A Platinum Open Access Journal for Organic Chemistry

Account

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (6) 202412331

Photochemistry and structural complexity

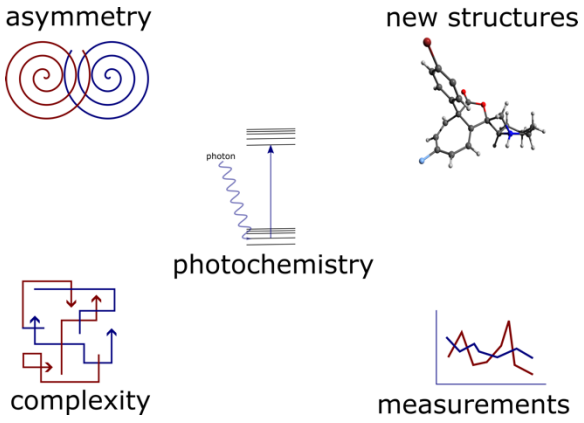
Zarko Boskovic

Department of Medicinal Chemistry, University of Kansas, 1567 Irving Hill Road, Lawrence, KS 66045, United States of America
Email: zarko@ku.edu; photochemistry@ku.edu

Received 11-23-2024 **Accepted** 01-07-2025 **Published on line** 02-19-2025

Abstract

This is an account of my views on the relationship between structural complexity and photochemistry of small organic molecules. Exploration of the benefits of photochemical reactions for efficiently accessing novel structures has shaped my research interest over the past decade. Operating within the build-couple-pair paradigm, high energy intermediates obtained through the absorption of a photon are especially useful in the pairing phase. They enable intramolecular cyclizations that often significantly increase structural complexity and rigidify the saturated carbon frameworks. Computing complexity of a molecule is easy, but developing new reactions is difficult. So, most of my lab's day-to-day work is dedicated to solving synthetic problems. We think that measuring structural complexity can productively direct our synthetic efforts by focusing attention on transformations that increase it significantly and quickly. We hope that structures which are the product of such efforts can also reveal something new, primarily in the context of bioactive molecules.



Keywords: Photochemistry, structural complexity, stereochemistry

Table of Contents

1. Introduction

Kansas is the eighth sunniest state in the US. (Florida, the Sunshine state, is ranked 10.)[1] One day we measured 0.5 mmol/(sec×m^2) of photons reaching our Hatchard-Parker actinometer.[2] To do photochemistry in a place where sunshine is plentiful was also obvious to Giacommo Ciamician, who pioneered converting the energy of photons into chemical bonds in the early 20th century in sunny (or so I imagine) Bologna, Italy.[3] Today, as we are pondering renewable sources of energy for a sustainable future of our species, we are again turning towards the Sun as the ultimate source of renewable energy for the foreseeable future, because wind and hydro both depend on the Sun.

Another quirk of doing photochemistry in Kansas is that our state flower is the sunflower, a heliotrope that turns its oil-heavy seed-head in sync with the Sun. Figure 1 shows my research group over the years (2020, 2023, and 2024) in a field of sunflowers near Lawrence, KS. Those pictured are the ones who did the work: most of all Manvendra Singh, now at Arena BioWorks in Cambridge; Zach Pearson contributed to multiple projects as a coding chemist; Bryce Gaskins, a very talented and motivated undergrad now a PhD student at Caltech in Stoltz group, pioneered some S_8-mediated photo-ozonolysis; Victor Fadare, and Mauricio Bahena Garcia are now in the group and exploring enantioselectivity in photochemistry.

Unlike most photochemists who spend at least their PhD years learning the intricacies of the field, I came to photochemistry late, during my postdoctoral training in Stuart Schreiber's lab at the Broad Institute of MIT and Harvard. Armed with what I could grasp from "Turro" and "Calvert and Pitts," I crossed the Charles River to Boston University where Aaron Beeler[4] and his group members showed me how to set up my first photochemical reactions. We still use his setup for photochemistry in flow.[5] Oliver Kappe told me at a Gordon Research Conference that flow is the right way to do photochemistry. I agree, but he may be biased.[6,7]

The Broad Institute at that time was heavily devoted to screening small molecules in various sophisticated assays that would reveal their biological activity. My interest in tapping the potential of excited state reactivity was piqued when I learned about the problems associated with increasing percentages of "flat" molecules populating screening decks in large and small pharmaceutical companies.[8] The origin of the problem is in the fact that chemists became really good at connecting sp^2-hybridized atoms together by using transition metal-catalyzed aryl-aryl or amide coupling.[9] Unfortunately, these compounds are often too crystalline, tend to aggregate in solution,[10] and sometimes fluoresce on their own and confuse the screening measurements which often rely on fluorescent readouts.[11]

Figure 1. The group in the field of sunflowers over the ages. 2020 : Zach Pearson, Sri Kolluru, Vishva Shah, Manvendra Singh, ZB, Amar Kumar, Cybelle Areye, Bryce Gaskins ; 2023 : Mauricio Bahena Garcia, Elizabeth Miller, Victor Fadare, ZB, Manvendra ; 2024 standing: Mauricio, Victor, Ian Shire, ZB ; kneeling : Zhe Wang, Alhamza Hamza.

In view of these considerations, I reasoned that if we need to "escape from flatland,"[8] as the phrase went, why not take advantage of the absorption characteristics of such flat and often aromatic molecules, and transform them photochemically into non-flat molecules that are still rigid, but with lots of interlocked sp^3 carbons and nitrogens? Can photochemistry help us turn the abundance of sp^2 carbons into stereogenic centers, and make polycyclic fused, spiro, bridged structures, thus rigidifying them in a distinctly non-2-dimensional way?

