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Streamlined Work-Up for High-Throughput Experimentation Using Automated Filtration

Gregory Gaube* and Gilian T. Thomas*

Automated pipetting is a valuable tool for the preparation of high-throughput experimentation screens; however, automation in postreaction processing (work-up) steps is often overlooked. Opentrons has created an affordable commercial pipetting robot that unlocks automated liquid dispensing and transferring for even the early-career researcher. This article demonstrates the utility of this affordable automated pipetting solution for postreaction processing through four case studies, selectively sampling biphasic mixtures when applicable. Work-up procedures appropriate for high-throughput screening of academic and industrially relevant reactions, including Suzuki–Miyaura coupling, Buchwald–Hartwig coupling and Miyaura borylation, are described. An additional protocol is designed for determining the appropriate aqueous wash to reduce protodeboronation for both an aryl boronic acid and aryl boronic pinacol ester.

1. Introduction

Today's synthetic chemist is at the precipice of an automation revolution that will undoubtedly alter the landscape of chemistry forever. These changes are already starting to be felt as the likes of automated chromatography are becoming commonplace not only in industry, but in the academic setting as well. However, as Hein et al. described in their 2021 publication, *Automation isn't automatic*,[1] there are many factors to consider when implementing automation. Nearly 4 years later, many of the same issues still hold true, yet we are witnessing the development of commercial technologies that make automated processes more accessible.

Research groups are typically motivated to pursue automation for three main reasons.[1] First, automation enables scientists to carry out tasks more efficiently. Second, it enhances reproducibility and allows processes to continue without the need for constant human presence. Third, and often overlooked, automation can significantly improve laboratory safety by reducing researchers' direct exposure to hazardous chemicals. Despite these advantages, many routine tasks in standard laboratories are still performed manually. This often results in inefficient workflows, repetitive labor, and potential safety risks. A major barrier is the perception that commercial automation solutions are prohibitively expensive or overly time-consuming to implement.

High-throughput experimentation (HTE) is an excellent testing ground for automation practices. HTE allows scientists to conduct a large number of experiments quickly and efficiently.[2–4] There are several recent articles detailing how a new research group may want to design HTE experiments,[5,6] implement HTE,[7,8] or even establish a facility.[9] The best-equipped labs are utilizing fully autonomous synthesis platforms such as those commercialized by Chemspeed Technologies, Unchained Labs, or Tecan.[10–12] These platforms can be extremely valuable but require a well-trained user and considerable capital investment which is not accessible to most research groups. Some universities and national foundations have used their shared capital to invest in facilities to increase accessibility of automation in synthetic chemistry, such as the SwissCat+ project at Eidgenössische Technische Hochschule (ETH) Zürich and École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, the Center for Rapid Online Analysis of Reactions (ROAR) at Imperial College London in the United Kingdom, or the HTE facilities found at the Institut Català d'Investigació Química (ICIQ) in Spain, University of Ottawa in Canada, or the University of Delaware and the University of Pennsylvania in the United States of America, but this is hardly the norm.

As automation in chemistry continues to advance, there has been considerable attention paid to new technologies that can aid in postreaction analysis such as computer vision. The Hein group has developed HeinSight,[13–15] an open-source modular hardware platform for numerous procedures including liquid level detection and liquid–liquid extraction. The Kapur group and AstraZeneca have developed a computer vision algorithm for determining liquid–liquid separation during reaction work-up.[16] Most recently, the Cooper group have combined Opentrons' accessible robotics with computer vision to develop an HTE colourimetric titration workstation.[17] Now the field is looking at fully autonomous laboratories, where artificial

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G. Gaube
Faculty of Chemistry and Biochemistry
Ruhr-Universität Bochum
150 Universitätsstrasse, 44801 Bochum, Germany
E-mail: gregory.gaube@rub.de

