient as their respective literature precedents, despite focusing on different reaction condition sets. For example, a Pd-catalyzed C–H functionalization using visible light photoredox Ru catalysis was successfully achieved under similar literature conditions,[37] for which the amount of $Ru(bpy)_3Cl_2$ and diazo building block constituted the key parameters for the outcome. In another case, *O*-glycosylation of tyrosine was achieved under more diluted substrate conditions (0.4 versus 1.0 M), which promoted improved dissolution of the substrate and an ~28% higher yield relative to the reference method.[38]

We have recently developed chemistry for the facile transformation of cysteine into lysine residue mimics.[39] Despite its general applicability, we have found important limitations (optimized yield of 50% in the literature) in the installation of aminoalkynes for posterior functionalization of the C2Am protein, a protein that can be used as an apoptosis marker to follow cancer treatments.[42] This could be confirmed here through the Initializer-suggested reactions: 70% of them afforded 0% yield of modified protein (Table S36). Such a poor level of conversion can affect downstream fluorophore installation and signal detection, as well as limit the translation of labeled C2Am to clinics as diagnostics tool. More broadly, this inefficient labeling restricts the scope of both imaging studies and payload conjugations. LabMate.ML was able to mitigate this perceived limitation; it efficiently established a protocol providing near-quantitative yield of the required C2Am-labeled product (>95%) by searching for an appropriate reactant amine and reaction conditions. With the exception of the amine concentration, which was assigned higher importance (Table S38), LabMate.ML found all of the features to be equally important for the reaction outcome. Optimization of the amine concentration, in conjunction with fine-tuning of the reaction temperature, appears to be key; albeit an unwritten rule, this correlation had not been previously identified and exploited.[39] Our data show again the ability of our probability-driven method in formalizing intuition and rapidly learning guidelines for chemistry optimization from scratch and, more impressively, from highly skewed and negative data. It is important to keep in mind that the identified relationships are not necessarily universal for a certain type of chemistry or even reaction, and that the number of initialization reactions suggested by LabMate.ML may have to be adapted according to the descriptor dimensionality.

Figure 5. LabMate.ML Is Applicable to Diverse Chemistries

The LabMate.ML combination of random reaction selection (Initializer) with a machine learning routine (Optimizer) is applicable to scaffold building and functionalization of small molecules, glycosides, and proteins, using minimal training data. The *in silico* tool identifies local maxima and is competitive with chemical intuition, supporting the use of mechanism-agnostic descriptors and the self-evolving architecture of LabMate.ML. Optimal parameters are highlighted in blue and yields obtained via literature methods are given in parentheses. The literature values were obtained by reproducing the reported reaction conditions for the indicated building blocks.

However, the results advocate that productively applicable local optima can be identified from a given set of parameters.

In all of the examples, LabMate.ML was able to identify optimized reaction conditions toward different pre-defined goals from small-size datasets and augment chemical knowledge. Other types of models may be productively applied. For example, neural networks have been tailored for reaction optimization problems and may find applicability in these and similar use cases.[43] Our method showed superior prospective performance compared to an out-of-the-box, adaptive feed-forward deep learning heuristics ($p = 0.0008$, $n = 3$, Welch's t test; Table S13). Nonetheless, the choice of model may be driven by the researcher's preference, the computational and economical means, and the availability of data to train models with varying complexity. LabMate.ML is robust and capable of optimizing a large number of reaction variables simultaneously from limited, self-suggested training data. Such modeling is beyond what is efficiently intelligible to humans[44] and accessible off-the-shelf to the gold standard statistics routine SNOBFIT.[45] The performance of our self-evolving heuristics is bound to different factors, such as a correct pre-selection of reaction variables to optimize, their boundaries, and the number of learning iterations allowed (i.e., the reaction budget), all of which are initially set by a chemist. As an example, we optimized the Ugi reaction from a dataset of five random reactions (5/27,000 or ≈0.02% of search space) instead of 10 (≈0.04% of search space; Table S14). Our workflow still identified conditions with significantly increased yield compared to the best random reaction over five iterations. However, these conditions were ≈50% inferior relative to the success of our preferred implementation relying on 10 training data points ($p = 0.0005$, $n = 3$, Welch's t test; Tables S12 and S14). The number of variables modeled in our proof-of-concept test cases is appropriate for most chemistry optimization problems. Yet, the relationship between number of variables, size of training set, and search space is expected to be critical for a good overall performance of LabMate.ML. Finally, we used the RF feature importance to quantify changes in model architecture, track the computational optimization path, and compare the machine-based optimization to human intuition. The generated insights could be confirmed by mutual information computations (Figure S29; Tables S39–S41; Note S1). For all of the performed optimizations, we observed dynamic changes in the feature importance values. In general, the most important features for LabMate.ML differed from the intuition of the human experts consulted.