While at the Broad, I secured internal funding for what I called a "build-couple-glare" project, and in tandem with two amazing Harvard graduate students, Bruce Hua and Chris Gerry, we started shining light on molecules.[12] This approach fit well with the "NextGen chemistry" zeitgeist at the Institute at that time. Schreiber and coworkers at the Broad, and also at KU, funded by the NIH CMLD program, have been designing synthetic pathways towards small organic molecules that are rich in stereocenters for over a decade. As the next logical steps in the evolution of the Science of Therapeutics and diversity-oriented synthesis several new approaches were evaluated. Fate would have it that I escaped the molecular flatland by finding a faculty position in one of the flatter states, at least by reputation (again, Florida is flatter than Kansas).[13]

2. Structural Complexity

Earlier in my training, I saw compounds as a goal, something to be prepared. Now I see chemical structures as encoding information.[14] Asymmetry in a molecule leads to the possibility of isomers. With *N* elements of asymmetry, each one allowing for two distinct spatial arrangements, there can be as many as 2^N stereoisomeric structures.[15] A tremendous diversity of shapes emerges from this simple combinatorics. For instance, in 6-carbon monosaccharides (hexoses) four points of asymmetry (stereogenic carbons) can generate sixteen stereoisomers (excluding diastereomeric hemiacetals). Each of these stereoisomers has a unique structure, and as a result, it interacts with biological systems in distinct ways.[16] This diversity of non-flat structures, within the confines of isomeric chemical compositions, enables a corresponding diversity of biological activities and behaviors, leading to a greater combinatorial space of possible outcomes. This is very life-like!

It has become common to refer to the set of all conceivable chemical structures as the "chemical space." The size of this set is mind-bogglingly large even when limits on the number of atoms are imposed.[17,18] But is it really a space? In mathematics, a space requires that an internal structure exist between the objects that comprise it. It can be remarked that because chemical structures are discrete objects, it is not possible to interpolate between them (what is between an ethyl group and a methyl group?) and the framework connecting various chemical compounds is not known. It may be more difficult to navigate a set than a space, but it seems evident that this set is "denser" in regions where isomers are possible, i.e., there is only one toluene, but there are three xylenes. This possibility of isomers is measured by structural complexity of molecules.

In this paper, I will use a measure of structural complexity developed by Böttcher in 2016.[19] This measure can be thought of as a mapping between a chemical structure and a real number line. The mapping is achieved by computing five numbers for each heavy atom in the molecule, multiplying those numbers either directly or as their logarithms, and adding the products for all the atoms, making sure to subtract the symmetry equivalent contributions. This approach is rooted in information theory and is distinct from the graph-based approaches in which unique sub-graphs of a molecular graph are counted.[20] Sarpong has recently compiled and contextualized a useful overview of various methods for computing structural complexity.[21]

To make computation of these indices more facile, my group (Zach Pearson, in particular) developed our own Python programing language-based implementation, using RDKit functions,[22] for calculating them in practice (https://github.com/boskovicgroup/bottchercomplexity), but we struggled to properly account for several edge cases. Shortly after, the Forli lab developed a convenient web-based app for computing the index by simply pasting the SMILES string (https://forlilab.org/services/bottcher/). I will use the numbers computed through the Forli lab web app in the remainder of this article. Since that time, however, my group has associated with each one of our papers a GitHub page ("git commit, git push") containing all the NMR assignments in the structured data format, the code for analyzing the data and generating the figures, and the computational log files, etc. I believe this is how we can make research more reproducible.

The **build-couple-pair** formalism (Figure 2) systematizes a nature's approach for efficiently exploring the chemical space through biosynthesis.[23] It can be illustrated on the example of biosynthesis of terpenoids. In the *build* phase, dimethylallyl alcohol **1** (activated as a pyrophosphate) and isopentenyl alcohol are synthesized. These building blocks have relatively low structural complexity[19,24] and can exist as either two or one isomers, respectively. The *coupling* phase involves connecting these building blocks into a linear trimer **2**. The complexity of the trimer is proportional to the complexity of the monomer: the trimer is approximately three times more complex than the monomer. In terms borrowed from fractal research,[25] the trimer is "self-

similar" to the monomer, meaning that its structure contains little new chemical information compared to the monomer. Strikingly, it is in the ***pairing*** phase, specifically through intramolecular cyclization reactions, when complexity jumps abruptly. In the example provided, the isomerization (i.e., a reaction in which no new atoms are added to the structure) of **2** converts three double bonds into three rings, resulting in the creation of five stereocenters in **3**. This transformation significantly increases the complexity index, the structure becomes more rigid, and nearly every proton in the NMR spectrum becomes distinct.

