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# Celebrating women in process research at MSD

**Rebecca T. Ruck**

*Process Research & Development, Merck & Co., Inc., Rahway, NJ, USA*
*Email: rebecca_ruck@merck.com*

**Dedication: for the many outstanding women who came before me, thank you for your courage in carving a difficult path. For those who succeed me, keep aiming higher!**

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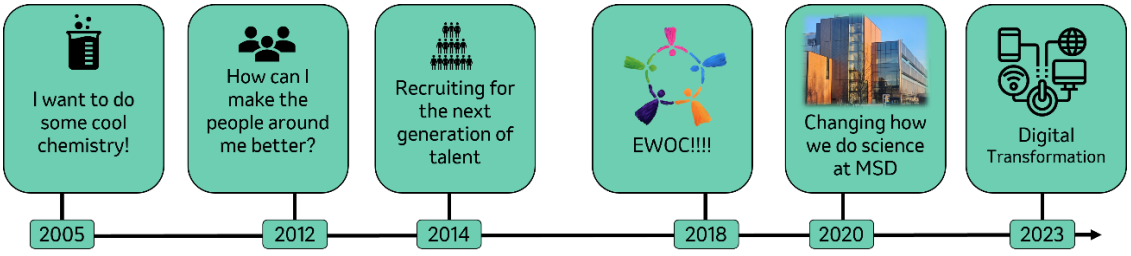
## Abstract

Over the past decade, many experiments have emerged to drive increased representation of women in chemistry across all stages of the career pipeline. I have had the good fortune to be able to get in on the ground floor of many such efforts, including the establishment of the Empowering Women in Organic Chemistry (EWOC) conference. As de facto host for the 6th annual event held in June 2024, I was honored to provide a keynote about my experiences in the field, which I reprised as part of the 2025 European iteration. The talk showcased some of the innovative MSD Process Research stories led by women within my team, shining a critical spotlight on the nexus of women, creativity and human health. This manuscript will review the impressive case studies I feel privileged to be able to communicate here to the broader chemistry community with a backdrop of my own personal experiences to provide context and learnings.




**Keywords:** Women in chemistry, process research, reaction mechanism

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## 1. Introduction

Since 2014, MSD Process Research & Development has proactively sought to identify, attract and recruit talented women chemists to bolster our levels of creativity, ingenuity and collaboration in our mission to deliver life-saving medicines to patients. These efforts have transformed the make-up of our department, and more importantly, coincided with exceptionally high productivity and innovation in the development of our manufacturing processes. While it is impossible to draw a conclusion on correlation vs. causation in these concurrent events, it is extremely encouraging that, in many examples, these same women have been at the epicenter of this science.

Operating in tandem with our local efforts to increase women in chemistry representation,[1] initiatives across the field are now in full flight.[2,3] One such engagement is the Empowering Women in Organic Chemistry (EWOC) conference (and its associated local chapters).[4] As one of the EWOC founders, I have had a front-row seat to the impact this organization has had on the community – and me, personally – in recent years. I feel extreme gratitude and love for all who have been instrumental to its success, ranging from the other founders to those who join us online for events. As a company, we were fortunate to host the 6$^{th}$ annual EWOC conference at our Rahway, NJ site in June 2024, and I was tasked with giving the closing keynote for the event.[5] I subsequently reprised this lecture at the 2025 EWOC Europe conference recently held at Novartis in Basel, Switzerland.[6] For me, these presentations were a tremendous opportunity to give back to Women in Chemistry *and* showcase the innovative and impactful work of the talented women at MSD Process. This article will serve to translate this talk into a review of some of these resounding achievements to be shared with the broader organic chemistry community overlaid with some of my own reflections and learnings along the way.

## 2. Personal Story

At EWOC, we ask each of our speakers to complement their chemistry details with a personal story that highlights their experiences, learnings and/or challenges. This approach provides a unique opportunity to showcase success in the face of adversity and help the early career attendees appreciate that they too can overcome their struggles. In my case, I chose to focus on the intersectionality as a woman in chemistry with an

invisible disability. Specifically, at the end of my first year of graduate school, after a year of pain, uncertainty and hospital visits, I was diagnosed with Crohn's Disease. Since then, I have endured any number of complications, as well as two major surgeries to remove portions of my terminal ileum. These experiences have rendered me stronger and more resilient as I strive to demonstrate that my condition not only fails to slow me down, but actually represents a superpower. I can provide genuine empathy for what many others experience and, hopefully, help them believe that they, too, can climb the summit that sometimes seem insurmountable when battling fatigue and anguish.

