Towards AI-Driven Recommendation of Liquid Chromatography Conditions for Chemical Reactions

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Abstract

Liquid Chromatography (LC) is a foundational tool for chemical analysis, but applying it to complex reactions is challenging. The primary difficulty lies in establishing conditions that achieve simultaneous detection and chromatographic resolution for multiple reactants and products with diverse properties. In this work, we investigate the capability of Large Language Models (LLMs) in agentic LC condition recommendation for comprehensive chemical reaction analysis. We present an LLM-based multi-agent system comprising chemistry-aware sub-agents that emulate the decision-making process of an analytical chemist. The system processes a chemical reaction and user-defined analytical requirements expressed in natural language to autonomously search relevant literature, reason over compound properties, and propose plausible LC conditions that can detect all reaction components within a single analytical run. We demonstrate its effectiveness through a case study on organic electronic materials. The source code is available at `https://github.com/seokhokang/lc_agent`.

1. Introduction

Liquid Chromatography (LC) serves as a valuable tool for monitoring chemical reactions because it allows both separation and identification of compounds in complex mixtures (Ray et al., 2018). Successful reaction monitoring requires that all associated reactants and products within a reaction be detectable and chromatographically resolvable in a single analytical run, with each compound exhibiting a distinct retention time. Establishing unified and practical LC conditions that allow simultaneous detection of multiple compounds represents a significant analytical challenge, as these compounds often possess diverse chemical and physical properties (Steiner et al., 2021; Fabregat-Safont et al., 2023; Mandal et al., 2024).

There exist common standards and practices for the LC analysis of individual compounds (Niessen, 2003; Holčapek et al., 2012). Numerous experimentally reported conditions can also be found in academic literature and application notes. However, such compound-specific methods may not be suitable for reaction-level analysis involving multiple distinct compounds. Parameters optimized for one compound may compromise the detection of others. For this reason, developing robust LC methods for reaction monitoring is inherently complex, requiring extensive empirical testing and expert knowledge. The main objective of this study is to systematically establish and optimize LC conditions that enable effective analysis of an entire chemical reaction within a single, unified analytical setup.

Recent advances in Large Language Models (LLMs) have shown remarkable potential for assisting scientific research, including applications in chemistry (Naveed et al., 2025; Zhang et al., 2025a). LLMs are further integrated into broader systems that incorporate external tools and interact with their environment, evolving into AI agents capable of autonomously solving complex, goal-driven tasks (Ferrag et al., 2025; Ramos et al., 2025). They have demonstrated the ability to extract knowledge from scientific documents (Vangala et al., 2024; Schilling-Wilhelmi et al., 2025), design and plan experiments (Boiko et al., 2023; Zhang et al., 2025b), autonomously perform analyses using external tools (M. Bran et al., 2024; Duponchel et al., 2025), reason based on a given context (Ouyang et al., 2024; Chen et al., 2025), and even propose hypotheses directed toward specific goals (Gottweis et al., 2025). Motivated by this progress, we leverage the capabilities of LLMs to develop an AI agent that assists in systematically determining LC conditions for comprehensive chemical reaction analysis.

In this work, we present an LLM-based agent system developed to recommend LC conditions for chemical reaction analysis. The proposed system comprises multiple

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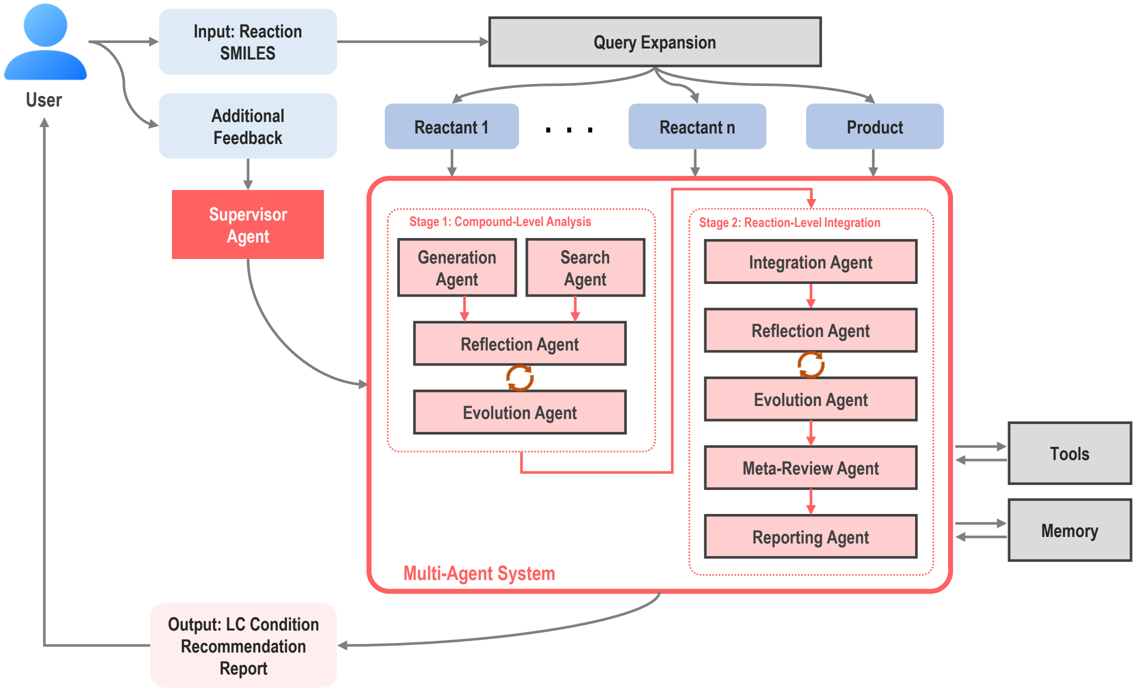

Figure 1. Schematic diagram of the proposed multi-agent system for LC condition recommendation.

sub-agents that are context-engineered to perform distinct functional roles, including hypothesis generation, literature-driven knowledge extraction, scientific reasoning, and iterative refinement, as illustrated in Figure 1. To equip general-purpose LLMs with domain-specific chemical awareness, the sub-agents are augmented with external tools that provide structured chemical knowledge, such as molecular descriptors for individual compounds. Given a chemical reaction and requirements specified in natural language, the system can autonomously generate, search, and reason to identify plausible LC conditions that can detect all components involved in the reaction. By emulating the decision-making process of analytical chemists, the agent system can assist in guiding parameter settings for LC instruments. This work lays the foundation for fully autonomous configuration of instrument parameters in automated analytical workflows.