G. T. Thomas
School of Chemistry
University of Leeds
Woodhouse, Leeds LS2 9JT, UK
E-mail: G.T.Thomas@leeds.ac.uk

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intelligence (AI) and machine learning (ML) in chemistry come together with robotics to culminate in self-driving labs.[18,19] Significant work in this field has been conducted by the Aspuru-Guzik group at the University of Toronto,[20–22] the Abolhasani group at North Carolina State,[18,23,24] and the Noël group at the University of Amsterdam.[25,26] While these advances are undoubtedly the future of automation in chemistry, currently there are commercial automation solutions that can be used to improve productivity in the meantime. These tools are particularly useful and accessible to new appointees who face challenges related to fiscal restrictions and fluctuating supply chains.[27]

The Opentrons platforms can be remarkably beneficial to a newly established research group, but specifically the OT-2 (**Figure 1**a) is an exceptional combination of utility and affordability. This fully customizable and chemically compatible platform has seen considerable usage in biological sciences,[28–30] but adoption in chemistry is a recent innovation. This is despite excellent chemical compatibility, something that many commercial liquid handlers lack.[31] For example, Roche has published an account of integrating the OT-2 platform into an existing workflow, specifically for pipetting and assay development.[32] The Greenaway lab has implemented a number of OT-2 units into their laboratory, most notably using them to automate liquid dispensing in their high-throughput discovery of porous organic cages.[33] The Crimmin group has used an OT-2 unit in conjunction with Unchained Laboratories optimization sample reactor (OSR) to filter sampled aliquots before analysis.[34] Lin and Liu have demonstrated use of the OT-2 in the context of electrochemistry.[35] Finally, the Wilson group has used the OT-2 platform to automate viscosity measurements in a high-throughput manner.[36] These use cases may be daunting for the newly founded research group, but new users of the Opentrons platforms can be assured that they benefit from a strong (online) network of other researchers who use the same instrument.

Automation thrives when it replaces menial, repetitive tasks. Postreaction processing, or reaction work-up is an integral, but often neglected, component of wet chemistry. This importance is amplified when new appointees are dependent on shared or department analysis instrumentation. Improper care during work-up can result in unintentionally damaging expensive columns, or inadequate spectra acquisition, which ultimately results in analysis needing to be repeated. Herein, we describe the use of a commercially available Opentrons OT-2 dispensing platform to automate postreaction processing (work-up) of HTE plates for analysis, including case studies of commonly researched cross-coupling procedures and products.

2. Results and Discussion

All protocols run on an Opentrons OT-2 need to be designed on a separate computer before implementation. The open-source software of the OT-2 allows the user to create a custom python code to control the robotic platform or use the online Opentrons Protocol Designer. To demonstrate ease of use for the average chemist, the Opentrons Protocol Designer was used to generate the protocols for all case studies reported herein. This program allows the user to create protocols in a drag and drop fashion before exporting the functional code. Preliminary test runs were conducted using water to ensure the protocols were acceptable before introducing chemicals and conducting experiments (**Figure 2**b). For all case studies, solutions were prepared in advance and loaded on the deck according to the provided protocol. We have demonstrated these case studies as 24 experiments in a 96-well, shell vial plate. All protocols are available to download, and their details can be found in the Supporting Information.

2.1. Case Study 1: Selective Extraction and Filtration of a Biphasic Suzuki–Miyaura Cross-Coupling Reaction

We began with a high-throughput screen of a Suzuki–Miyaura cross-coupling reaction (**Figure 3**). This was chosen because this highly popular reaction is typically biphasic,[37] which offers a unique challenge in the work-up as the pipette tip needs to be calibrated for the appropriate height to avoid sampling the aqueous layer. Using a 2-MeTHF/water system, the organic phase formed the upper layer. To ensure the z-position of the pipette was programmed correctly, the height range of the desired