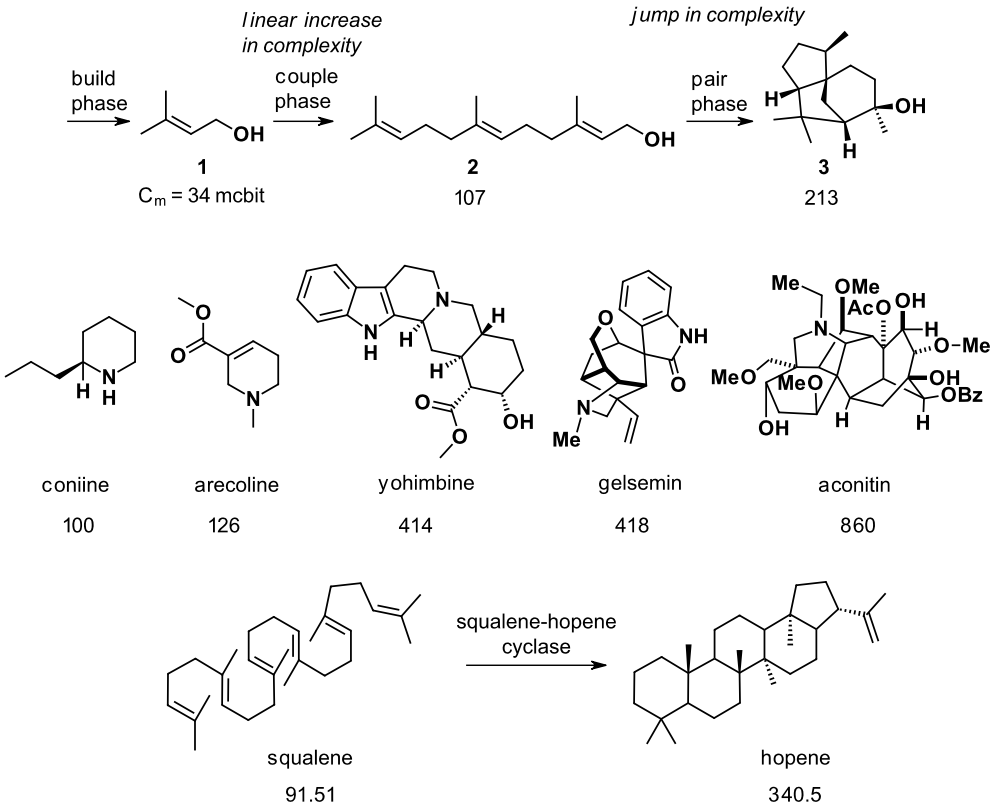


Figure 2. Build-couple-pair : Example from sesquiterpene biosynthesis ; Structures of several alkaloids ; Cyclization of squalene to hopene.

Several structures of naturally occurring alkaloids also nicely illustrate the range of complexities achieved through biosynthetic reactions and point again to the stereocenter content within small molecular frameworks (high information density)[24] as representative of nature's way of exploring chemical space. I hope that someday "chemical archeology" will reveal to us how aconitin evolved.

3. Photochemistry

Photochemistry is concerned with the reactivity of excited states.[26,27] Instead of using heat or highly energetic (and often non-selective) reagents to promote thermodynamically unfavorable reactions, as is typically done in ground state chemistry, substrates are provided with excess energy through the absorption of a photon. Desirable products with strained rings or high levels of steric congestion are often thermodynamically "downhill" from such highly energetic excited states. The price to pay is often a decrease in selectivity. Indeed, the field of synthetic organic chemistry is still learning how to exert control over these states and derive maximal synthetic benefit from them.[28]

When a molecule is photoexcited, the behavior of its functional groups can be altered, which is manifested as a change in their reactivity. For example, a normally electrophilic carbon in a carbonyl group becomes more carbanion-like, while a typically Lewis basic oxygen becomes highly electrophilic.[29]

I will now discuss several examples of synthetic sequences in which photochemistry played a central role in increasing structural complexity of the final products, and which inspired the work in my lab.

The photochemistry of alkylpyridinium salts, like **4** (Figure 3), was first disclosed by Kaplan,[30] and then developed by Mariano into a number of useful synthetic methods for accessing stereotriads on cyclopentenes.[31] When **4** is irradiated in wet acetonitrile, product **5** is obtained in a single synthetic step,[32] in a sequence that can be named {Kaplan-Mariano}–{Ritter} to facilitate its identification. Excited state of **4** rearranges to cyclopentenyl cation-fused aziridine ***A*** whose positive charge attracts nucleophilic acetonitrile to give rise to nitrilium ***B***. Finally, small amounts of water in the solvent add to the nitrilium and upon deprotonation give ***C***, which cyclizes by opening the vinyl aziridine to give **5**.

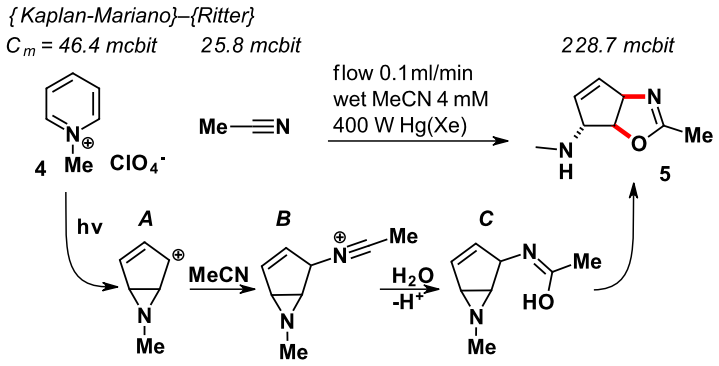


Figure 3. From flat pyridines to bicyclic stereotriads via cyclopentenyl cation-fused aziridine.

Notably, the complexity of **5**, with three contiguous stereocenters, two heteroatoms, and a *cis* double bond, is about three times higher than the combined complexities of its precursors (i.e., **4**, acetonitrile and water). Its rigid structure, with three hydrogen bond acceptors and one donor, and low lipophilicity made it appealing from the standpoint of chiral fragments synthesis[33] where the goal was to create diverse, but small organic molecules with an abundance of stereocenters and use them in binding experiments against proteins of interest, either through saturation transfer difference NMR or soaking with protein crystals and examining x-ray diffraction.

A similar {Kaplan-Mariano} vinyl aziridine generated from **6** in methanol (Figure 4) can be converted *in situ* to cyclopentene-fused imidazolidinones **7** with catalytic palladium and arylisocyanates.[34] Here, methanol traps the cation, and Pd readily inserts into the vinyl aziridine. For similar reasons as for **5**, the product here has about 2-3 times higher complexity than the precursors. Diastereoselective formation of the aziridine, and stereospecific addition of one of C-N bonds of aziridine over the π system of the isocyanate is an attractive feature of this sequence of transformations. Trost has shown that chiral ligands on Pd lead to enantioenriched products of the opening of acyclic vinyl aziridines with arylisocyanates,[35] suggesting further studies on this appealing sequence are warranted.