2. Method

2.1. Problem Definition

A chemical reaction is a process in which substances, called reactants, are transformed into new substances, called products, through the breaking and formation of chemical bonds. When LC is used to analyze a chemical reaction, its operating conditions must be optimized to effectively separate and identify all reactants and products involved.

Our objective is to develop an agent system that takes as input a chemical reaction represented in reaction SMILES format, along with user-specified constraints and requirements expressed in natural language, such as available instruments, maximum run time, and preferred column type. Based on these inputs, the system autonomously analyzes the reaction to infer plausible LC conditions, with chromatographic performance characterized in terms of resolution, peak capacity, and separation efficiency for the reaction mixture. The system outputs a comprehensive report recommending reaction-level LC conditions for comprehensive and separable detection of all compounds present in the given reaction.

2.2. Agent System Overview

We adopt a multi-agent architecture by decomposing tasks into a workflow of specialized sub-tasks (Li et al., 2024; Gottweis et al., 2025). This design helps mitigate fundamental limitations of single-agent architectures, particularly performance degradation caused by excessive contextual burden and long-horizon reasoning. Each agent operates within a role-specific context by distributing functional roles across multiple agents to reduce context dilution. This also enables the parallel execution of heterogeneous sub-tasks, allowing multiple solution paths, verifications, and refinements to be explored simultaneously while agents collaborate effectively with one another. Context engineering (Mei et al., 2025) enhances role fidelity by tailoring each agent's system prompt, memory scope, and tool set to optimize the overall multi-agent system. Properly engineered contexts ensure that each agent consistently operates within its intended

Table 1. Molecular descriptors incorporated into query expansion.

Descriptor	Description
SMILES	Canonical SMILES representation of the compound
IUPAC name	Name following the standardized IUPAC nomenclature system
Molecular formula	Elemental composition of the compound
Exact mass	Monoisotopic mass calculated using the most abundant isotopes
LogP	Wildman–Crippen approximation of the logarithm of the partition coefficient
TPSA	Topological polar surface area
HBA/HBD	Numbers of hydrogen-bond acceptors and donors
No. aromatic rings	Number of aromatic rings in the compound
No. halogen atoms	Number of halogen atoms (`F`, `Cl`, `Br`, `I`) in the compound
No. functional groups	Numbers of hydroxyl (`-OH`) and amine (`-NH`, $-NH_2$) groups in the compound

role, resulting in improved reliability and overall system performance.

The proposed multi-agent system is illustrated in Figure 1. When a user queries a reaction SMILES and constraints for LC analysis, the system operates according to the following procedure. First, query expansion enumerates key descriptors relevant to LC for each reactant and product. Second, compound-level analysis is performed for each compound to derive LC conditions specific to that compound. Third, reaction-level integration combines and optimizes the compound-specific LC conditions to produce a unified set of parameters applicable to the entire reaction. Finally, a report recommending LC conditions is generated and presented to the user. The user can also interact with the system through a conversational interface to provide feedback or request explanations of the report.

To achieve this functionality, the multi-agent system consists of several specialized sub-agents and external tools, each assigned a distinct role. The sub-agents are context-engineered for their respective tasks. The tools are employed to incorporate detailed chemical knowledge and extract information from the literature.

2.3. Query Expansion

To guide LLMs toward better chemical reasoning for recommending appropriate LC conditions, we derive the SMILES, IUPAC name, molecular formula, and a set of molecular descriptors relevant to LC for each compound within the query reaction, as listed in Table 1. This information is used to augment the query and incorporated into the prompt provided to the LLM.

The partition coefficient (LogP) reflects compound hydrophobicity; higher values lead to stronger interactions with the stationary phase and consequently longer retention times under typical reversed-phase conditions (Bandini et al., 2025). Topological polar surface area (TPSA) captures overall molecular polarity and can therefore influence retention behavior (Shi et al., 2025). Hydrogen-bond acceptors (HBA) and donors (HBD) impact physicochemical properties such as solubility, permeability, and binding affinity (Bandini et al., 2025). The numbers of certain functional groups, such as hydroxyl (`-OH`), amine (`-NH`, $-NH_2$), and halogens (`F`, `Cl`, `Br`, `I`), also modulate polarity, significantly influencing retention (Shi et al., 2025). Exact mass is directly related to the target mass-to-charge ratio (m/z) and can influence ion detection sensitivity in Mass Spectrometry (MS) (Yergey, 2020).

2.4. Sub-Agents

Our multi-agent system is organized following the decision-making process of an analytical chemist, comprising nine specialized sub-agents assigned to individual sub-tasks that an analytical chemist would perform when determining the LC conditions. Each sub-agent is context-engineered for a distinct role and equipped with a tailored toolset for its task, such as condition generation, literature search, reflection, refinement, integration, meta-review, and reporting. A supervisor agent orchestrates the activities of the entire system based on the chat history to determine which sub-agent to activate and how to direct their actions toward achieving the target goal.

Each sub-agent is implemented as a LangChain[1] ReAct agent, which iteratively calls tools until a stopping condition is met. As the LLM backbone, we use Gemini 3 Flash model[2]. The LLM is configured with a temperature of 0.1, a top_p of 0.95, and a `medium` thinking level. It should be noted that the LLM backbone can be substituted with any alternative LLM APIs or open-source models.

Generation Agent Given information about a target compound and user-specified LC constraints, the generation agent proposes diverse and chemically plausible LC conditions for that compound, exploring both standard and exploratory design spaces based on the learned knowledge of the LLM. The generated LC conditions are returned in JSON format.

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[1] https://www.langchain.com/

[2] https://ai.google.dev/gemini-api

Search Agent Given information about a target compound and LC constraints, the search agent uses search tools to retrieve diverse and experimentally reported LC conditions for any compounds expected to exhibit comparable LC behavior. While some fields may be missing, the column and mobile phase must be present in the source. The retrieved LC conditions are returned in JSON format.

Reflection Agent Given an LC condition for a compound or reaction, the reflection agent reviews the condition and provides suggestions to improve clarity, correctness, and consistency to ensure full coverage and suitability for the given compound or reaction. It also proposes reasonable values for missing or unclear fields. If needed, it may use search tools to incorporate external knowledge, such as recent LC practices and compound-specific conditions, from credible sources.