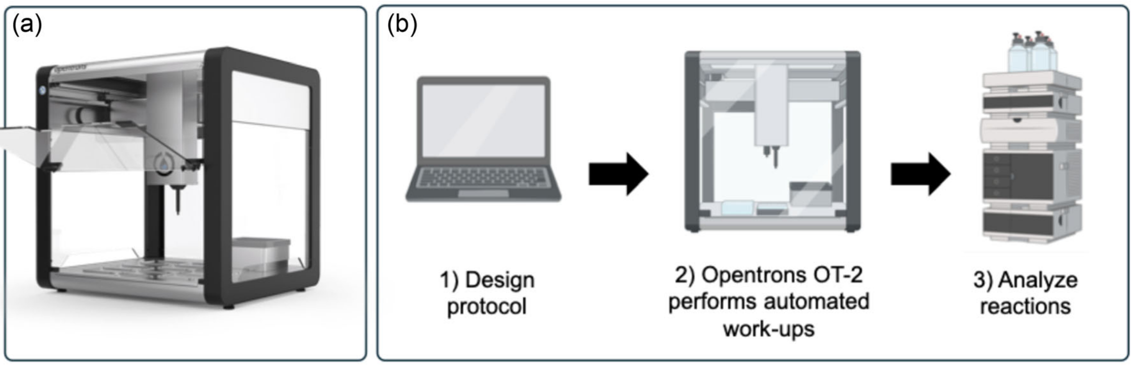


Figure 1. a) Opentrons OT-2.[46] b) Simplified workflow described in this manuscript consisting of designing a protocol for the Opentrons OT-2 liquid handler, using the protocol to perform an automated work-up, and finally analyzing the reactions.

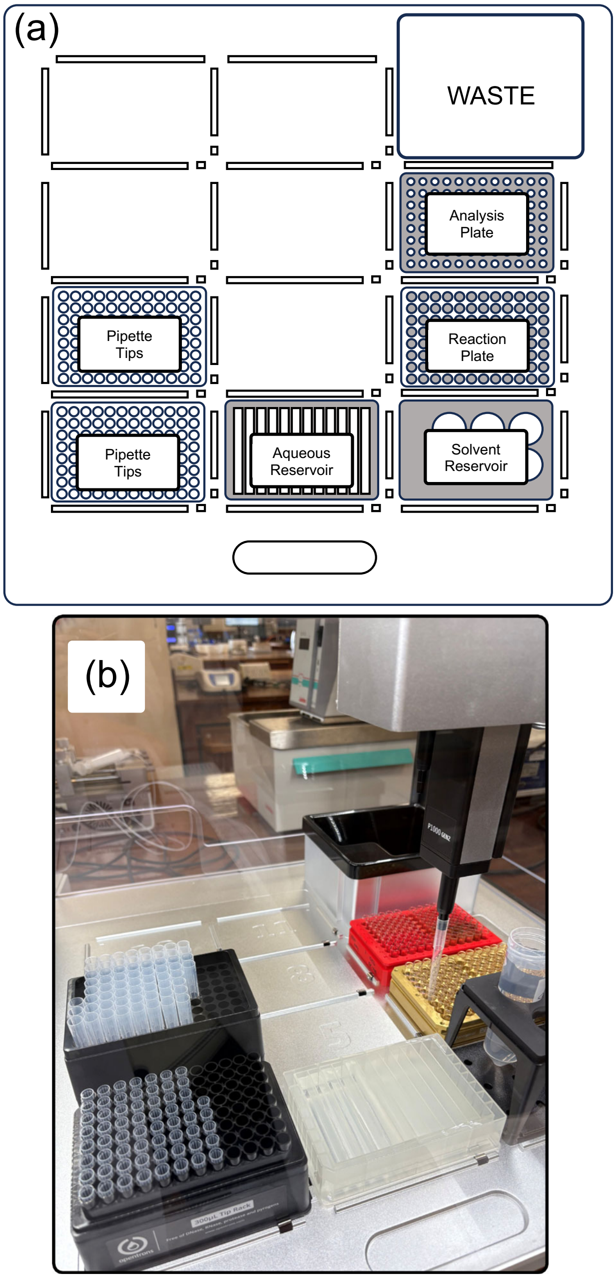


Figure 2. a) Simplified aerial-view of Opentrons OT-2 floorplan used during Case Study 4 experimentation. b) Opentrons OT-2 during Case Study 4 experimentation.

organic layer was measured in a control vial. With that in mind, the pipette tip height (aspirate tip position, z-position) was set to be centered in the organic layer to avoid pipetting the aqueous phase. If the desired sampling volume is large, or the solvent combination results in the organic layer being on the bottommost layer, the z-position will require appropriate adjustment.