Moreover, from the vantage point of bioactivity of such rigid yet saturated structures, compound **7** (aka BRD3975) is being explored as an enantiospecific inhibitor of sulfide-quinone oxidoreductase (SQOR) enzyme, after initial screening revealed its ability to shrink a tumor organoid model of pancreatic cancer.[34]

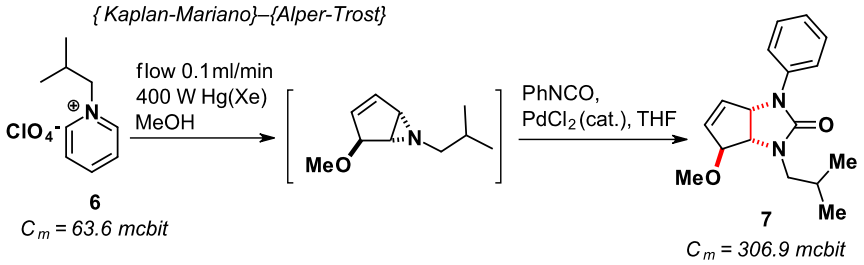


Figure 4. Allylic aziridines are efficiently prepared through photochemistry; Palladium reliably catalyzes insertion of one of the C-N bonds into isocyanates.

While examples with **4** and **6** relied on exceedingly simple starting materials, Kutateladze has developed a photochemical transformation that requires a slightly more complex "coupling phase" product **8** (Figure 5) as the photochemical substrate.[36] The payoff is the concurrent formation, in compound **9**, of two new C-C bonds, two new C-N bonds, and two new O-H groups, generating six new stereocenters and four new rings in a single step. This is achieved by converting two unsaturations from the furan ring and two from the activated carbonyls into the new rings, thus displaying a level of cascade reactivity and concomitant stereogenicity rivaling the polycyclization of squalene to hopene (Nature still wins, Figure 2).[37]

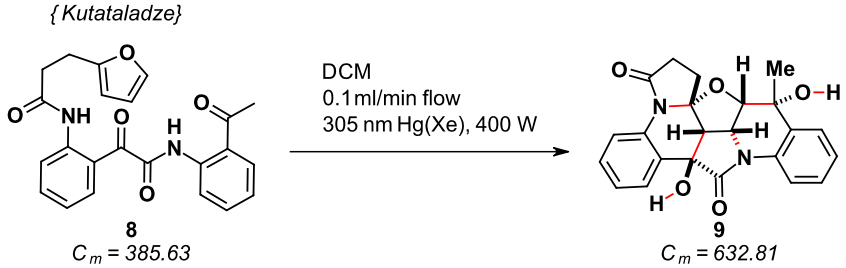


Figure 5. Furans act as remarkable rigidifying elements.

4. Towards more elaborate photo-synthetic schemes

We also explored products of arylpyrrolinium irradiation as substrates for further structural diversification.[38] Irradiation of **10** leads to the formation of two chromatographically separable isomers **11** and dihydrosemibullvalene **12**, a product of *meta* cycloaddition. The complexity of these products is about double that of their flat sp^2-rich precursors and is primarily due to the formation of two new stereocenters. Notably, **11** and **12** are structurally very distinct, having Tanimoto similarity of 0.167. This underscores the notion that, in addition to complexity, photochemistry can be a useful tool for accessing structurally diverse products, as well.

Similar to the use of vinyl aziridine described above for the subsequent transformation, the photochemically generated amine can be used as a nucleophile together with a cis amide for the *N,N*-acetalization of an aromatic aldehyde as in **13**. Selective functionalization of the aromatic portion of **10** necessitated using newly-developed thiantrenation chemistry[39,40] to install a thiantrenyl "pseudo-halide" for Pd-catalyzed Suzuki and Sonogashira reactions to arrive at **14**. Overall, by applying this strategy, we synthesized a collection of 27 related molecules whose biological activity we profiled using the cell painting technique.[41–43]

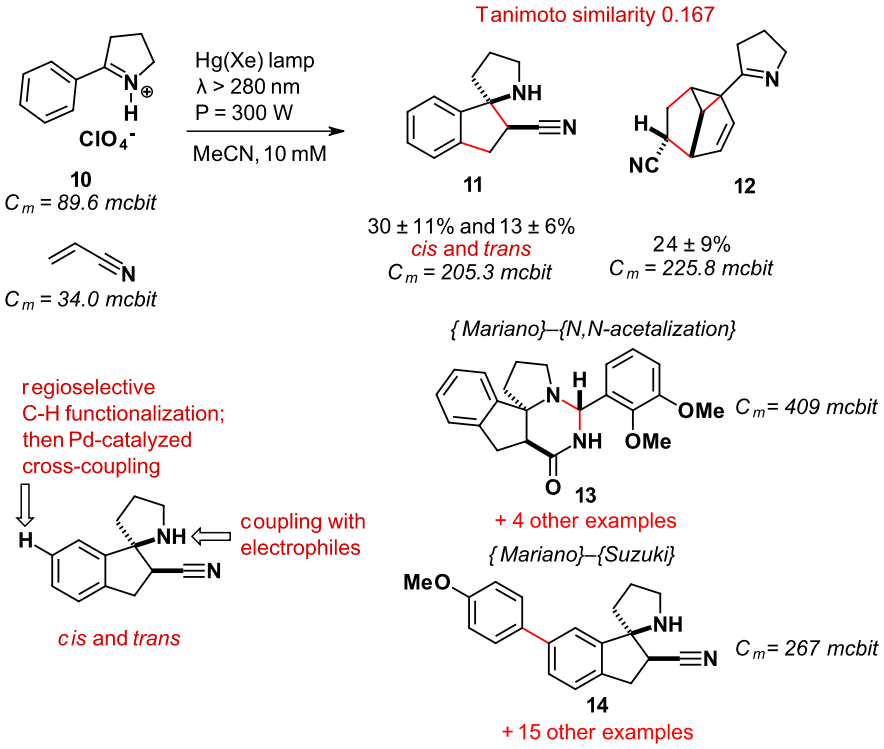


Figure 6 Synthesizing a collection of spiroindane pyrrolidines through phenylpyrrolinium photochemical coupling with electron-defficient olefins. Subsequent transformations include selective C-H thiantrenation, followed by Pd-catalyzed couplings, or N acylations.