Evolution Agent Given an LC condition and the reflection produced by the reflection agent, the evolution agent refines the condition by completing all fields to ensure adequate coverage and suitability for the compound or reaction with respect to separation quality, robustness, and reproducibility. The refined LC condition is returned in JSON format.

Integration Agent Given compound-level LC conditions for individual compounds within a reaction, the integration agent produces unified, practical, and safe reaction-level conditions optimized to ensure all compounds are detectable and chromatographically resolved. The generated LC conditions are returned in JSON format.

Meta-Review Agent Given a set of candidate LC conditions for a reaction, the meta-review agent evaluates and ranks the candidates based on their analytical performance, including reaction coverage, solvent/additive compatibility, peak resolution/selectivity, and retention behavior.

Reporting Agent Given a set of candidate LC conditions with associated rankings, the reporting agent generates the elements needed to assemble the final report. These include an executive summary that highlights the expected chromatographic behavior and performance of the recommended conditions, as well as a comparison table that summarizes their key characteristics, advantages, and trade-offs.

Supervisor/Chat Agents Given the user's latest message and the chat history, the supervisor agent determines the user's intent and orchestrates the overall workflow. Specifically, it classifies whether the request involves explanatory discussion or modifications to the existing report. Based on this classification, the supervisor agent triggers the appropriate process to generate or update the final report or delegates the request to the chat agent for a direct response. The chat agent generates responses grounded primarily in the accumulated LC conditions and analytical results contained in the chat history.

2.5. Tools

In the context of agents, a tool is an external capability that an LLM can call when it cannot perform a task sufficiently well on its own or cannot do it reliably (M. Bran et al., 2024; Ferrag et al., 2025). The LLM extends its abilities beyond its learned knowledge by invoking tools. Grounded in the results returned by these tools, the LLM can generate more accurate, reliable, and context-aware answers. In our agent system, we utilize four types of tools to help sub-agents perform their roles more effectively.

Chemistry Tool This tool augments and systematizes the information for a given chemical compound. An LLM may invoke it when supplied with the SMILES string or the IUPAC name of a compound and a more detailed analysis is required. Upon invocation, the chemistry tool computes the descriptors for the specified compound and returns them as structured output. The chemistry tool is accessible to all sub-agents within the system.

Web Search Tool This tool enables the retrieval of up-to-date information from the web. We employ the Tavily[3] Search API to execute search queries generated by the LLM and to return high-relevance, summarized results that support the LLM in producing grounded responses. This tool is used by both the search agent and the reflection agent.

Scholarly Search Tool Optionally, this tool can be employed when publisher-specific licenses are available to access their scholarly articles. It interfaces with Google Programmable Search Engine[4] and publishers' Text and Data Mining (TDM) APIs to retrieve relevant articles based on search queries generated by the LLM. In our implementation, we link with TDM APIs from three publishers: Elsevier[5], Wiley[6], and SpringerNature[7]. These APIs are available upon request at no cost for academic institutions, whereas commercial use requires a separate licensing agreement. The search agent leverages this tool to obtain reported LC conditions from the retrieved articles.

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[3] `https://www.tavily.com/`

[4] `https://programmablesearchengine.google.com/`

[5] `https://dev.elsevier.com/`

[6] `https://onlinelibrary.wiley.com/library-info/resources/text-and-datamining`

[7] `https://www.springernature.com/gp/researchers/text-and-data-mining`

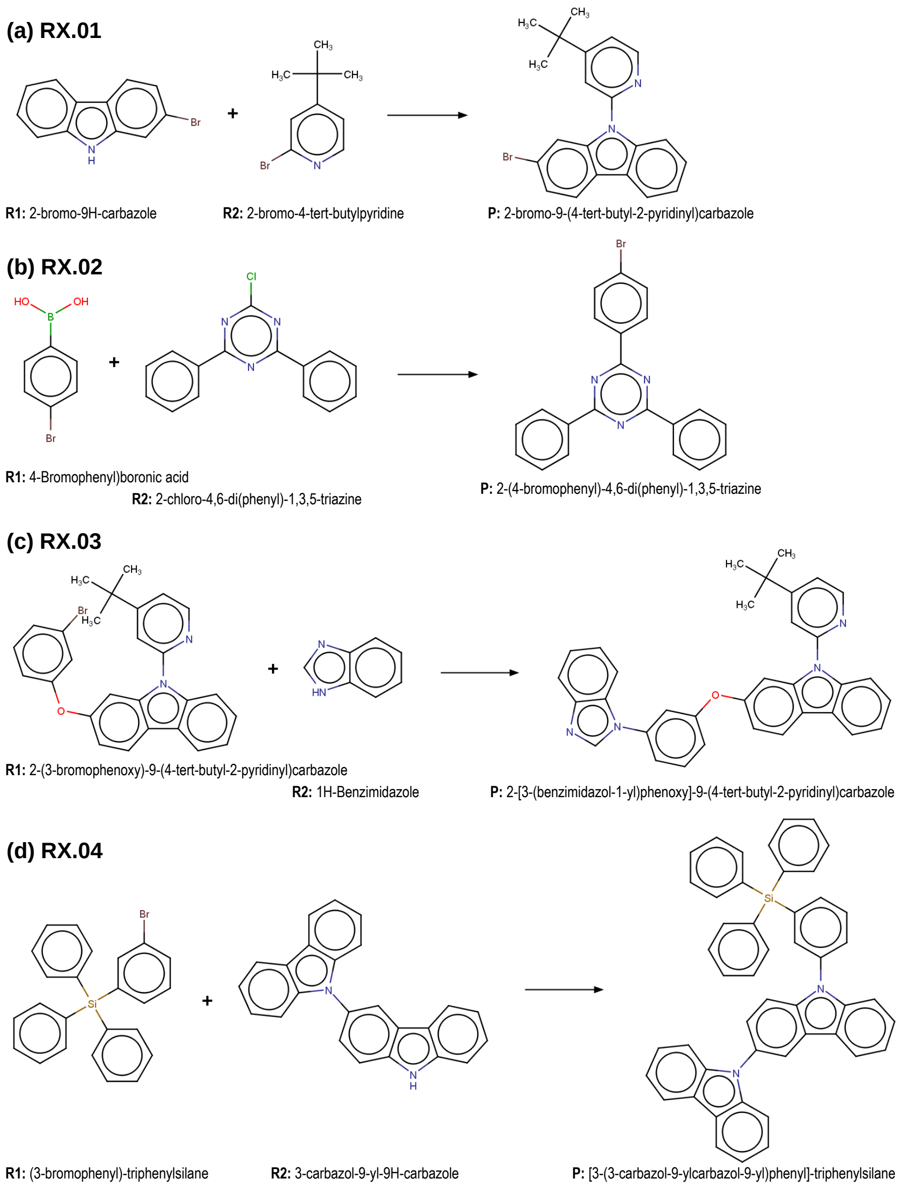


Figure 2. List of chemical reactions for the case study

Extraction Tool This tool is used to extract detailed content from specified URLs, typically those identified by the search tool. Converting a web page into clean text enables downstream sub-agents to further process the information with higher fidelity.

