# Electrocatalytic deprotections of functionalized azetidines enabled by a novel high-throughput electrocatalysis platform

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## 1. Introduction

Nitrogen-containing heterocycles represent a valuable component within the domain of contemporary medicinal chemistry, with a preponderance of FDA-approved small-molecule drugs comprising these motifs.[1] Their prevalence has increased from 59% (1938–2012) to 82% (2013–2023), largely due to the synthetic accessibility of five- and six-membered ring systems.[1,2] Azetidines, saturated, four-membered, nitrogen-containing *N*-heterocycles, are used as a motif in drug design (Figure 1A), but remain underrepresented, despite demonstrating beneficial pharmacokinetics when incorporated in place of larger, unsaturated *N*-heterocycles.[3-5] A mere 4, or 1%, of FDA-approved drugs incorporate an azetidine,[3] reflecting the limited availability of readily installable azetidines required for late-stage diversification. Crucial to addressing this paradigm is the availability of free (NH) azetidine building-blocks.

Recent developments by our group and others have established several reliable methods to construct functionalized azetidines in a direct [2+2]-photocycloaddition between alkenes and imines, known as the aza Paternò–Büchi reaction (Figure 1B).[6-9] Despite these developments, this strategy overwhelmingly relies on the reactivity of imine analogues, such as oximes, hydrazones, and sulfonylimines, resulting in N–X (X = O, S, N) protected azetidines (Figure 1B), respectively.[6,8] Removing the corresponding protecting groups (PG) requires harsh conditions, which are incompatible with most functional groups, and promote undesirable ring opening of the azetidine (Figure 1C), precluding downstream *N*-diversification or installation of these valuable building-blocks.[10] In the past decade of developments in aza Paternò–Büchi reactions, only three reports demonstrate a single example of a chemoselective deprotection to access free azetidines.

Considering the reductive nature of these deprotections, ee hypothesized that, in contrast to stoichiometrics metal reductants, electroreductive conditions could be more appropriately tuned to chemoselectively favor the deprotection of these structures (Figure 1C).[10,11]

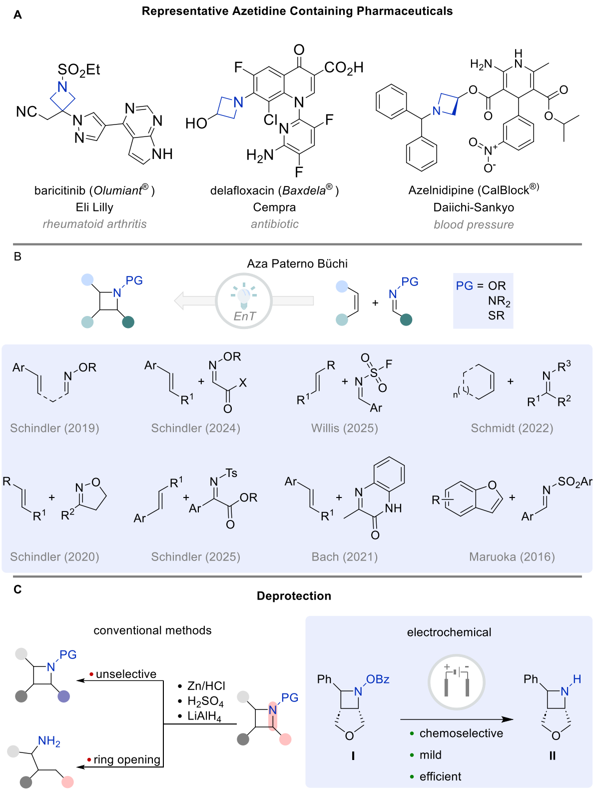

Figure 1: A) Azetidine motif in drug molecules. B) Accessing highly functionalized azetidines through the Aza Paterno Büchi reaction.[6,8,9,12-16] C) Advantage of the new deprotection method over conventional routes.