Cell painting is a technique pioneered by Anne Carpenter at the Broad. It can be used in many contexts to reveal changes in cell morphology as a reporter on different perturbations. For small molecules, the cells, usually osteosarcoma U2OS, are treated for 24 hours, and then six organelle- or sub-cellular structure-specific dyes are added, cells are fixed and automated fluorescent microscope is used to capture images of cells. The key is in the analysis of these image. CellProfiler is a program that allows relatively straightforward extraction of numerical data from such images. When the analysis is done, each treatment (i.e., a compound at a given concentration) can be associated with a numerical vector of around one to two thousand components. These vectors can then be compared to those produced by known bioactive compounds, with the underlying assumption that compounds with similar mechanisms of action would produce similar morphological changes in cells.

In our hands, preliminary data suggests that **14** induces unique and reproducible changes in cell morphology, while its trans diastereomer does not. This finding may hint towards a selective interaction with a biological target (or targets) whose identity is still unknown. A path is clear for synthesizing a suitable probe for a proteomic experiment which may provide an answer to this important question.

Surprises abound in photochemistry, which is why, I suspect, many are drawn to the field. When we attempted a similar photochemical reaction on an analog of **10** containing an electron-donating group at the para-position (Figure 7), we unexpectedly obtained a product **16** in which the two fragments of **15** added in a 1,2-fashion to the electron-poor double bond of acrylonitrile.[44] This reaction is reminiscent of a De Mayo reaction[45] and likely proceeds through the intermediacy of an intramolecular charge-transfer state ***A*** (Figure 7).[46] The electrons residing in HOMO of the excited state, which is the iminium π* orbital, add in a conjugate addition sense to the electron-poor olefins producing ***B***. On return to the ground state electrons reorganize

and attempt radical recombination as in ***C***. This would lead to highly strained system, and instead, the electrons from nitrogen assist in cleaving the sigma bond and rearomatize the molecule.

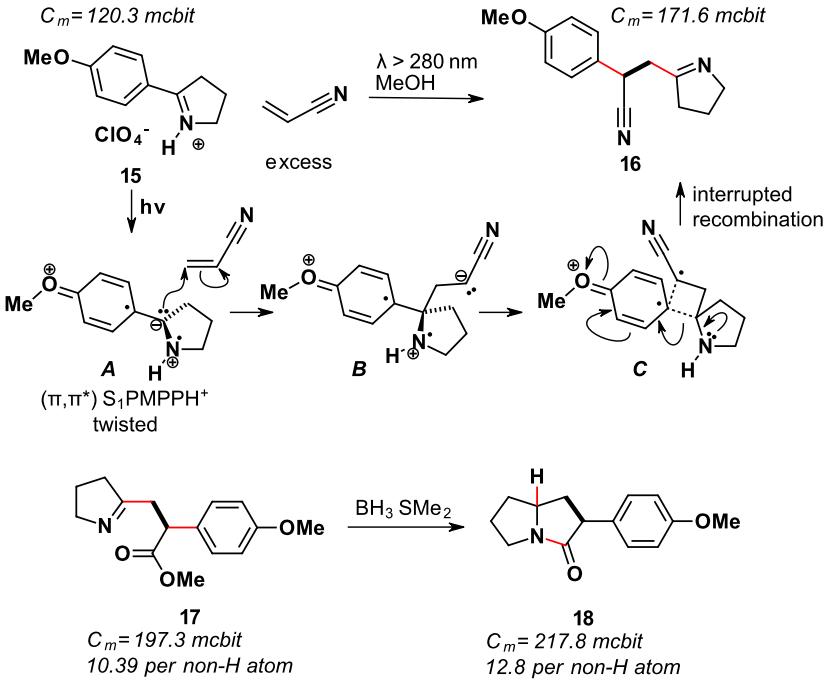


Figure 7. Fragmentative addition of TICT over an olefin. Photochemical pathways can be sensitive to small structural changes in reactants. Introduction of electron-donating substitutent into phenyl pyrrolinium salts enabled access to pyrrolizidines, following reductive cyclization.

The complexity increase here is only modest, about 40%. If ester is used as an electron-withdrawing group on the olefin, reductive lactamization on **17** can furnish 5-5 fused pyrolizidones like **18**, with virtually no diastereoselectivity. Parallel to an overall complexity of the molecule, it may be worthwhile to compute complexity relative to the number of non-hydrogen atoms. With such a metric, transformation of **17** to **18** increases this relative complexity by about 30%.

We explored similar strategy by developing the {aza-Yang}–{Buchner} synthetic sequence (Figure 8) in which three simple starting materials (acetophenones **19**, piperidines **20**, and arylacetic acids **21**) are converted to products like **25** which contain 4, 5, 6, and 7-membered rings, three stereocenters including an all-carbon quaternary one, an azetidine ring and a gamma-lactone.[47] The complexity of the product is about 2 times higher than the sum of complexities of the starting materials.

The key reaction we developed for realizing this sequence is the isomerization of phenacyl piperidine **22** into azetidinol **23**. This aza-Yang reaction was enabled by protonating the tertiary amine in **22** with sulfonic acids. It proceeds through the intermediacy of ***A*** (Figure 8) which is an n,π* triplet formed after electrophilic carbonyl O of the excited state abstracts the γ hydrogen. Diastereoselectivity of the reaction is high because the N-H-O salt bridge rigidifies the structure.