Machine intelligence to enable sustainable and informed synthetic chemistry is of high value and widespread interest. However, applications leveraging "big data," complex algorithms and descriptors, and the absence of direct comparison to human performance may reduce trust/deployability and thereby hinder its implementation in daily laboratory routines. Here, we implemented a modular tool, coalescing random reaction selection for unbiased initialization and machine learning for knowledge expansion and optimization. Active learning is the enabling concept for our algorithm but remains underexplored in synthetic chemistry,[46] despite its utility for the design of experiments.[43,47–50] We[30,51] and others[28,52,53] had previously used 5%–10% of all of the available data in active learning applications to obtain proficient models. In those cases, models were built with hundreds or thousands of data points,[28] which is not practical if quality data are not easily accessible or are expensive to acquire. We have provided proof-of-concept for a software and machine-learning concept through its application in multiple relevant chemistries and objectives. Our self-driving method can use as few as five data points together with simple yet motivated real-valued/categorical descriptors. It leverages an

interpretable algorithm to acquire chemical knowledge and navigate uncharted reaction condition spaces. Ultimately, LabMate.ML identified optimized reaction conditions, predicted conversion values, and provided hitherto neglected reactivity insights. This was achieved by exploiting negative data or by fine-tuning already well-performing yet serendipitous reactions from the initialization step. Our autonomous learning approach is agnostic to the identity of the modeled reaction by virtue of the descriptors used. Therefore, it may be applied to any chemical transformation, as exemplified here. Furthermore, it is orthogonal to the big data requirement dogma for successful machine learning deployment and the imperative need of expert knowledge for chemistry optimization. LabMate.ML can be at least as proficient and inventive as expert human chemists, thus opening new research avenues. This does not refute the importance of true chemical expertise. Rather, it shows that our technology can afford an alternative path to rapidly and efficiently identify optimized reaction conditions by augmenting chemical perception. We expect that coupling random experiments to active learning will find broad applicability to accelerate discovery chemistry, democratize chemical syntheses with limited experimental budget, eliminate non-informative experiments, minimize reagent feedstocks, and free chemists for non-routine tasks.

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Further information and requests should be directed to the Lead Contact, Dr Tiago Rodrigues (tiago.rodrigues@ff.ulisboa.pt)

Materials Availability

Reactions were carried out as reported in the literature or as modified by the LabMate.ML. No new materials were generated in this research.

Data and Code Availability

All of the data supporting the findings are presented within the article and the Supplemental Information. Details on the LabMate.ML workflow are provided in the Supplemental Experimental Procedures and code can be accessed at https://github.com/tcorodrigues/ActiveLearning.

LabMate.ML

LabMate.ML entails two distinct modules whose combined goal is the identification of optimized reaction conditions. The first module (Initializer) suggests a user-defined number of random experiments (5 or 10 in this study) for initialization and preliminary model building. The second module (Optimizer) uses active learning heuristics for goal-oriented reaction optimization. Specifically, the Optimizer uses RF regressors and exhaustively optimizes hyperparameters (number of trees [100–1,000 with a step of 100], tree depth [0, 2, 4], and number of features [auto or sqrt]) to build a prediction model that is subjected to leave-one-out or 10-fold cross-validation, depending on the size of the training set. In total, >600,000 decision trees are screened, and a prediction and its variance can be calculated from the final/best RF model. This model is then used to predict a target value from all of the possible reaction conditions that have not yet been tested. The target value is the amount of product formed (assessed through LC-UV-vis-MS traces), either uncorrected or corrected according to reaction scale. Based on these predictions, the next experiment is selected sequentially according to a pre-defined selection policy.

In case of the first Ugi optimization, an exploration approach is taken for the first 10 iterations, LabMate.ML Optimizer (iterations 1–10), by selecting the conditions whose reaction output prediction has the highest variance, irrespective of the predicted target value (a measured AUC in LC-MS traces). For the following iterations (11–20), an exploitative (greedy) approach is pursued to maximize the target value of the studied chemical reaction. This is carried out through distinct approaches:

If maximum target value (iterations 1–10) $\geq$ 4 × maximum target value (random reactions 1–10):
Select reaction with lowest variance among the predicted top five high-yielding reactions.
If maximum target value (iterations 1–10) < 4 × maximum target value (random reactions 1–10):
Select reaction with the highest variance among the predicted top 10 high-yielding reactions.

Alternatively, LabMate.ML Optimizer follows only a greedy approach from iteration 1 by selecting the reaction with lowest variance among the predicted top five high-target-value reactions (i.e., without any explorative component in the selection policy). The LabMate.ML software evolves with each added data point by refining its predictive model through full re-training. This involves hyperparameter selection, model fitting, and updating predictions for all of the remaining conditions. The LabMate.ML software and data analyses were fully implemented in Python 2.7.10, using the NumPy 1.11.3, Pandas 0.19.2, and Scikit-learn 0.18.1 libraries, and was run (5–10 min) on an Apple Mac Pro machine (3.5 GHz 6 core processor, 32 Gb RAM).

Chemistry

For details on synthetic procedures and analytics see the Supplemental Experimental Procedures section and Figures S5–S27.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.xcrp.2020.100247.

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AUTHOR CONTRIBUTIONS

D.R. contributed ideas to the software, experiments, and performed data analyses. E.A.H. performed the protein modification chemistry and analyzed data under the supervision of G.J.L.B. T.R. designed and implemented the LabMate.ML software, performed chemistry, analytics, data analyses, and conceived and designed the study. T.R. and D.R. wrote the manuscript, with contributions from E.A.H. and G.J.L.B. All authors agreed on submitting the current version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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