Prior to gas chromatography–mass spectrometry (GC-MS) analysis, the organic phase from the Suzuki–Miyaura reaction was filtered to eliminate any remaining palladium particulate, ensuring safe and reliable injection. The protocol was designed to aspirate a 20 μL aliquot of the reaction solution, and dispense it into a collection plate equipped with a Pall filter plate containing celite. Again, the z-position was tested in advance to ensure the pipette tip does not come into contact with the filter plate or celite. The OT-2 was then programmed to wash the aliquot through the filter using 700 μL ethyl acetate. This volume was chosen to ensure that the solvent did not overflow the filter well, and provide sufficient dilution for GC–MS analysis. GC–MS spectra were then acquired for all samples, and the results of the high-throughput screen are depicted in Figure 3.

With this procedure we saw a range of reactivity throughout the reaction screen, with relatively clean GC–MS spectra (see Supporting Information for representative spectra). The in situ combination of Pd_2dba_3/XPhos was the best result, and $Pd(OAc)_2$/DPPF, along with (allyl)$PdCl_2$/XPhos were nearly as successful.

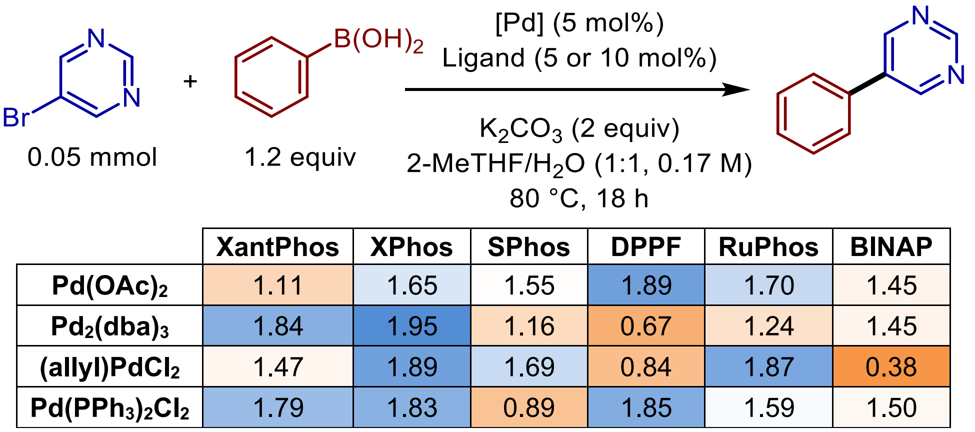
2.2. Case Study 2: Aqueous Wash, Selective Extraction, and Filtration of Buchwald–Hartwig Cross-Coupling Reaction

We then expanded this protocol to include an aqueous wash prior to filtration. The Buchwald–Hartwig cross-coupling reaction serves as an appropriate case study as these reactions often form insoluble inorganic salts which can be detrimental to analytical instrumentation.[38] To conduct an effective aqueous wash without moving the high-throughput plate to another stirrer, we needed to simulate a chemist using a separatory funnel with the robotic pipette. We created a protocol to include a 300 μL dispense of H_2O into the reaction vial, followed by the pipette aspirating the full reaction mixture and dispensing it back into the same vial three times consecutively. This gave effective mixing and allowed us to then target the organic layer for analysis. In a toluene/H_2O mixture, the organic layer was once again the upper layer, and we targeted the center point of the organic layer using the same procedure described in Case Study 1. If an increased sampling volume is desired, or the solvent combination results in the organic layer being on the bottommost layer, the z-position will require appropriate adjustment. The 20 μL aliquot of the organic layer was filtered and diluted, followed by GC–MS analysis (**Figure 4**) using the same procedure as described in Case Study 1.

Overall, reactivity varied across the screen, including three completely unsuccessful reactions. The in situ combination of (allyl)$PdCl_2$/XPhos was the distinctly best result from this screen.