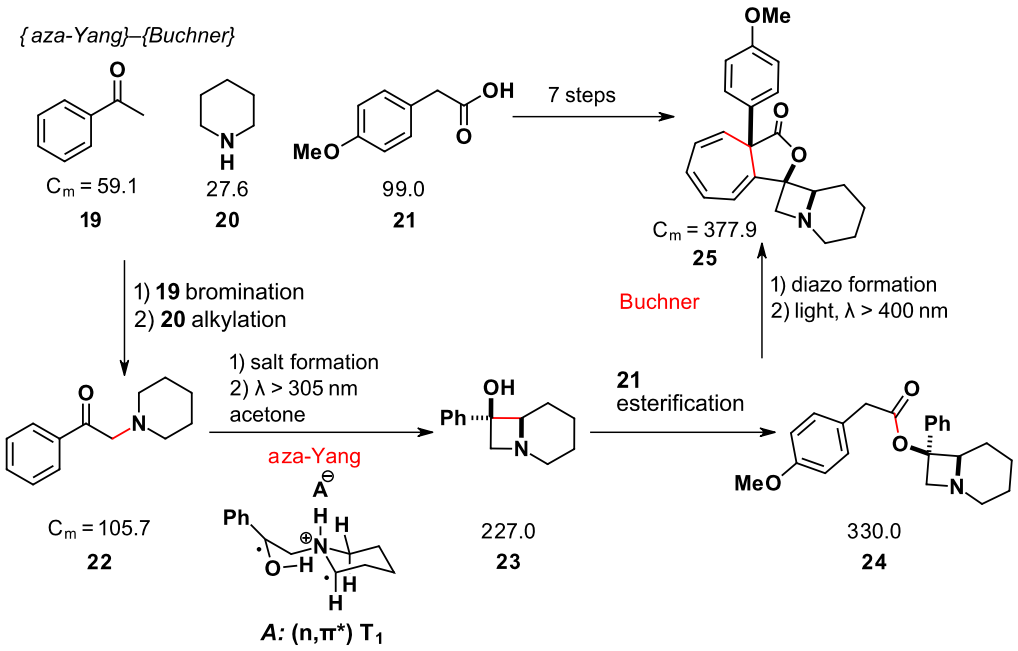


Figure 8. {Aza-Yang}–{Buchner} sequence. Acetophenones, secondary amines, and arylacetic acids can be converted to cycloheptatriene-containing azetidine lactones in seven easy steps, two of which are photochemical.

The structural complexity in this isomerization doubles as two new stereocenters are formed. Because the alcohol is the new functionality formed in this step, the subsequent acylation was a logical step to produce **24**. The structural complexity increase is relatively large in this coupling reaction, but this is mainly due to the new atoms and connectivity introduced by merging two approximately equal-sized fragments. Phenyl group was needed in **19** to improve efficiency of the photochemical reaction. This same group was now used as a target of an intramolecular carbene addition (Buchner reaction), following the installation of a diazo functionality on aryl acetate. This step furnishes a γ-lactone and a cycloheptatriene. Diastereomeric products of this reaction were separated by HPLC.

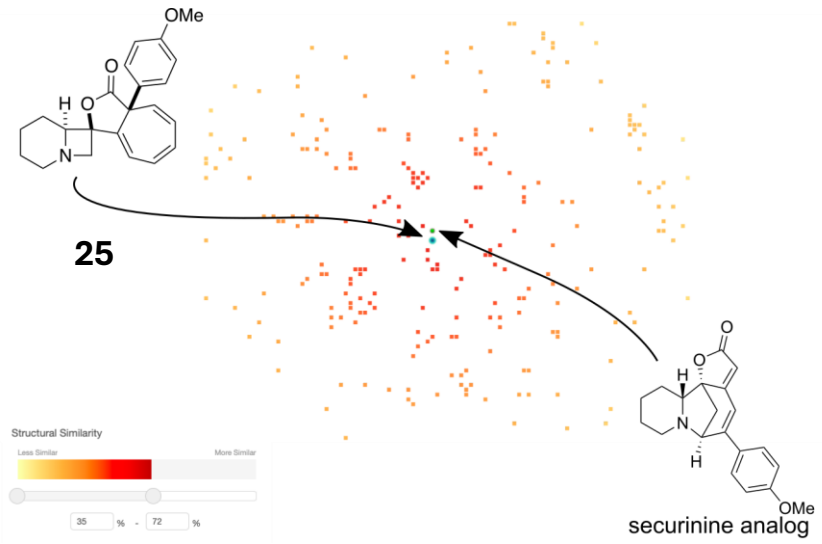


Figure 9. Are we reaching new chemical space? Chemscape analysis.

The key question following a campaign in diversity-oriented synthesis, such as in the ones described above, is to what extent are we really reaching the new chemical space. One possible answer can be obtained for the {aza-Yang}–{Buchner} sequence by searching the SciFinder database for the most structurally similar compounds of **25** and computing the Tanimoto similarity[48] of those structures. Tanimoto index measures similarity between two vectors that can be created by "binning" various substructures present in a molecule. Value of 0 means no structural similarity is shared between two molecules, and 1 means that the two vectors are perfectly aligned. A Chemscape visualization of such an analysis on several hundred most similar compounds is presented in Figure 9. This visualization is a two-dimensional projection of the compound fingerprint vectors in which similar structures cluster together. Excluding other molecules from the collection we prepared, a molecule most similar to **25** is an analog of the natural product securinine. The similarity stems from the presence of a γ-lactone, a tertiary amine embedded in a bicyclic structure, and the *p*-methoxyphenyl group. Overall, however, the structural similarity is fairly low, reaching only 0.387.

Conclusions

Strategies for systematically accessing new chemical space can be evaluated and optimized by measuring the difference in structural complexity between the building blocks and products of such synthetic strategies.[21] The "finality" of any such scheme is arbitrary and is limited only by creativity of the chemist and the availability of synthetic transformations that can be applied to a given structure.

