Young Career Focus: Dr. Anat Milo (Ben-Gurion University, Israel)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Anat Milo (Ben-Gurion University, Israel).

Biographical Sketch

Dr. A. Milo

Anat Milo received her B.Sc./B.A. in Chemistry and Humanities from the Hebrew University of Jerusalem (Israel) in 2001, M.Sc. from UPMC Paris (France) in 2004 with Berhold Hasenknopf, and Ph.D. from the Weizmann Institute of Science (Israel) in 2011 with Ronny Neumann. Her postdoctoral studies at the University of Utah (USA) with Matthew Sigman focused on developing physical organic descriptors and data analysis approaches for chemical reactions. In October 2015, she returned to Israel and joined the Department of Chemistry at Ben-Gurion University, where her research group develops experimental, statistical, and computational strategies for identifying molecular design principles in catalysis with a particular focus on stabilizing and intercepting reactive intermediates by second-sphere interactions.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. A. Milo My research group integrates experimental, computational, and statistical methods to design and construct modular catalyst libraries and provide strategies for discovering and optimizing selective catalytic reactions. We also develop physical-organic analysis methods for exposing structure–activity and structure–selectivity relationships within reaction manifolds. These methods entail: (1) obtaining reaction outputs, such as rate, enantio-, regio-, or chemoselectivity of experimental libraries; (2) correlating the reaction outputs with molecular descriptors of different reaction components (catalyst, substrate, directing group, solvent) for the concurrent interrogation of mechanistic hypotheses and optimization of catalytic processes; and (3) combining advanced data visualization, multidimensional mathematical modelling, and computational chemistry in order to reveal trends within complex datasets. This strategy serves to predict reaction outcomes, advance mechanistic understanding, and accelerate the development of new efficient catalytic systems. Predicting *a priori* which catalyst structure would be optimal for a given reaction remains the Holy Grail in the field of catalyst design, particularly in complex catalytic systems involving multiple components. By preparing catalyst libraries that provide access to focused yet diverse experimental datasets and synergistically combining statistical and computational methods to study these datasets, our approach aims to uncover general design principles for catalyst design.

SYNFORM *When did you get interested in synthesis?*

Dr. A. Milo My interest in synthesis was ignited during my M.Sc., mentored by Prof. Berni Hasenknopf at Pierre and Marie Curie University (UPMC, Paris 6). Our aim was to tether an

 Synform **2021/04**, A58–A61 • Published online: March 18, 2021 • DOI: 10.1055/s-0039-1691249