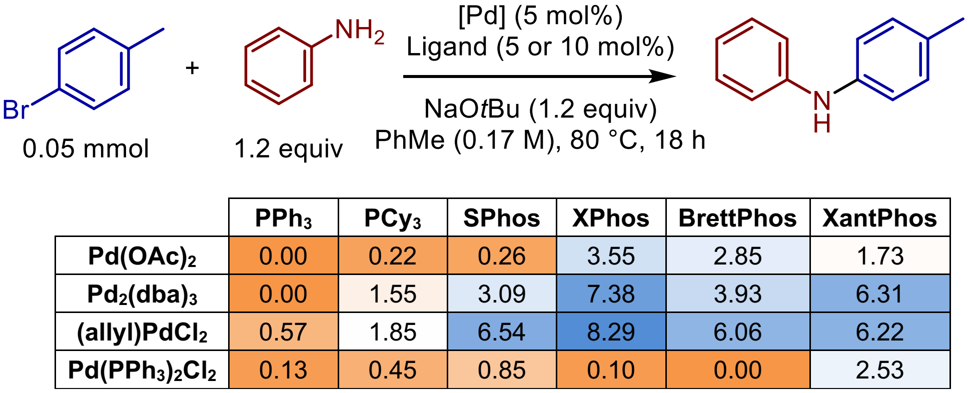
2.3. Case Study 3: Extraction and Filtration of Miyaura-Borylation Cross-Coupling Reaction

To demonstrate the Opentrons OT-2 can effectively prepare reactions for analysis without an aqueous wash, the Miyaura borylation reaction was selected as a case study due to the relatively mild reaction components and industrial relevance.[39,40] A representative Miyaura borylation high-throughput screen was performed (see Supporting Information)whereby only sampling and dilution were required. The z-position for these reactions was set to the midpoint of the 300 μL toluene rsolution, much lower in comparison to the previous case studies. If an increased



	XantPhos	XPhos	SPhos	DPPF	RuPhos	BINAP
$Pd(OAc)_2$	1.11	1.65	1.55	1.89	1.70	1.45
$Pd_2(dba)_3$	1.84	1.95	1.16	0.67	1.24	1.45
$(allyl)PdCl_2$	1.47	1.89	1.69	0.84	1.87	0.38
$Pd(PPh_3)_2Cl_2$	1.79	1.83	0.89	1.85	1.59	1.50

Figure 3. Microscale high-throughput experimentation results comparing Pd catalyst/ligand combinations for a Suzuki coupling reaction of 5-bromopyrimidine and phenylboronic acid. Color gradient indicates product peak area/external standard peak area (orange = low; white = midpoint; blue = high) determined by GC–MS.



	PPh_3	PCy_3	SPhos	XPhos	BrettPhos	XantPhos
$Pd(OAc)_2$	0.00	0.22	0.26	3.55	2.85	1.73
$Pd_2(dba)_3$	0.00	1.55	3.09	7.38	3.93	6.31
$(allyl)PdCl_2$	0.57	1.85	6.54	8.29	6.06	6.22
$Pd(PPh_3)_2Cl_2$	0.13	0.45	0.85	0.10	0.00	2.53

Figure 4. Microscale high-throughput experimentation results comparing Pd catalyst/ligand combinations for a C–N coupling reaction of 4-bromotoluene and aniline. Color gradient indicates product peak area/external standard peak area (orange = low; white = midpoint; blue = high) determined by GC–MS.