3. Case Study

3.1. Organic Electronic Materials Development

We validate the capability of the proposed agent system through a case study focused on recommending LC conditions for a set of chemical reactions in organic electronic materials development. We evaluate whether the proposed agent system can establish suitable LC conditions for chemical reactions. We employ four reaction schemes involving known OLED intermediates from the literature as representative validation cases: RX.01 (Fleetham et al., 2015), RX.02 (Park et al., 2018), RX.03 (Sun et al., 2022), and RX.04 (Kim et al., 2022), as listed in Figure 2.

The analytical challenge in this case study lies in establishing suitable LC conditions under practical laboratory constraints. The LC conditions must be determined within a restricted design space defined by environmental, instrumental, and operational requirements. In our experimental setup, we identify five such constraints, which are provided as additional input to the agent system:

- Authorized LC instrument (Pump): Vanquish Flex
- Authorized MS instrument: Thermo Scientific TSQ Quantis Plus (Triple Quadrupole)
- Available LC columns: (1) Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm; (2) Waters, ACQUITY UPLC Amide, 2.1 × 50 mm, 1.7 µm; (3) Waters, ACQUITY APC XT45, 4.6 × 150 mm, 1.7 µm; (4) Waters, SunFire PrepSilica, 4.6 × 150 mm, 5 µm; (5) YMC, YMC-Pack SIL, 4.6 × 250 mm, 5 µm; (6) Thermo Scientific, Hypersil GOLD aQ, 2.1 × 20 mm, 1.9 µm; (7) Imtakt, Scherzo SM-C18, 2.0 × 50 mm, 3 µm
- Total run time should be under 10 minutes.
- UV detection is the default detector option.

3.2. Results and Discussion

For each of the four chemical reactions, we evaluated the best LC conditions initially recommended by the agent system. Based on the experimental outcomes, we provided targeted feedback identifying observed limitations, which enabled the agent system to refine its recommendations. Overall, the initial conditions generated under explicit constraints produced results that more closely satisfied the requirements compared to the reference conditions generated without constraints, indicating that the incorporation of constraints effectively guides the agent system toward practically applicable LC parameters. Moreover, the agent system proved its capability to adaptively modify certain parameters upon requests for updating LC conditions. By incorporating experimental feedback to overcome specific limitations, it yielded improved results tailored to the intended goals. This demonstrates the capability to iteratively refine LC conditions through a human-in-the-loop procedure.

3.2.1. REACTION RX.01

The chromatograms for the initial and updated conditions are presented in Figure 3. For the initial condition, crude compounds were separated using a Waters Cortecs C18 column, which employs core–shell particles. As shown in the initial LC chromatogram Figure 3(a), clear separation was achieved for all three compounds with a resolution R_s significantly exceeding the standard threshold of 1.5. However, a limitation was observed in that the peak shape of Reactant 2 exhibited significant tailing. To address this, the agent system was provided with targeted feedback: *”Reactant 2 shows a higher asymmetry factor than the other two peaks. Improve the peak shape of the Reactant 2 peak while maintaining sufficient resolution.”* In response, the agent system refined the LC parameters, notably switching the column to an Imtakt Scherzo SM-C18, which utilizes both ion-exchange and reversed-phase mechanisms and is expected to mitigate peak tailing, and adjusting the mobile phase and elution gradient accordingly. As shown in Figure 3(b), the updated condition significantly improved the peak symmetry with a marginal decrease in R_s for Reactant 2 compared to the initial chromatogram.

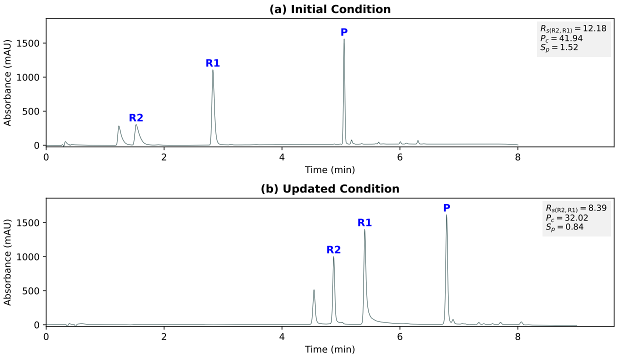


Figure 3. LC chromatograms for Reaction RX.01

3.2.2. REACTION RX.02

The chromatogram for the initial condition is shown in Figure 4(a). While all three reaction components were detectable, Reactant 1 exhibited a disproportionately low peak intensity. To address this, the agent system was provided with targeted feedback: *”Reactant 1 shows a relatively small peak area compared to the other peaks. Enhance the detectability of the Reactant 1 peak.”* In response, the system suggested shifting the UV wavelength to 210 nm, alongside minor adjustments to other LC parameters. Since the initial condition already provided sufficient peak resolution, we isolated and tested the impact of the wavelength shift to 210 nm while maintaining all other initial parameters. The resulting chromatogram, shown in Figure 4(b), confirms a significant increase in peak intensity for Reactant 1. The wavelength shift effectively resolved the challenge of a low signal-to-noise ratio for Reactant 1, enabling a more reliable and precise quantitative evaluation of the reaction components.