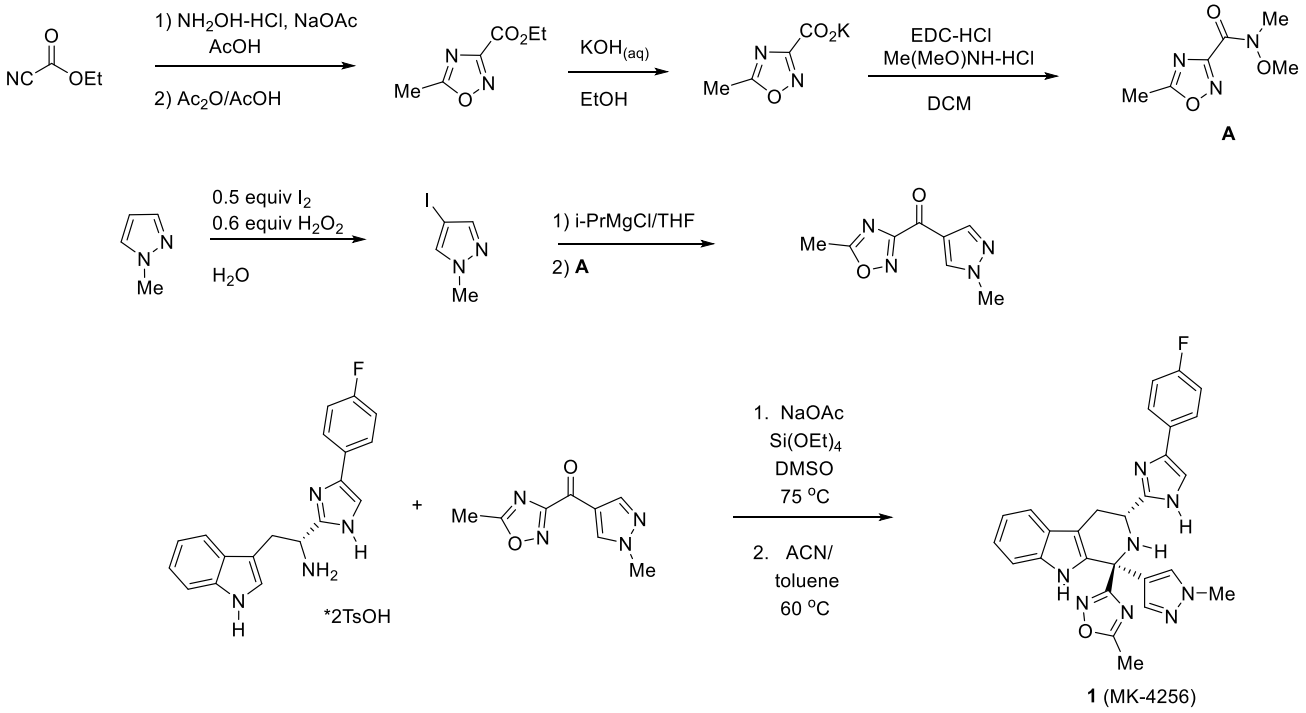
## 3. Chemistry

After sharing this personal reflection, I pivoted to the exciting chemistry driven by so many amazing women colleagues. The examples provided illustrate the ever-changing nature of the field and are of personal significance, in the chemistry performed, the practitioners of that chemistry and the lessons that I have derived from the experience.

### 3.1. MK-4256

To set the stage, I highlighted a project I worked on about three years into my career for the 1st GMP delivery of MK-4256 (**1**), an antagonist of somatostatin subtype receptor (SSTR3) that was an investigational therapy for type 2 diabetes.[7] In this example, a small team I had the opportunity to lead was expected to deliver >3 kg of the Active Pharmaceutical Ingredient (API) in only four months. The process was an exercise in heterocycle synthesis, with five heterocycles and eight nitrogen atoms present in the molecule. Ultimately, we delivered >6 kg of MK-4256 by developing a novel green iodination of pyrazole substrates,[8] an efficient 1,2,4-oxadiazole synthesis and a convergent Pictet-Spengler reaction that allowed for the upgrading of a 60:40 diastereomeric mixture to the desired compound by crystallization (Scheme 1).[9] While I am proud of the team's work here, the importance of my personal learning far exceeds the scientific accomplishments achieved. In particular, I had the privilege of working with two early career women scientists (Mary Kim and Wynne Kandur) who had both recently completed their bachelor's degrees at Bryn Mawr College. Given their common ages and training, it would be easy to conclude that they applied similar skillsets and mindsets to their work. What I came to appreciate is the individual natures of all of the people with whom I work – they have different motivations, different ways they like to engage, and different thought processes. While this conclusion seems obvious (and maybe even more obvious today than 18 years ago), it remains difficult to tailor one's style to someone else's but is a critical act of leadership. I am grateful for Mary and Wynne's patience with me during this experience and have tried to carry that lesson forward as my professional orbit has become more and more diverse.