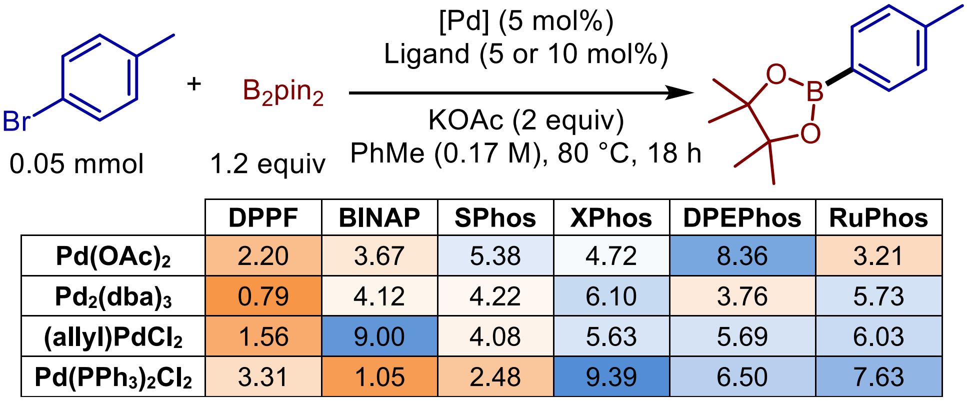
sampling volume is desired the z-position may need to be adjusted appropriately. In this protocol, a 20 μL aliquot of the reaction solution was transferred to a collection plate fitted with a Pall filter plate containing celite. The aliquot was then diluted and washed through the filter with 700 μL ethyl acetate. GC–MS spectra were then acquired for all samples (**Figure 5**).

In this screen, variations of reactivity were observed, but all reactions were productive to some extent. The most productive in situ combination was $Pd(PPh_3)_2Cl_2$/XPhos, followed closely by $(allyl)PdCl_2$/BINAP.

2.4. Case Study 4: Aqueous Wash Screening of Boronated Products

Two of the three previous case studies involved directly working up reactions with aqueous media in preparation for analysis, however many products are unstable in aqueous conditions. An exemplary class of compounds are boronates as they are often subject to an aqueous work-up in preparation for their immediate further cross-coupling.[41] While the Lloyd-Jones group has conducted thorough studies detailing the mechanism and kinetics of protodeboronation of numerous boronated compounds,[42–44] the susceptibility of a compound to protodeboronation is a highly specific to the individual structure. If the desired product is outside the scope of the aforementioned studies, these products may need to be tested individually to mitigate against detrimental protodeboronation during work-up.

This protocol was designed to dispense a series of aqueous washes to a set of stock solutions containing the desired compound to be studied, in this case 2,4,6-trifluorophenylboronic acid and the corresponding pinacol boronic ester derivative, 4,4,5,5-tetramethyl-2-(2,4,6-trifluorophenyl)-1,3,2-dioxaborolane. Similar to Case Study 2, the instrument was programmed to simulate a liquid–liquid extraction by dispensing the desired aqueous wash solution, aspirating the complete reaction solution, dispensing it back into the same vial, and repeating this in triplicate before moving on to the next sample. This procedure was carried out using the same 1 mL HTE shell vials employed in Case Studies 1–3, and performed in triplicate to assess the reproducibility of the extraction process. Again, the robotic pipette was programmed to transfer a 20 μL aliquot of the organic layer to a separate collection plate. These samples were then diluted with 700 μL of 4:1 MeCN/H_2O and subject to liquid chromatography–mass spectrometry (LC-MS) analysis (**Figure 6**). To ensure that



	DPPF	BINAP	SPhos	XPhos	DPEPhos	RuPhos
$Pd(OAc)_2$	2.20	3.67	5.38	4.72	8.36	3.21
$Pd_2(dba)_3$	0.79	4.12	4.22	6.10	3.76	5.73
$(allyl)PdCl_2$	1.56	9.00	4.08	5.63	5.69	6.03
$Pd(PPh_3)_2Cl_2$	3.31	1.05	2.48	9.39	6.50	7.63

Figure 5. Microscale high-throughput experimentation results comparing Pd catalyst/ligand combinations for the borylation of 4-bromotoluene. Color gradient indicates product peak area/external standard peak area (orange = low; white = midpoint; blue = high) determined by GC–MS.