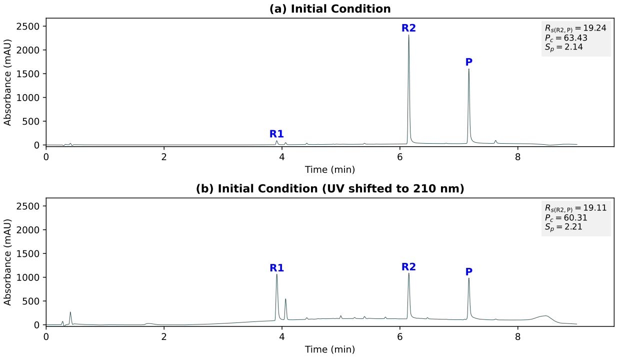
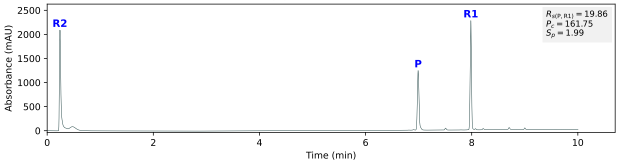


Figure 4. LC chromatograms for Reaction RX.02

3.2.3. REACTION RX.03

As shown in the chromatogram under the initial condition Figure 5(a), clear separation was observed among the three compounds. The identified analytical issue is that Reactant 2 exhibited a very low retention time of 0.34 min. This proximity to the solvent front introduces a high risk of co-elution with unretained polar impurities, which could lead to an overestimation of the peak area for Reactant 2. To rectify this, the agent system was provided with targeted feedback: *”Increase the retention time of Reactant 2 while maintaining the current separation between Reactant 1 and Product.”* The agent system modified the column and implemented a more refined gradient profile. As shown in Figure 5(b), the updated condition successfully extended the retention time of Reactant 2 to 0.92 min, effectively shifting the peak away from the solvent front while only slightly compromising the resolution between Reactant 1 and Product.

(a) Initial Condition



(b) Updated Condition

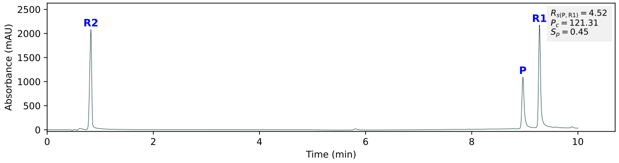


Figure 5. LC chromatograms for Reaction RX.03

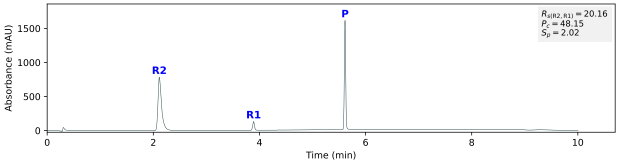
3.2.4. REACTION RX.04

Similar to the results for Reaction RX.02, the chromatogram under the initial condition Figure 6(a) showed low peak intensity for Reactant 1. Thus, we provided the agent system with the same feedback: *”Reactant 1 shows a relatively small peak area compared to the other peaks. Enhance the detectability of the Reactant 1 peak.”* The system suggested shifting the UV detector wavelength from 254 nm to 210 nm. While there were minor adjustments to other LC parameters, we tested whether shifting the UV wavelength alone from the initial condition was sufficient to increase the peak area of Reactant 1. The resulting chromatogram Figure 6(b) showed a significant increase in the peak intensity for Reactant 1 while maintaining the clear detectability of the other peaks.

4. Conclusion

In this study, we presented an AI agent system for recommending plausible LC conditions for chemical reactions. Through a case study on organic electronic materials, we experimentally validated the suitability of the proposed LC conditions for chemical reactions. We further demonstrated that providing targeted feedback to the agent system can refine LC conditions in the desired direction, realizing a human-in-the-loop procedure for determining the parameters of LC instruments. Given the demonstrated feasibility of an agent system for LC condition recommendation, this line of development has the potential to evolve into a fully integrated analytical coordinator that can autonomously interpret user queries, propose suitable analytical methods, and automatically generate the required experimental parameters to support analytical chemists and even non-expert users. By advancing a human-over-the-loop paradigm, it would substantially streamline method development and accelerate the realization of self-driving laboratories.

(a) Initial Condition



(b) Initial Condition (UV shifted to 210 nm)

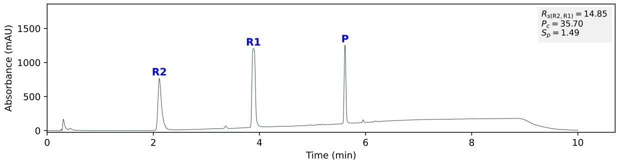


Figure 6. LC chromatograms for Reaction RX.04

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A. Chemical Reactions in Case Study

Table A.1 lists the chemical reactions investigated in our case study on organic electronic materials, along with descriptors derived via query expansion. For each compound, we convert the SMILES string into its corresponding IUPAC name using the CACTUS Chemical Identifier Resolver[8] or the PubChem database[9]. The remaining descriptors are calculated using RDKit[10] functions.

Table A.1. Chemical reactions and their compound descriptors.