**Scheme 1.** Process for the preparation of MK-4256.

### 3.2. Ruzasvir

The next story involved a significant fast-forward to my time leading our Catalysis, Automation and Flow Chemistry group. This proved a transformative time in my career as it cultivated my passion for developing Enabling Technologies, which has been reflected in multiple subsequent roles of increasing responsibility. Ruzasvir (**2**, Figure 1a) was an investigational pan-genotypic NS5a inhibitor for the treatment of Hepatitis C Virus.[10] Our Process team had previously discovered a dynamic kinetic asymmetric C-N coupling to prepare the chiral hemiaminal core in elbasvir (**3**, Figure 1b), an earlier NS5a inhibitor and part of the marketed therapeutic Zepatier®.[11] In preliminary mechanistic experiments, colleagues shared that the bis-phosphine ligand QuinoxP* underwent mono-oxidation to the corresponding bis-phosphine monoxide under the reaction conditions, with the hemi-lability of the P=O linkage critical for the desired asymmetric catalysis.

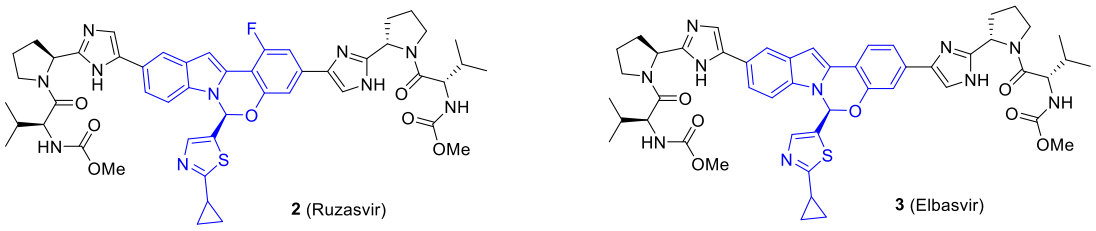
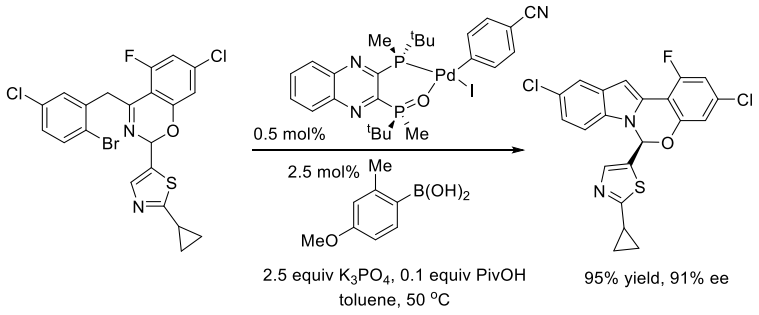



**Figure 1.** (a) Ruzasvir; (b) Elbasvir.

Gratifyingly, this methodology translated well to the synthesis of Ruzasvir, albeit at an increase from 1 to 5 mol% catalyst, which we attributed to the presence of an electron-withdrawing fluorine atom on the core. While this five-fold increase in catalyst would likely be viewed as negligible in an academic setting, the added cost of the metal, and even more so, the QuinoxP* ligand was deemed problematic for manufacturing scales. To reduce

the catalyst loading, Yining Ji, who had recently been hired to help resuscitate our physical organic chemistry efforts, led a detailed mechanistic investigation into better understanding this novel transformation. With a comprehensive set of experiments, including kinetics and spectroscopic studies, isotopic labelling, isolation of intermediates, and computational investigation, Yining and the team were able to derive incredible insights into the C-N coupling. Application of this mechanistic understanding fuelled the rational design of a novel pre-catalyst and associated reaction conditions that enabled a 10-fold reduction in catalyst loading for the preparation of Ruzasvir and established a new class of catalysts for use in Pd chemistry (Scheme 2).[12] Furthermore, not only did it validate the investment we had made in mechanistic understanding, but it set the stage for an ongoing commitment to using these insights to drive process improvements.[13]