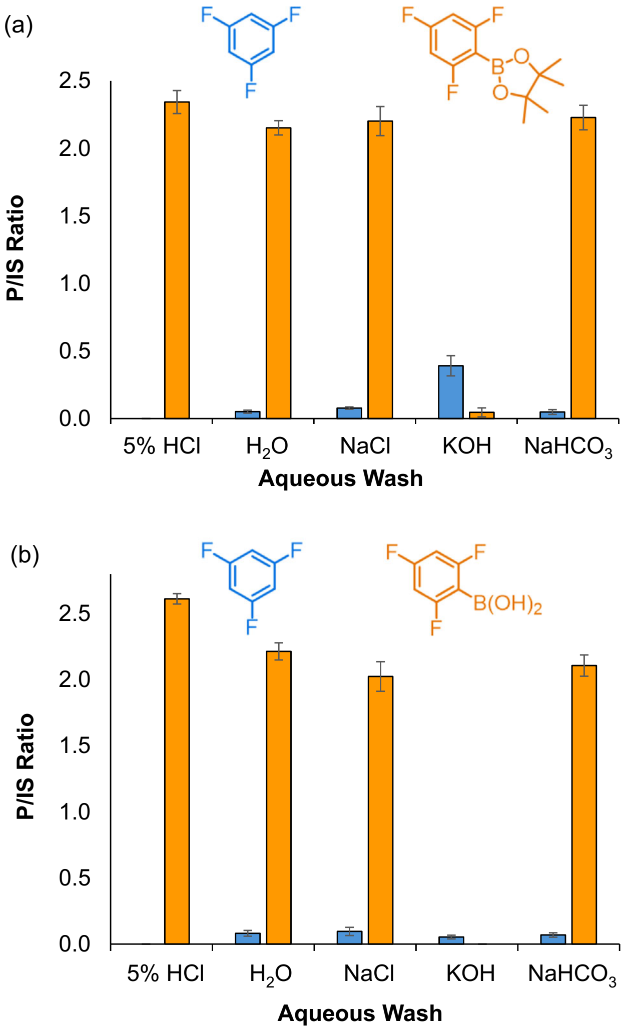


Figure 6. Automated screen of aqueous washes conducted using the Opentrons OT-2 robot for analysis of protodeboronation of a) 4,4,5,5-tetramethyl-2-(2,4,6-trifluorophenyl)-1,3,2-dioxaborolane, and b) 2,4,6-trifluorophenylboronic acid. Product/internal standard ratios determined by LC using 1,3,5-trimethoxybenzene as internal standard.

protodeboronation was not occurring in the 4:1 MeCN/H_2O analysis solvent, both compounds were monitored in the analysis solvent over 15 h using LC–MS and protodeboronation was not observed (see Supporting Information).

The results obtained highlighted how seemingly benign aqueous washes can negatively impact product yield. Across the series of washes tested, the pinacol boronic ester consistently demonstrated greater stability than the corresponding boronic acid. Both boronates remained relatively unaffected by the 5% HCl wash. However, the boronic acid exhibited mild protodeboronation when exposed to H_2O, NaCl, and $NaHCO_3$ solutions. Additionally, the boronic acid was not detected at all following the KOH wash, whereas some boronic ester remained intact, further confirming its superior stability under these conditions. The absence of a protodeboronation product from the boronic acid suggests that additional degradation pathways beyond protodeboronation may be at play in highly basic environments.

3. Conclusion

We have produced four protocols to perform automated postreaction processing (work-up) using the Opentrons OT-2 pipetting robot. These case studies include appropriate work-up conditions for Suzuki–Miyaura coupling, Buchwald–Hartwig coupling, and Miyaura Borylation reactions—three cross-coupling reactions with incredible academic and industrial relevance. The protocols were designed to accommodate GC–MS and LC–MS analysis, however these protocols could easily be tailored for NMR analysis by changing the z-position and increasing the sampling volume. For example, this methodology would be compatible with recent innovations in ^{19}F-NMR, which show promising potential for quantitative analysis in HTE.[45]

Overall, these protocols serve as a stepping stone into automation that is not only accessible to all levels of skill in regard to automation, but accessible to nearly all budgets as well. While chemical synthesis has been described as a labor-intensive field of science, small implementations of automation can significantly reduce this notion. We hope to encourage research groups to embrace automation through accessible commercial robotic platforms.

Supporting Information

The authors have cited additional references within the Supporting Information.[29,30]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: accessible robotics in chemistry · catalysis · high-throughput experimentation · laboratory automation · work-up

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