Adopting such a broad view of synthetic goal frees a chemist from over-focusing on a particular molecular target. It also points to many "missing" synthetic methodologies that reveal themselves in a particular structural context; methods that may be enabling for efficient exploration of new chemical "space." Ultimately however, the work of developing new chemical reactions rests on careful analyses and understanding of underlying physico-chemical principles and the use of computational tools to aid in these analyses.

Acknowledgements

I would like to thank Prof. Emeritus Robert Hanzlik (KU) for critical reading of the manuscript and for numerous helpful suggestions and support over the years. In academia, like elsewhere, nothing gets done without the financial support. For this, I would like to thank the NIH COBRE Chemical Biology of Infectious Disease (P20GM113117) Pilot project and the director of COBRE Prof. Scott Hefty. I also want to acknowledge the NSF Access Project (CHE200120) for computational resources. Most of all, thanks go to the group members : Manvendra Singh, Bryce Gaskins, Sri Kolluru, Zach Pearson, Nathan Garza, Pawan Dhote, Alhamza Hamza, Vishva Shah, Mauricio Bahena Garcia, Koki Takemoto, Jax Rosekrans, Matt McCurry, Amar Kumar, Ambrosee Wilkinson, Elizabeth Miller, Ian Shire, Victor Fadare for contributing significant effort to the projects described in this manuscript.

References

1. *Sunniest States 2024*. https://worldpopulationreview.com/state-rankings/sunniest-states (accessed 2024-11-19).

2. Hatchard, C.; Parker, C. A New Sensitive Chemical Actinometer-II. Potassium Ferrioxalate as a Standard Chemical Actinometer. *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* **1956**, *235* (1203), 518–536. https://doi.org/10.1098/rspa.1956.0102
3. Ciamician, G. The Photochemistry of the Future. *Science* **1912**, *36* (926), 385–394. https://doi.org/10.1126/science.36.926.385
4. Beeler, A. B. Introduction: Photochemistry in Organic Synthesis. *Chemical Reviews* **2016**, *116* (17), 9629–9630. https://doi.org/10.1021/acs.chemrev.6b00378
5. Telmesani, R.; Park, S. H.; Lynch-Colameta, T.; Beeler, A. B. [2+2] Photocycloaddition of Cinnamates in Flow and Development of a Thiourea Catalyst. *Angewandte Chemie International Edition* **2015**, *54* (39), 11521–11525. https://doi.org/10.1002/anie.201504454
6. Hone, C. A.; Kappe, C. O. Towards the Standardization of Flow Chemistry Protocols for Organic Reactions. *Chemistry-Methods* **2021**, *1* (11), 454–467. https://doi.org/10.1002/cmtd.202100059
7. Williams, J. D.; Sagmeister, P.; Kappe, C. O. Dynamic Flow Experiments for Data-Rich Optimization. *Current Opinion in Green and Sustainable Chemistry* **2024**, 100921. https://doi.org/10.1016/j.cogsc.2024.100921
8. Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752–6756. https://doi.org/10.1021/jm901241e
9. Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59* (10), 4443–4458. https://doi.org/10.1021/acs.jmedchem.5b01409
10. Irwin, J. J.; Duan, D.; Torosyan, H.; Doak, A. K.; Ziebart, K. T.; Sterling, T.; Tumanian, G.; Shoichet, B. K. An Aggregation Advisor for Ligand Discovery. *Journal of medicinal chemistry* **2015**, *58* (17), 7076–7087. https://doi.org/10.1021/acs.jmedchem.5b01105
11. Arrowsmith, C. H.; Audia, J. E.; Austin, C.; Baell, J.; Bennett, J.; Blagg, J.; Bountra, C.; Brennan, P. E.; Brown, P. J.; Bunnage, M. E.; Buser-Doepner, C.; Campbell, R. M.; Carter, A. J.; Cohen, P.; Copeland, R. A.; Cravatt, B.; Dahlin, J. L.; Dhanak, D.; Edwards, A. M.; Frederiksen, M.; Frye, S. V.; Gray, N.; Grimshaw, C. E.; Hepworth, D.; Howe, T.; Huber, K. V. M.; Jin, J.; Knapp, S.; Kotz, J. D.; Kruger, R. G.; Lowe, D.; Mader, M. M.; Marsden, B.; Mueller-Fahrnow, A.; Müller, S.; O'Hagan, R. C.; Overington, J. P.; Owen, D. R.; Rosenberg, S. H.; Ross, R.; Roth, B.; Schapira, M.; Schreiber, S. L.; Shoichet, B.; Sundström, M.; Superti-Furga, G.; Taunton, J.; Toledo-Sherman, L.; Walpole, C.; Walters, M. A.; Willson, T. M.; Workman, P.; Young, R. N.; Zuercher, W. J. The Promise and Peril of Chemical Probes. *Nat Chem Biol* **2015**, *11* (8), 536–541. https://doi.org/10.1038/nchembio.1867
12. Gerry, C. J.; Hua, B. K.; Wawer, M. J.; Knowles, J. P.; Nelson Jr., S. D.; Verho, O.; Dandapani, S.; Wagner, B. K.; Clemons, P. A.; Booker-Milburn, K. I.; Boskovic, Z. V.; Schreiber, S. L. Real-Time Biological Annotation of Synthetic Compounds. *J. Am. Chem. Soc.* **2016**, *138* (28), 8920–8927. https://doi.org/10.1021/jacs.6b04614
13. Dobson, J. E.; Campbell, J. S. The Flatness of US States. *Geographical Review* **2014**, *104* (1), 1–9. https://doi.org/10.1111/j.1931-0846.2014.12001.x