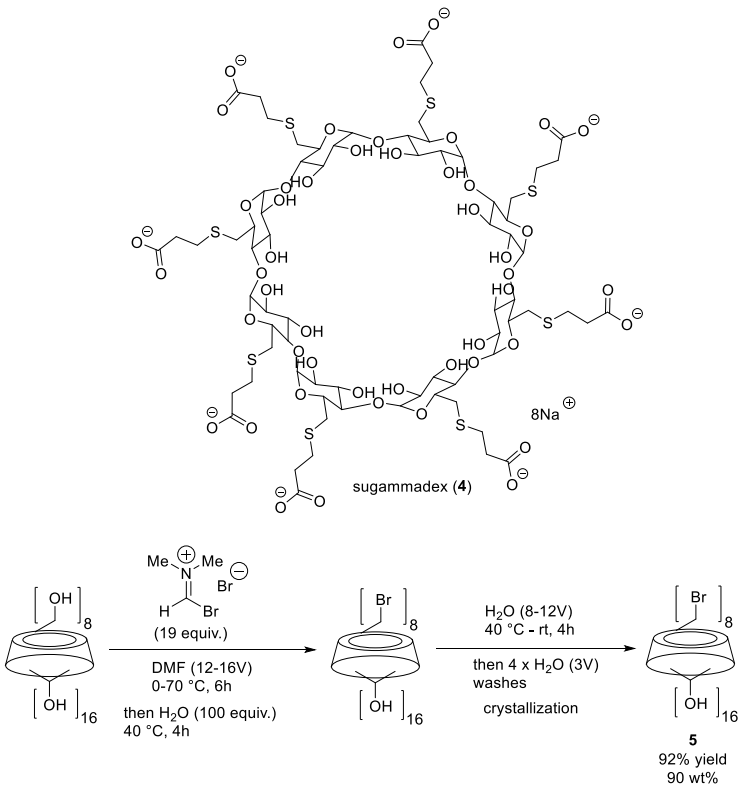



**Scheme 2.** Improved catalyst and reaction conditions for the preparation of Ruzasvir.

### 3.3. Sugammadex

Sugammadex (**4**) is the first selective relaxant binding agent (SRBA), a reversal agent for neuromuscular blockade in general anaesthesia; in layman's terms, this means it helps you wake up faster when you have been anesthetized. Marketed as Bridion®, the mechanism of action is directly linked to its ambiphilic γ-cyclodextrin structure with polar-charged tails that encapsulates rocuronium or vecuronium to remove either agent from the bloodstream. These structural features also serve to present unique synthetic challenges: each reaction needs to occur eight times, meaning that the total yield is equal to the yield of a single functionalization raised to the power of eight! For example, if one reaction has a 99% yield, you would expect the overall yield to equal $(0.99)^8$ or 92% yield. The molecule also has the tendency to irreversibly bind other molecules during synthesis, likewise diminishing reaction yields. As the demand for sugammadex increased, the need for a second-generation manufacturing process emerged. This process required that the team develop an improved two-step synthesis that leveraged a similar manifold as the original approach, with improved performance and safety. In accomplishing these goals, the team delivered a synthesis using an isolated Vilsmeier reagent and featuring an improved quench and crystallization of the octa-bromo intermediate **5**, with both innovations informed by detailed mechanistic experiments (Scheme 3).[14] The success of this work culminated in the 2022 FDA approval of this process, which was recognized by the American Chemical Society as part of a 2023 Heroes of Chemistry Award. In an exciting reflection of the evolution of the demographics of our department, four women played prominent roles in this accomplishment: Jamie McCabe Dunn served as project lead, Nadine Kuhl and Sue Zultanski drove the chemistry, and I was the Director responsible for managing the team where the work was conducted. In a fun confluence of events, three out of four of us were also beneficiaries of sugammadex after surgery in the years since we worked on this project.