## 2. Results and Discussion

Recently, in collaboration with Prof. Alan Aspuru-Guzik and the Matter Lab at the University of Toronto, our lab designed an HTE platform that consists of a 40-well miniaturized reaction block featuring a custom printed circuit board providing independent three-electrode connections and interchangeable electrode bundles for each of the 40 reaction wells. The individual wells are independently addressed by a multichannel potentiostat. To take full advantage of this system, we designed a backend software stack that allows us unrestricted and independent access to every channel. We called this backend software package SEVA (Figure 2). Putting the custom-designed 40-well reaction block and SEVA to work together allows for a multidimensional Bayesian optimization (BO) approach where a diverse set of electrochemical parameters can be explored simultaneously on the same plate. This makes each round of the BO extremely data-rich and cuts experimental time needed for the campaign down significantly.

We were excited to test our new system on an electrochemical transformation. Early investigations of the voltammetry profiles of differently protected azetidines formed via an aza Paternò–Büchi reaction revealed a promising redox profile for OBz-protected azetidines, derived from a photoreactive O-Bz oximeFrom compound I (Figure 1C), we achieved a mild electrochemical deprotection in a divided (H-type) cell in 12% yield using Pt electrodes. To optimize these preliminary results, we started a BO-campaing with 6 electrochemical parameters (working electrode material, counter electrode material, electrolyte, electrolyte conzentration, current magnitude and charge cutoff (Figure 2). All parameters were explored simultaneously on a single reaction-plate for each round of the BO. The workflow is shown in Figure 2. Using this iterative workflow, reaction performance progressively improved, and the yield was increased to 70% after only 5 rounds. A central operational achievement of the BO campaign was the transition to an undivided cell system and the replacement of platinum electrodes in favor of inexpensive, readily available materials while maintaining chemoselectivity.

We were able to refine the rection conditions post BO-campaign with screening reaction parameters not used in the original campaign.Under these refined conditions, the yield was increased to up to 96%, representing near-quantitative conversion while maintaining structural integrity of the azetidine core. The robustness of the optimized methodology was further validated through scale translation. Conditions initially developed under HTE (high-throughput experimentation) were successfully transferred to a conventional laboratory batch setup. In batch mode, the reaction consistently delivered >90% yield, confirming that the transformation is operationally stable and not restricted to microscale or screening environments – a common concern with heterogeneous catalysis.

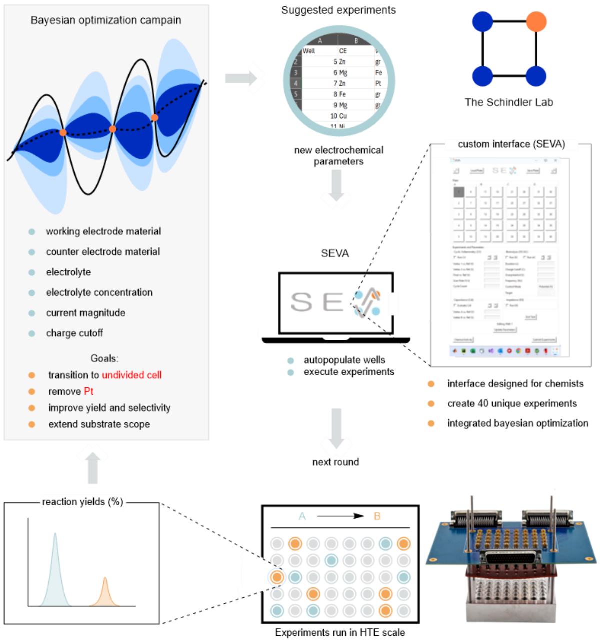

Figure 2: A) Parameters and workflow used for the Bayesian optimization. SEVA is a custom-designed software that enables per-well control and automated data acquisition. Custom-designed 40-well miniaturized reaction block in the bottom right corner.

In summary, this project has delivered a mechanistically informed and data-optimized electrochemical deprotection strategy for azetidines formed via the aza Paternò–Büchi reaction. The principal achievements to date include: (i) identification of selective N–O bond cleavage without ring degradation; (ii) iterative yield improvement from2% to 96% through an integrated BO workflow; (iii) elimination of platinum via transition to an undivided cell using zinc and graphite electrodes; (iv) transition from HTE to batch-scale performance (>90% yield). Together, these results remove a critical synthetic barrier in azetidine chemistry and provide a practical foundation for expanding the chemical space of strained nitrogen heterocycles in medicinal chemistry and electroorganic synthesis.

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