ID	Descriptor	Reactant 1 (R1)	Reactant 2 (R2)	Product (P)
RX.01	SMILES	`Brc1ccc2c(c1)[nH]c1ccccc12`	`CC(C)(C)c1ccnc(Br)c1`	`CC(C)(C)c1ccnc(-n2c3ccccc3c3ccc(Br)cc32)c1`
	IUPAC Name	2-bromo-9H-carbazole	2-bromo-4-tert-butylpyridine	2-bromo-9-(4-tert-butyl-2-pyridinyl)carbazole
	Mol Formula	C12H8BrN	C9H12BrN	C21H19BrN2
	Exact Mass	244.98	213.02	378.07
	LogP	4.08	3.14	6.24
	TPSA	15.79	12.89	17.82
	HBA Count	0	1	2
	HBD Count	1	0	0
	Aromatic Ring Count	3	1	4
	Halogen Count	F (0), Cl (0), Br (1), I (0)	F (0), Cl (0), Br (1), I (0)	F (0), Cl (0), Br (1), I (0)
	Functional Group Count	-OH (0), -NH2 (0), -NH (1)	-OH (0), -NH2 (0), -NH (0)	-OH (0), -NH2 (0), -NH (0)
RX.02	SMILES	`OB(O)c1ccc(Br)cc1`	`Clc1nc(-c2ccccc2)nc(-c2ccccc2)n1`	`Brc1ccc(-c2nc(-c3ccccc3)nc(-c3ccccc3)n2)cc1`
	IUPAC Name	(4-Bromophenyl)boronic acid	2-chloro-4,6-di(phenyl)-1,3,5-triazine	2-(4-bromophenyl)-4,6-di(phenyl)-1,3,5-triazine
	Mol Formula	C6H6BBrO2	C15H10ClN3	C21H14BrN3
	Exact Mass	199.96	267.06	387.04
	LogP	0.13	3.86	5.64
	TPSA	40.46	38.67	38.67
	HBA Count	2	3	3
	HBD Count	2	0	0
	Aromatic Ring Count	1	3	4
	Halogen Count	F (0), Cl (0), Br (1), I (0)	F (0), Cl (1), Br (0), I (0)	F (0), Cl (0), Br (1), I (0)
	Functional Group Count	-OH (2), -NH2 (0), -NH (0)	-OH (0), -NH2 (0), -NH (0)	-OH (0), -NH2 (0), -NH (0)
RX.03	SMILES	`CC(C)(C)c1ccnc(-n2c3ccccc3c3ccc(Oc4cccc(Br)c4)cc32)c1`	`c1ccc2[nH]cnc2c1`	`CC(C)(C)c1ccnc(-n2c3ccccc3c3ccc(Oc4cccc(-n5cnc6ccccc65)c4)cc32)c1`
	IUPAC Name	2-(3-bromophenoxy)-9-(4-tert-butyl-2-pyridinyl)carbazole	1H-Benzimidazole	2-[3-(benzimidazol-1-yl)phenoxy]-9-(4-tert-butyl-2-pyridinyl)carbazole
	Mol Formula	C27H23BrN2O	C7H6N2	C34H28N4O
	Exact Mass	470.1	118.05	508.23
	LogP	8.03	1.56	8.61
	TPSA	27.05	28.68	44.87
	HBA Count	3	1	5
	HBD Count	0	1	0
	Aromatic Ring Count	5	2	7
	Halogen Count	F (0), Cl (0), Br (1), I (0)	F (0), Cl (0), Br (0), I (0)	F (0), Cl (0), Br (0), I (0)
	Functional Group Count	-OH (0), -NH2 (0), -NH (0)	-OH (0), -NH2 (0), -NH (1)	-OH (0), -NH2 (0), -NH (0)
RX.04	SMILES	`Brc1cccc([Si](c2ccccc2)(c2ccccc2)c2ccccc2)c1`	`c1ccc2c(c1)[nH]c1ccc(-n3c4ccccc4c4ccccc43)cc12`	`c1ccc([Si](c2ccccc2)(c2ccccc2)c2cccc(-n3c4ccccc4c4cc(-n5c6ccccc6c6ccccc65)ccc43)c2)cc1`
	IUPAC Name	(3-bromophenyl)-triphenylsilane	3-carbazol-9-yl-9H-carbazole	[3-(3-carbazol-9-ylcarbazol-9-yl)phenyl]-triphenylsilane
	Mol Formula	C24H19BrSi	C24H16N2	C48H34N2Si
	Exact Mass	414.04	332.13	666.25
	LogP	3.83	6.42	9.26
	TPSA	0.0	20.72	9.86
	HBA Count	0	1	2
	HBD Count	0	1	0
	Aromatic Ring Count	4	6	10
	Halogen Count	F (0), Cl (0), Br (1), I (0)	F (0), Cl (0), Br (0), I (0)	F (0), Cl (0), Br (0), I (0)
	Functional Group Count	-OH (0), -NH2 (0), -NH (0)	-OH (0), -NH2 (0), -NH (1)	-OH (0), -NH2 (0), -NH (0)

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[8] https://cactus.nci.nih.gov/chemical/structure

[9] https://pubchem.ncbi.nlm.nih.gov/

[10] https://www.rdkit.org/

B. Experimental Protocol

For all experiments, validation samples were prepared to systematically evaluate LC conditions under well-defined settings while reducing the complexity associated with raw reaction mixtures. For each reaction, the target product was synthesized and isolated through a purification step. Since reactants are typically consumed upon reaction completion, the final samples were prepared by mixing the isolated product with the starting materials to ensure that all key components were present for analysis. These samples were then subjected to LC analysis. It should be noted that residual substances not fully removed during purification may account for the additional peaks observed in the LC chromatograms.

MS detection was performed in full-scan mode using Atmospheric Pressure Chemical Ionization (APCI), regardless of the specific LC conditions under evaluation. The MS parameters were strategically fixed to prioritize the consistent monitoring of the separation between the two reactants and the single product. APCI was specifically selected to ensure consistent ionization efficiency during rapid screening and to verify the adequate separation of all reaction components. The MS parameters were standardized as follows: a scan range of m/z 110–1000, a scan rate of 1,000 Da/s, a positive ion discharge current of 4 μA, and sheath, auxiliary, and sweep gas flow rates of 45, 10, and 2 arb, respectively. The ion transfer tube and vaporizer temperatures were maintained at 325°C and 400°C. The LC chromatograms were acquired using a Diode-Array Detector (DAD). When multiple monitoring wavelengths were available, the 254 nm channel was preferentially selected for analysis as it is the most representative absorption wavelength for aromatic compounds.

The chromatographic performance is quantitatively evaluated using three complementary metrics: resolution, peak capacity, and separation efficiency. Let t_i denote the retention time of the i-th peak, corresponding to individual components within the target reaction ($i \in \{1, 2, 3\}$). The Full Width at Half Maximum (FWHM) of the i-th peak is denoted as FWHM_i. Each metric is defined as follows:

- **Resolution** (R_s) quantifies the degree of separation between adjacent peaks. To capture the most critical separation, this metric is calculated as the minimum resolution among the adjacent peak pairs. A resolution value greater than 1.5 is generally considered indicative of complete separation.

$$R_s = 1.18 \times \min\left(\frac{t_2 - t_1}{\text{FWHM}_1 + \text{FWHM}_2}, \frac{t_3 - t_2}{\text{FWHM}_2 + \text{FWHM}_3}\right) \tag{1}$$

- **Peak capacity** (P_c) represents the theoretical maximum number of peaks that can be resolved within the effective separation window of a given analysis. This metric reflects the practical peak accommodation between the first and last eluting components.

$$P_c = 1 + \frac{t_3 - t_1}{1.7 \times \text{FWHM}_{\text{avg}}} \tag{2}$$

- **Separation efficiency** (S_p) evaluates the overall separation performance normalized by the total run time t_{run}, thereby accounting for analytical throughput. High resolution achieved at the expense of long run times reduces practical efficiency.

$$S_p = \frac{R_s}{t_{\text{run}}} \tag{3}$$

C. Recommended LC Conditions

The reference, initial, and updated LC conditions for Reactions RX.01, RX.02, RX.03, and RX.04 are summarized in Tables C.1, C.2, C.3, and C.4.