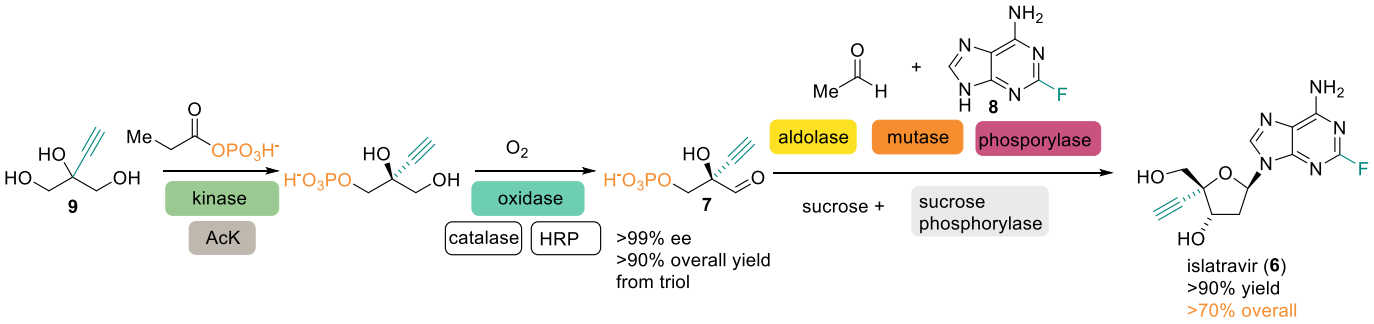

**Scheme 3.** 2nd generation process to prepare sugammadex.

### 3.4. Islatravir

Islatravir (**6**) is a nucleoside reverse-transcriptase translocation inhibitor (NNRTI) used for the treatment of Human Immunodeficiency Virus (HIV). A combination of islatravir and doravirine was recently filed with the U.S. Food and Drug Administration (FDA) as a novel HIV therapeutic. While effective and innovative, the clinical supply route to prepare islatravir required 16 linear steps, including multiple protecting-group manipulations, with an overall yield limited by the 1.8:1 β:α anomeric selectivity.[15] An evaluation of its nucleoside structure suggested that developing an enzymatic approach, which entailed effecting Nature's nucleoside salvage pathway in reverse, would provide an elegant and efficient process to prepare islatravir. To accomplish this goal, Ania Fryszkowska co-led a team that developed a biocatalytic cascade that combined acetaldehyde, a bespoke second aldehyde **7** and the requisite nucleobase **8** to produce the API; this achievement was predicated on incorporating sucrose and sucrose phosphorylase into the system to drive the equilibrium in the forward direction. Not satisfied with this impressive result, the team proceeded to extend this cascade to prepare aldehyde **7** in a 2-step, 5-enzyme from prochiral triol **9** (Scheme 4).[16,17] In a critical extension of this work within the Enabling Technologies team, Sumei Ren demonstrated that the second half of the cascade could also be conducted using $^{14}$C-labelled acetaldehyde to produce $^{14}$C-labelled islatravir; this material was used for a variety of quantitative whole-body autoradiography (QWBA), mass balance, and human absorption, distribution, metabolism, and excretion (hADME) studies, as well as environmental fate (EF) studies. Applying the enzymatic approach enabled a reduction in time cycle to produce $^{14}$C-labelled islatravir from four months to one and in the number of operations from nine to one, while achieving a five-fold increase in radiochemical yield.[18] Our Biocatalysis and Protein Engineering teams have resided in my organization since fall 2018 (after this work started, but before it was completed), and it has been amazing to watch the metamorphosis of this technology. The ability to forge new chemical bonds biocatalytically, especially through enzymatic cascades as exemplified

by the islatravir process, is revolutionizing how we make our molecules, and I feel extremely privileged to have a front-row seat for this transformation.



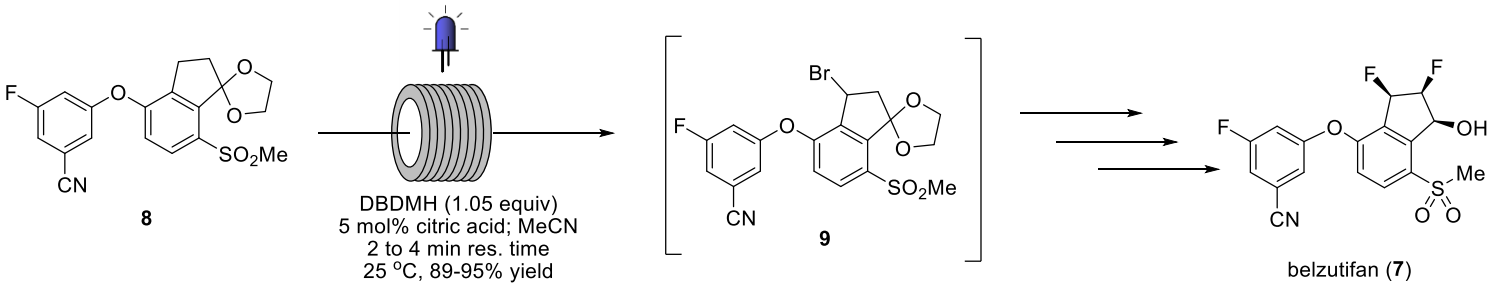

**Scheme 4.** Manufacturing process for islatravir.

### 3.5. Belzutifan

MSD announced the acquisition of Peloton Therapeutics in May 2019 to bolster our oncology pipeline with PT2977, a hypoxia-inducible factor 2α (HIF-2α) inhibitor for the treatment of Von-Hippel Landau (VHL) disease and renal cell carcinoma (RCC). Belzutifan (**7**, WELIREG™) was subsequently approved by the U.S. Food and Drug Administration in August 2021 for the former indication, and in December 2023 for the latter. This molecule has been the wellspring of innovative chemistry, with the women in Process R&D playing a critical role in its advancement.