organic moiety to an inorganic polyoxometalate cluster and at the end of my M.Sc., after a multistep synthesis, I only had a few milligrams of product. Looking back, I was not a proficient synthetic chemist to say the least, but I did realize the value of being able to prepare your own objects of study. As a result, during my Ph.D. studies, I spent an extensive amount of time honing my synthetic skills. I was lucky enough to have been trained by an extremely talented senior Ph.D. student, Maxym Vasylyev, who taught me how to plan reactions, dry solvents, use a Schlenk line, and generally, how to think like a synthetic chemist.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Dr. A. Milo Our society, and with it the chemical industry, has always been defined by two orthogonal developments, communication and automation. Both will gain more traction in my opinion due to the world pandemic we are living through, as we witness the advantages provided by modern communication and automation of work processes. We now also have the means to automate many of the tasks that were once reserved for highly skilled synthetic chemists, such as reaction design, conditions screening, reaction optimization, product purification, etc. This has, on the one hand, democratized the discovery process and made it easier to access starting materials and drug leads, which can then also be automatically tested in biological assays. On the other hand, it may seem that these advancements have stripped synthetic chemists of their traditional roles. This observation may be true to some extent, however, as I see it, merely preparing compounds is not our calling as chemists. Our role was and remains the invention of new more efficient, sustainable processes, and we now have more means at our disposal to do so at an increased pace.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. A. Milo My group's main research focus currently is establishing a straightforward and systematic strategy for modifying organocatalyst structures in the reaction vessel by combining highly modular catalytic systems with mathematical modelling techniques to facilitate the discovery and prediction of secondary-sphere design principles.[1–4] This methodology provides a tunable handle for the nuanced recognition of substrates by their geometry and electronic properties, thus enabling the discovery and optimization of organocatalytic systems. Traditionally, optimizing the reactivity and selectivity of catalytic reactions is accomplished by modifying reaction conditions and catalyst structures in a rational and incremental manner. For example, the classical strategy for optimizing selectivity is founded on steric biasing by installing units that impart repulsion and leave only one of the quadrants of the catalyst available for an approaching substrate.[5–8] Nonetheless, the application of non-covalent interactions has been gaining traction in recent years because they offer a powerful handle for controlling reactivity and selectivity through transition-state stabilization rather than destabilization of undesired pathways.[9–18] Although these interactions are considered weak, their influence at a distance, through networks of interacting molecular units, such as those comprising the secondary sphere, cannot be overstated.[16,19,20] The significant advantage of our approach stems from the development of mathematical models to predict optimal secondary-sphere modifiers for diverse organocatalyst and substrate classes. Curation and systematic analysis of these models serve to construct a conceptual framework for the rational design and fruitful incorporation of orthogonal secondary-sphere modifiers into countless organocatalytic systems. The modularity and predictability of these organocatalyst libraries make them easily adaptable to new substrates and reactions without the need for an elaborate synthetic effort. Ultimately, this research program aims to transform organocatalyst development by providing a highly modular platform for their design, preparation, mechanistic elucidation, optimization, and performance prediction.

SYNFORM *What is your most important scientific achievement to date and why?*

Dr. A. Milo Our group has provided a proof-of-concept for the ability of secondary-sphere modifiers to provide a handle for the optimization of organocatalytic reactions.[4] The secondary-coordination sphere was first described more than a century ago in the context of organometallic complexes as groups that are not directly bonded to a metal, but are coordinated to its ligands.[21,22] This definition has since been expanded to any moiety in the molecular microenvironment of coordination compounds that influences the orientation and electronic properties of their ligands by introducing non-covalent interactions, such as hydrogen bonding, electrostatic forces, and hydrophobic effects.[23–25] Although it is now well established that such interactions have a fundamental effect on reactivity and selectivity in enzymatic catalysis,[26–28] metal-mediated processes and transition-metal chemistry,[23–25,29–33] there is a scarcity of studies explicitly incorporating secondary-sphere modifiers into organocatalytic systems. We

  • Published online: March 18, 2021 • DOI: 10.1055/s-0039-1691249

define the secondary sphere in the context of organocatalysis as moieties that are not covalently bonded to an active site, yet are located in proximity to it, and are closely involved in its mechanism of action through dynamic or non-covalent interactions. These interactions control the geometry and electronic properties of the reaction intermediates and transition state(s). Our proof-of-concept of this approach was focused on dynamic-covalent binding between boronic acids (BAs) and catalysts with available hydroxy groups (see Figure 1). The binding mode of the modifier was orthogonal to catalytic activity, avoiding catalyst inhibition. Likewise, the modifier was located in close proximity to the active site and possessed the capacity for dynamic and non-covalent interactions that guided reactivity and selectivity.