Table C.1. Recommended LC conditions for Reaction RX.01

Field	Reference Condition (w/o constraints)	Initial Condition (w/ constraints)	Updated Condition (w/ constraints & feedback)
Column	Waters, ACQUITY UPLC BEH C18, 2.1 × 100 mm, 1.7 µm, 45 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 50 °C	Imtakt, Scherzo SM-C18, 2.0 × 50 mm, 3 µm, 50 °C
Mobile Phase	A: 5 mM Ammonium Formate and 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (90:10, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (95:5, v/v)	A: 20 mM Ammonium Formate in Water (pH 3.0, adjusted with Formic Acid); B: Acetonitrile
Flow Rate	0.45 mL/min	0.5 mL/min	0.5 mL/min
Injection Volume	1 µL	0.5 µL	1 µL
Elution	[Gradient] 0–0.5 min: 35% B; 0.5–7.0 min: 35–100% B; 7.0–10.0 min: 100% B; 10.0–10.1 min: 100–35% B; 10.1–13.0 min: 35% B; Total run time: 13 min	[Gradient] 0–0.5 min: 40% B; 0.5–4.5 min: 40–100% B; 4.5–6.5 min: 100% B; 6.5–6.6 min: 100–40% B; 6.6–8.0 min: 40% B; Total run time: 8 min	[Gradient] 0–0.5 min: 10% B; 0.5–6.0 min: 10–98% B; 6.0–7.5 min: 98% B; 7.5–7.6 min: 98–10% B; 7.6–9.0 min: 10% B; Total run time: 9 min
Detector	UV: 254 nm, 290 nm, 330 nm	UV: 254 nm, 290 nm, 330 nm	UV: 254 nm, 280 nm

Table C.2. Recommended LC conditions for Reaction RX.02

Field	Reference Condition (w/o constraints)	Initial Condition (w/ constraints)	Updated Condition (w/ constraints & feedback)
Column	Waters, XBridge BEH C18, 2.1 × 100 mm, 2.5 µm, 40 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 50 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 40 °C
Mobile Phase	A: 5 mM Ammonium Acetate in Water; B: Acetonitrile/Isopropanol (90:10, v/v)	A: 5 mM Ammonium Formate and 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile
Flow Rate	0.4 mL/min	0.5 mL/min	0.4 mL/min
Injection Volume	1 µL	1 µL	2 µL
Elution	[Gradient] 0–1.0 min: 5% B; 1.0–10.0 min: 5–100% B; 10.0–12.0 min: 100% B; 12.1–15.0 min: 5% B; Total run time: 15 min	[Gradient] 0–1.0 min: 5% B; 1.0–5.5 min: 5–98% B; 5.5–7.0 min: 98% B; 7.0–7.1 min: 98–5% B; 7.1–9.0 min: 5% B; Total run time: 9 min	[Gradient] 0–1.0 min: 5% B; 1.0–7.0 min: 5–100% B; 7.0–8.5 min: 100% B; 8.5–8.6 min: 100–5% B; 8.6–10.0 min: 5% B; Total run time: 10 min
Detector	UV: 254 nm, 280 nm	UV: 254 nm	UV: 210 nm, 254 nm

Table C.3. Recommended LC conditions for Reaction RX.03

Field	Reference Condition (w/o constraints)	Initial Condition (w/ constraints)	Updated Condition (w/ constraints & feedback)
Column	Agilent, Zorbax RRHD Eclipse Plus C18, 2.1 × 100 mm, 1.8 µm, 50 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 55 °C	Imtakt, Scherzo SM-C18, 2.0 × 50 mm, 3 µm, 50 °C
Mobile Phase	A: 10 mM Ammonium Formate in Water (pH 3.0, adjusted with Formic Acid); B: 0.1% Formic Acid in Isopropanol/Acetonitrile (50:50, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (70:30, v/v)	A: 10 mM Ammonium Formate in Water (pH 4.0, adjusted with Formic Acid); B: Acetonitrile/Isopropanol (50:50, v/v)
Flow Rate	0.35 mL/min	0.55 mL/min	0.4 mL/min
Injection Volume	1 µL	1 µL	1 µL
Elution	[Gradient] 0–1.0 min: 5% B; 1.0–10.0 min: 5–100% B; 10.0–14.0 min: 100% B; 14.0–17.0 min: 5% B; Total run time: 17 min	[Gradient] 0–0.5 min: 10% B; 0.5–8.0 min: 10–100% B; 8.0–9.0 min: 100% B; 9.0–9.1 min: 100–10% B; 9.1–10.0 min: 10% B; Total run time: 10 min	[Gradient] 0–3.0 min: 2% B; 3.0–8.0 min: 2–100% B; 8.0–9.2 min: 100% B; 9.2–10.0 min: 2% B; Total run time: 10 min
Detector	UV: 254 nm, 280 nm, 310 nm, 330 nm	UV: 254 nm, 280 nm	UV: 254 nm

Table C.4. Recommended LC conditions for Reaction RX.04

Field	Reference Condition (w/o constraints)	Initial Condition (w/ constraints)	Updated Condition (w/ constraints & feedback)
Column	Thermo Scientific, Accucore C30, 2.1 × 150 mm, 2.6 µm, 60 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 55 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 55 °C
Mobile Phase	A: 5 mM Ammonium Formate in Methanol; B: 5 mM Ammonium Formate in Tetrahydrofuran/Methanol (90:10, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (50:50, v/v)	A: 5 mM Ammonium Acetate in Water; B: 5 mM Ammonium Acetate in Acetonitrile/Isopropanol (70:30, v/v)
Flow Rate	0.3 mL/min	0.5 mL/min	0.5 mL/min
Injection Volume	1 µL	1 µL	2 µL
Elution	[Gradient] 0–12.0 min: 20–100% B; 12.0–16.0 min: 100% B; 16.0–16.5 min: 100–20% B; 16.5–20.0 min: 20% B; Total run time: 20 min	[Gradient] 0–0.5 min: 55% B; 0.5–5.0 min: 55–100% B; 5.0–7.5 min: 100% B; 7.5–7.6 min: 100–55% B; 7.6–10.0 min: 55% B; Total run time: 10 min	[Gradient] 0–1.0 min: 60% B; 1.0–6.0 min: 60–100% B; 6.0–8.5 min: 100% B; 8.5–8.7 min: 100–60% B; 8.7–10.0 min: 60% B; Total run time: 10 min
Detector	UV: 254 nm, 290 nm, 340 nm	UV: 254 nm, 280 nm	UV: 210 nm, 340 nm

D. Ablation Study of the Proposed Agent System

The proposed agent system was evaluated against two ablation settings. In the first ablation, we removed external search capabilities from the proposed agent system. Specifically, the search agent, web search tool, scholarly search tool, and extraction tool were excluded. In the second ablation, we implemented a single-agent baseline, in which a single agent with simplified instructions directly recommends LC conditions based on the user-provided reaction SMILES and constraints.