With only 20 months between acquisition and filing, and a large swath of that time during the Covid-19 pandemic, the team relied heavily upon the existing route to ensure delivering this critical therapeutic to VHL patients. A radical bromination initiated by azobisisobutyronitrile (AIBN) at elevated temperature to functionalize the indane core **8**, emerged as a potential liability when applying the inherited chemistry. In particular, as the scale of process batches increased, the robustness of this step proceeded to decrease. To mitigate this challenge, the team sought to identify an alternative approach to forge this critical C-Br bond. Cecilia Bottecchia and the flow chemistry team leveraged investments the group had been making in photochemistry to demonstrate that a light-mediated bromination was more reproducible than the traditional conditions. Notably, Yining Ji used LED-NMR spectroscopy, which she had helped to develop,[19-20] to show that progression of the reaction could be controlled via a light on-light off experiment (Figure 2).[21] For scaling purposes, the team then developed a photo-flow process to produce the desired bromoindane **9**, with the flow reactor simultaneously enabling light penetration to promote the bromination while subject to illumination, and enabling product stability once the material had passed through the set-up. This first-to-MSD photo-flow process was scaled internally and externally by 'numbering up' to eight units in series to achieve GMP production of ~150 kg/day at >94% average yield and was recognized with the 2021 Peter J. Dunn Award for Green Chemistry & Engineering (Scheme 5).[22] I am very proud of the team's work on this process because the current iteration of our flow-chemistry team emerged during my earlier time as a Director, and the work itself required a three-year prospective investment in photochemical technologies to be ready to deliver on this urgent opportunity.




**Scheme 5.** Photo-flow bromination enroute to belzutifan (**7**).

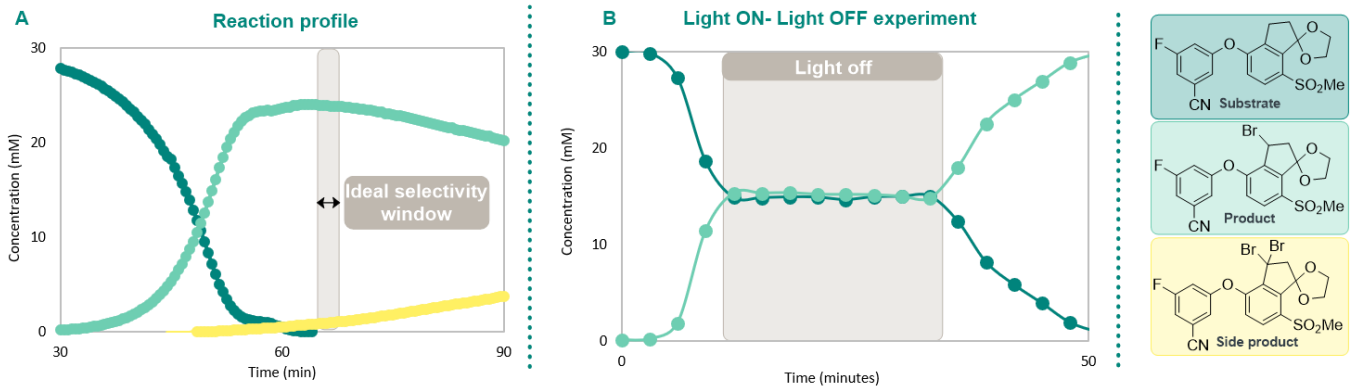
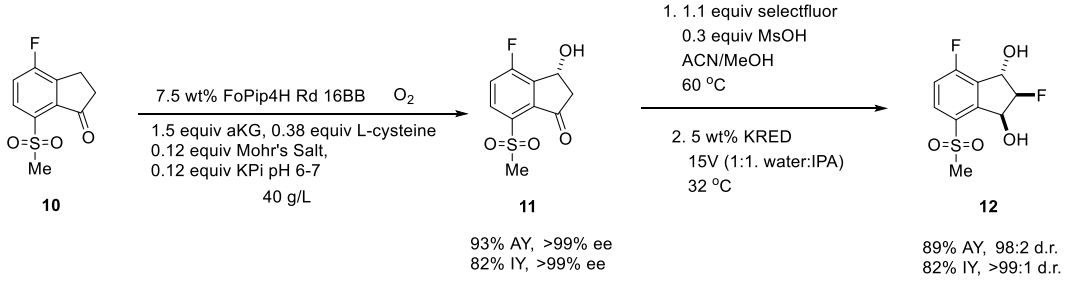