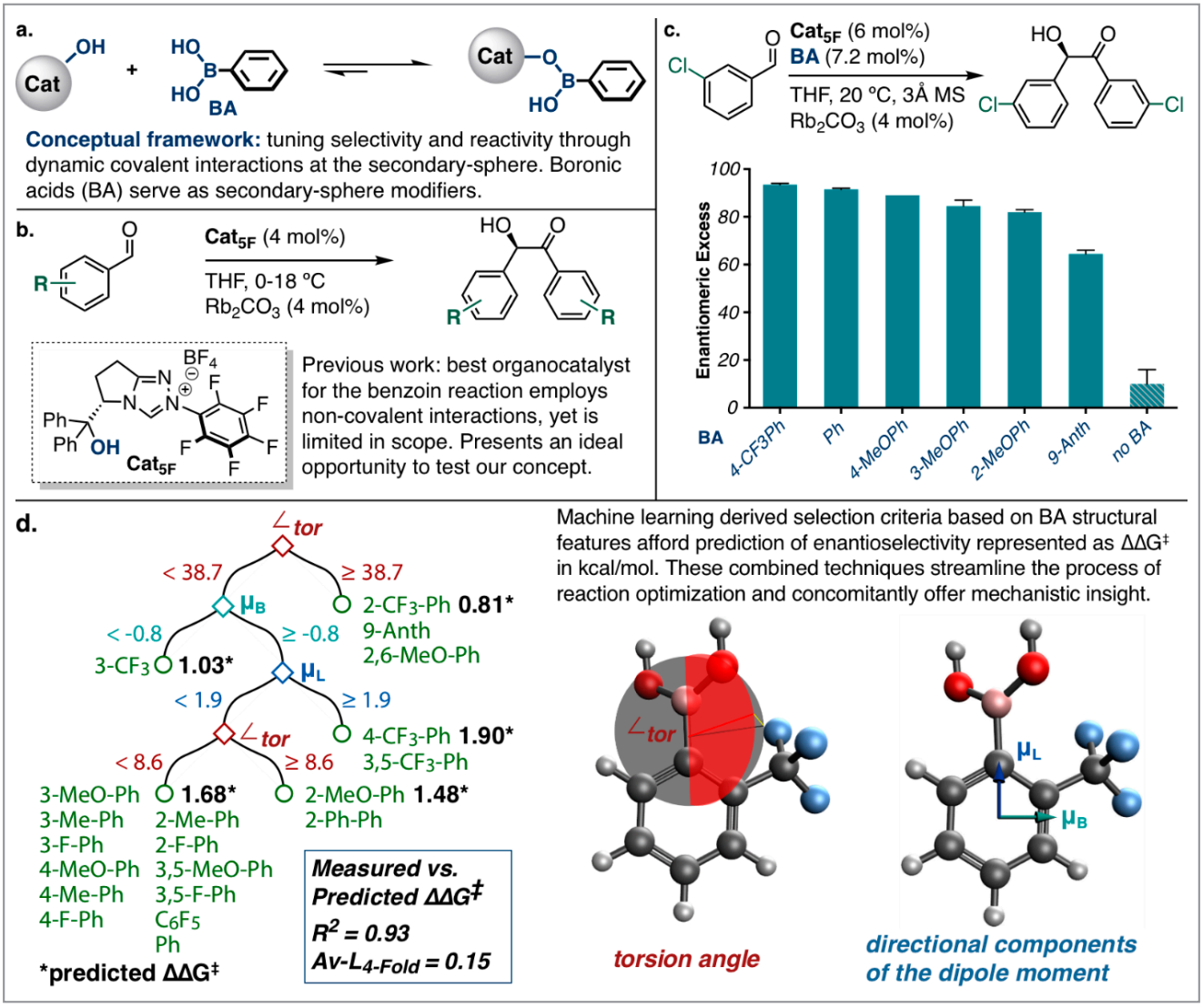

Figure 1 (**a**) Modifying catalyst structures in the reaction vessel by forming dynamic boronic ester bonds *in situ* under catalytically relevant conditions. (**b**) Catalytic system developed by Zeitler and Connon containing a hydroxy group that is involved in enantioselectivity-controlling non-covalent interactions.[34] (**c**) Comparison of the enantioselectivity obtained in the benzoin condensation using several BA modifiers with a challenging model substrate containing an electron-withdrawing group, 3-chlorobenzaldehyde. (**d**) Mathematical model for reactions with 3-chlorobenzaldehyde as substrate and different BAs: decision tree based on the mean standard error decrease at each node provides a prediction of enantioselectivity. Goodness-of-fit represented by R^2 and the average L (predictive loss) value of a 4-fold validation performed 500 times on randomized sets.

 Synform **2021/04**, A58–A61 • Published online: March 18, 2021 • DOI: 10.1055/s-0039-1691249

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