The initial LC conditions generated by the proposed system and the two ablation settings are compared in Tables D.1, D.2, D.3, and D.4 for reactions RX.01, RX.02, RX.03, and RX.04, respectively. Firstly, the LC conditions obtained without external search were similar to those of the full proposed system for each reaction, showing only slight variations in gradient starting points or solvent compositions. No significant deterioration in separation performance is anticipated relative to the recommendations of the full proposed system. This suggests that comparable LC outcomes can be achieved without requiring access to web search APIs or publishers' TDM services. Secondly, the single-agent baseline produced nearly identical LC conditions for all four reactions, indicating reliance on generic LC settings with limited adaptability across different reactions. Because the elution strength of the solvents appears relatively weak for a C18 column, certain reaction components may not elute within the 10-minute window. This may constrain the attainable resolution when analyzing complex reaction mixtures.

Table D.1. Ablation study results of the proposed agent system on Reaction RX.01

Field	Proposed Agent System	w/o External Search	Single-Agent Baseline
Column	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 50 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 50 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 40 °C
Mobile Phase	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (95:5, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (90:10, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile
Flow Rate	0.5 mL/min	0.6 mL/min	0.5 mL/min
Injection Volume	0.5 µL	1 µL	1 µL
Elution	[Gradient] 0–0.5 min: 40% B; 0.5–4.5 min: 40–100% B; 4.5–6.5 min: 100% B; 6.5–6.6 min: 100–40% B; 6.6–8.0 min: 40% B; Total run time: 8 min	[Gradient] 0–0.5 min: 10% B; 0.5–6.5 min: 10–100% B; 6.5–7.5 min: 100% B; 7.5–7.6 min: 100–10% B; 7.6–9.0 min: 10% B; Total run time: 9 min	[Gradient] 0–0.5 min: 20% B; 0.5–6.0 min: 20–95% B; 6.0–8.0 min: 95% B; 8.0–8.2 min: 95–20% B; 8.2–10.0 min: 20% B; Total run time: 10 min
Detector	UV: 254nm, 290 nm, 330 nm	UV: 254 nm, 290 nm, 330 nm	UV: 254 nm

Table D.2. Ablation study results of the proposed agent system on Reaction RX.02

Field	Proposed Agent System	w/o External Search	Single-Agent Baseline
Column	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 50 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 45 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 40 °C
Mobile Phase	A: 5 mM Ammonium Formate and 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Methanol (95:5, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile
Flow Rate	0.5 mL/min	0.5 mL/min	0.5 mL/min
Injection Volume	1 µL	1 µL	1 µL
Elution	[Gradient] 0–1.0 min: 5% B; 1.0–5.5 min: 5–98% B; 5.5–7.0 min: 98% B; 7.0–7.1 min: 98–5% B; 7.1–9.0 min: 5% B; Total run time: 9 min	[Gradient] 0–0.5 min: 5% B; 0.5–6.5 min: 5–100% B; 6.5–8.0 min: 100% B; 8.0–8.1 min: 100–5% B; 8.1–10.0 min: 5% B; Total run time: 10 min	[Gradient] 0–0.5 min: 20% B; 0.5–6.0 min: 20–100% B; 6.0–8.0 min: 100% B; 8.0–8.1 min: 100–20% B; 8.1–10.0 min: 20% B; Total run time: 10 min
Detector	UV: 254 nm	UV: 254 nm, 280 nm	UV: 254 nm

Table D.3. Ablation study results of the proposed agent system on Reaction RX.03

Field	Proposed Agent System	w/o External Search	Single-Agent Baseline
Column	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 55 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 60 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 40 °C
Mobile Phase	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (70:30, v/v)	A: 0.1% Formic acid in Water; B: 0.1% Formic acid in Acetonitrile/Isopropanol (75:25, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile
Flow Rate	0.55 mL/min	0.5 mL/min	0.5 mL/min
Injection Volume	1 µL	1 µL	1 µL
Elution	[Gradient] 0–0.5 min: 10% B; 0.5–8.0 min: 10–100% B; 8.0–9.0 min: 100% B; 9.0–9.1 min: 100–10% B; 9.1–10.0 min: 10% B; Total run time: 10 min	[Gradient] 0–1.0 min: 5% B; 1.0–6.0 min: 5–100% B; 6.0–8.0 min: 100% B; 8.0–8.1 min: 100–5% B; 8.1–9.5 min: 5% B; Total run time: 9.5 min	[Gradient] 0–0.5 min: 20% B; 0.5–7.0 min: 20–100% B; 7.0–8.5 min: 100% B; 8.5–8.6 min: 100–20% B; 8.6–10.0 min: 20% B; Total run time: 10 min
Detector	UV: 254 nm, 280 nm	UV: 254 nm, 280 nm	UV: 254 nm, 280 nm

Table D.4. Ablation study results of the proposed agent system on Reaction RX.04

Field	Proposed Agent System	w/o External Search	Single-Agent Baseline
Column	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 55 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 55 °C	Waters, Cortecs C18, 2.1 × 50 mm, 1.6 µm, 45 °C
Mobile Phase	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (50:50, v/v)	A: 2 mM Ammonium Formate and 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (50:50, v/v)	A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile/Isopropanol (90:10, v/v)
Flow Rate	0.5 mL/min	0.45 mL/min	0.5 mL/min
Injection Volume	1 µL	1 µL	1 µL
Elution	[Gradient] 0–0.5 min: 55% B; 0.5–5.0 min: 55–100% B; 5.0–7.5 min: 100% B; 7.5–7.6 min: 100–55% B; 7.6–10.0 min: 55% B; Total run time: 10 min	[Gradient] 0–1.0 min: 60% B; 1.0–7.0 min: 60–100% B; 7.0–8.5 min: 100% B; 8.5–8.6 min: 100–60% B; 8.6–10.0 min: 60% B; Total run time: 10 min	[Gradient] 0–1.0 min: 40% B; 1.0–7.0 min: 40–100% B; 7.0–8.5 min: 100% B; 8.5–8.6 min: 100–40% B; 8.6–10.0 min: 40% B; Total run time: 10 min
Detector	UV: 254 nm, 280 nm	UV: 254 nm, 295 nm	UV: 254 nm, 290 nm