**Figure 2.** Light on-Light off experiment for belzutifan photochemical bromination.

Given the staged approvals for VHL and RCC, a streamlined process to prepare belzutifan in fewer steps was deemed necessary to accommodate the associated increased demand. While the aforementioned photo-flow bromination was impressive, the installed bromine is not part of belzutifan; rather, it is used as part of a four-step sequence to install a chiral alcohol moiety. A more efficient approach would be to conduct a direct asymmetric benzylic oxidation. Unfortunately, methodologies to effect this class of transformation, especially enantioselectively, are scarce. Taking advantage of our expertise in protein engineering and biocatalysis, Wai-Ling Cheung Lee and team identified and evolved a hydroxylase that catalyzed the conversion of indanone **10** to chiral indanone alcohol **11** in >99% ee and 93% assay yield at 7.5 wt % loading. Impressively, this engineering campaign enabled a 100,000-fold increase in enzyme activity and was facilitated by critical enzymology work to understand mechanistic pathways and de-activation scenarios (Scheme 6).[23] To navigate construction of the belzutifan stereotriad, the team developed a fluorination to prepare the intermediate fluoroindanone. Stephanie Chun and Birgit Kosjek then engineered a ketoreductase that operated under high organic solvent conditions to catalyze a dynamic kinetic reduction of the ketone and set two adjacent stereocenters, generating indane **12** in 80-85% isolated yield and high purity.[24] Collectively, these two enzymatic steps are foundational to a streamlined new process to prepare belzutifan that will be implemented for commercial supply. Further, the success of this work was predicated on the diverse capabilities that exist within Enabling Technologies, ranging from biocatalysis and protein engineering to mechanistic expertise and chemical engineering.




**Scheme 6.** Biocatalytic approach to belzutifan.

### 3.6. Digital: Automation, Experimentation and Data Science

The final section of the presentation took a more forward-looking view, focusing less on specific pipeline assets and more on new digital technologies the team is building and already beginning to apply to critical pipeline problems. We view such prospective technology investments as a critical part of our Enabling Technologies mission. An under-appreciated technical problem in process research is the work-up at the end of the reaction. Previously, our department published on the concept of salting-out to obtain clean phase separations.[25] The techniques described have been widely adopted across the field to facilitate this challenging task, as evidenced by the >150K article views to date. To maximize the impact of these findings, Alexandra Sun, Sarah Moor and team sought to develop an automated platform that would allow scientists to rapidly interrogate up to 96 different sets of work-up conditions in a single experiment. The robotic system they pioneered uses a Tecan liquid handler equipped with a TubeEyeX camera to carry out an automated protocol for liquid-liquid extraction (LLE, Figure 3). The sequence of events is: sample preparation > agitation and settling > image capturing and hit identification > organic and aqueous layer sampling > data processing and visualization.[26] The team has now applied this technique to a variety of pipeline problems, with significant value being delivered on understanding workups of biocatalytic processes where denatured protein often presents complex extraction challenges. Notably, this LLE platform was applied to our enzymatic cascade for the formation of molnupiravir (**13**, Scheme 7).[27] Across three screens covering solvents, salts and solvent ratios over 700 sets of conditions, the team identified 100 cases affording a phase split, and only *six* that provided a recovery yield of >70% product. Ultimately, the team employed a mixture of 44% 2-methyltetrahydrofuran/isopropanol in the presence of 60 wt % aqueous ammonium sulfate to recover 90% of the desired product in a single extraction.[26]

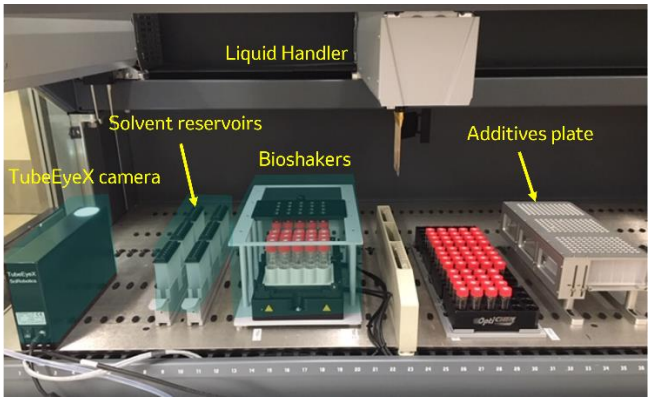
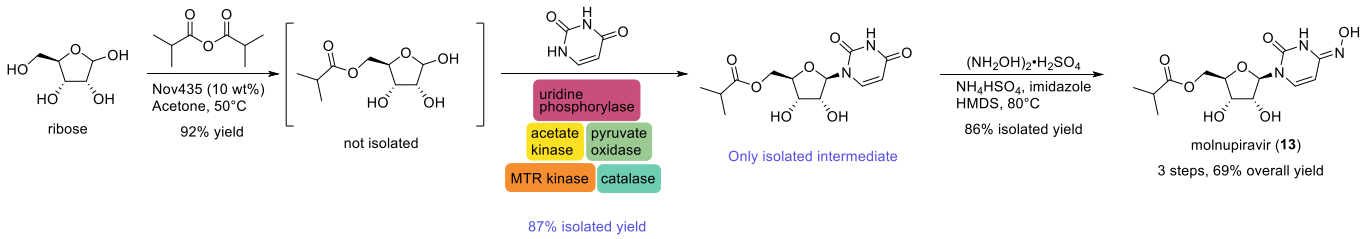


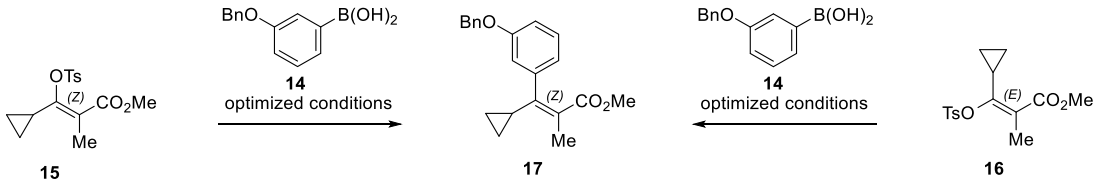

**Figure 3.** Liquid-Liquid Extraction Robotic Platform.




**Scheme 7.** Molnupiravir synthesis.

In a second example of digital transformation, I described the progression of a transformation from High Throughput Experimentation (HTE) to mechanistic investigation using online HPLC to autonomous process optimization. Melodie Christensen, the key player across this continuum, utilized HTE to study the Suzuki coupling of arylboronic acid **14** with either (*Z*)-enol tosylate **15** or (*E*)-enol tosylate **16** to convergently generate the corresponding (*Z*)-tetrasubstituted olefin **17** in support of a high-priority discovery program (Scheme 8).[28] Given this surprising result, it was desirable to obtain kinetic data to help understand where the unexpected isomerization of (*E*)-enol tosylate **15** was occurring. Instability of analytical samples was observed when utilizing automated sampling methods with offline HPLC for kinetic profiling, leading the team to develop a system featuring a Chemspeed liquid handling robot with an online Agilent HPLC. Using the obtained data, the team identified an induction period attributable to pre-catalyst activation, which was overcome with a more efficient method, to access the active catalyst and a five-fold increase in reaction rate.[29] The subsequent step entailed developing an Automated Closed Loop system that incorporated a machine learning algorithm with the previous technology, which was then employed to effect an autonomous process optimization of the Suzuki reaction to achieve a much-improved 2.5:1 *E*:*Z* product selectivity.[30] In another example of the realization of prospective technology investments, these tools are now being heavily leveraged in the group to rapidly discover, optimize and understand novel transformations.




**Scheme 8.** (*Z*)-selective Suzuki coupling.

## 4. Conclusions

There is an obvious conclusion to the talk: women's fingerprints are all over the work – both pipeline and technology - that is being conducted at MSD Process, which represents a seismic shift from only 10 or so years ago. This has not happened by chance but required local and global investments in attracting and retaining women in chemistry. More personally, I concluded with some reflections from my career. Specifically, it is a changing perspective of my own experiences, with this notion having a dual meaning. What started as a desire to develop cool and impactful chemistry has evolved to a passion for developing talent and a desire to get in on the ground floor of how we operate, whether through Diversity & Inclusion, operational improvement or digital

transformation, so simultaneously changing what motivates me but a persistent motivation to drive change. For the audience, the message is to find your own inspiration and pursue it with a level of passion that allows you to continually learn and grow. The outcome will be extremely fulfilling and has the potential to impact the field of chemistry more broadly and even contribute to improving human health.

## Acknowledgements

Thank you to the amazing EWOC community for providing me the forum to assemble and share this personally meaningful content.

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## Author's Biography

**Rebecca T. Ruck** is Associate Vice President, MSD Process Research & Development, where she leads the Enabling Technologies group, an innovation incubator of biologists, chemists, engineers and data scientists. Becky is a leader in women in chemistry efforts externally through the WCC-Merck Research Award and Empowering Women in Organic Chemistry (EWOC) conference and internally through expanded Diversity,

 

Equity & Inclusion accomplishments, such as a series of D&I-themed TED-style talks that have greatly impacted the department's understanding and appreciation of these important topics. She has been recognized with the 2018 ACS Award for Encouraging Women into Careers in the Chemical Sciences and as a 2020 HBA Rising Star and ACS Fellow. She currently holds positions on the ACS Petroleum Research Fund and the MIT Chemistry Visiting Committee and is an Executive Editor at *ACS Catalysis*. Becky graduated *summa cum laude* from Princeton University, obtained her PhD in chemistry from Harvard University in the lab of Prof. Eric Jacobsen and conducted NIH-funded post-doctoral research at the University of California-Berkeley with Prof. Robert Bergman.



 