14. Mannhold, R.; Krogsgaard-Larsen, P.; Timmerman, H. *QSAR: Hansch Analysis and Related Approaches*; John Wiley & Sons, 2008.
15. Barton, D. H. R. The Principles of Conformational Analysis. *Science* **1970**, *169* (3945), 539–544. https://doi.org/10.1126/science.169.3945.539
16. Lee, Y. C.; Lee, R. T. Carbohydrate-Protein Interactions: Basis of Glycobiology. *Acc. Chem. Res.* **1995**, *28* (8), 321–327. https://doi.org/10.1021/ar00056a001
17. Lipinski, C.; Hopkins, A. Navigating Chemical Space for Biology and Medicine. *Nature* **2004**, *432* (7019), 855–861. https://doi.org/10.1038/nature03193
18. Dobson, C. M. Chemical Space and Biology. *Nature* **2004**, *432* (7019), 824–828. https://doi.org/10.1038/nature03192
19. Böttcher, T. An Additive Definition of Molecular Complexity. *J. Chem. Inf. Model.* **2016**, *56* (3), 462–470. https://doi.org/10.1021/acs.jcim.5b00723
20. Bertz, S. H. The First General Index of Molecular Complexity. *Journal of the American Chemical Society* **1981**, *103* (12), 3599–3601. https://doi.org/10.1021/ja00402a071
21. Wright, B. A.; Sarpong, R. Molecular Complexity as a Driving Force for the Advancement of Organic Synthesis. *Nature Reviews Chemistry* **2024**, 1–17. https://doi.org/10.1038/s41570-024-00645-8
22. Landrum, G. Rdkit Documentation. *Release* **2013**, *1* (1–79), 4. https://www.rdkit.org/docs/
23. Schreiber, S. L. Molecular Diversity by Design. *Nature* **2009**, *457* (7226), 153–154. https://doi.org/10.1038/457153a
24. Demoret, R. M.; Baker, M. A.; Ohtawa, M.; Chen, S.; Lam, C. C.; Khom, S.; Roberto, M.; Forli, S.; Houk, K. N.; Shenvi, R. A. Synthetic, Mechanistic, and Biological Interrogation of Ginkgo Biloba Chemical Space En Route to (−)-Bilobalide. *Journal of the American Chemical Society* **2020**, *142* (43), 18599–18618. https://doi.org/10.1021/jacs.0c08231
25. Avnir, D.; Biham, O.; Lidar, D.; Malcai, O. Is the Geometry of Nature Fractal? *Science* **1998**, *279* (5347), 39–40. https://doi.org/10.1126/science.279.5347.39
26. Calvert, J. G.; Pitts, J. *Photochemistry*; John Wiley & Sons, 1966.
27. Turro, N. J.; Ramamurthy, V.; Scaiano, J. C. *Modern Molecular Photochemistry of Organic Molecules*; Viva Books University Science Books, Sausalito, 2017.
28. Goti, G.; Manal, K.; Sivaguru, J.; Dell'Amico, L. The Impact of UV Light on Synthetic Photochemistry and Photocatalysis. *Nat. Chem.* **2024**, *16* (5), 684–692. https://doi.org/10.1038/s41557-024-01472-6
29. Pearson, R. G. Symmetry Rules for Chemical Reactions. 1976.
30. Kaplan, L.; Pavlik, J.; Wilzbach, K. Photohydration of Pyridinium Ions. *Journal of the American Chemical Society* **1972**, *94* (9), 3283–3284. https://doi.org/10.1021/ja00764a089
31. Ling, R.; Yoshida, M.; Mariano, P. S. Exploratory Investigations Probing a Preparatively Versatile, Pyridinium Salt Photoelectrocyclization−Solvolytic Aziridine Ring Opening Sequence. *J. Org. Chem.* **1996**, *61* (13), 4439–4449.

https://doi.org/10.1021/jo960316i
32. Clark, M. A.; Schoenfeld, R. C.; Ganem, B. The Photochemistry of Pyrylium Salts: New Photohydrations and Photoamidations of Heterocycles Leading to Bicyclic Oxazolines and Functionalized Cyclopentenes. *J. Am. Chem. Soc.* **2001**, *123* (42), 10425–10426. https://doi.org/10.1021/ja0166040
33. Haftchenary, S.; Nelson Jr, S. D.; Furst, L.; Dandapani, S.; Ferrara, S. J.; Bošković, Ž. V.; Figueroa Lazú, S.; Guerrero, A. M.; Serrano, J. C.; Crews, D. K.; others. Efficient Routes to a Diverse Array of Amino Alcohol-Derived Chiral Fragments. *ACS Combinatorial Science* **2016**. https://doi.org/10.1021/acscombsci.6b00050
34. Hua, B. K.-Y. New Strategies to Discover Small-Molecule Probes and Clinical Candidates. PhD Thesis, Harvard University, 2020.
35. Trost, B. M.; Fandrick, D. R. Dynamic Kinetic Asymmetric Cycloadditions of Isocyanates to Vinylaziridines. *J. Am. Chem. Soc.* **2003**, *125* (39), 11836–11837. https://doi.org/10.1021/ja037450m
36. Cronk, W. C.; Mukhina, O. A.; Kutateladze, A. G. Photoinduced "Double Click" Cascade Offers Access to Complex Polyheterocycles from Readily Available Isatin-Based Photoprecursors. *Org. Lett.* **2016**, *18* (15), 3750–3753. https://doi.org/10.1021/acs.orglett.6b01775
37. Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. Enzyme Mechanisms for Polycyclic Triterpene Formation. *Angewandte Chemie International Edition* **2000**, *39* (16), 2812–2833. https://doi.org/10.1002/1521-3773(20000818)39:16<2812::AID-ANIE2812>3.0.CO;2-#
38. Singh, M.; Garza, N.; Pearson, Z.; Douglas, J.; Boskovic, Z. Broad Assessment of Bioactivity of a Collection of Spiroindane Pyrrolidines through "Cell Painting." *Bioorganic & Medicinal Chemistry* **2020**, *28* (13), 115547. https://doi.org/10.1016/j.bmc.2020.115547
39. Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. Site-Selective and Versatile Aromatic C-H Functionalization by Thianthrenation. *Nature* **2019**, *567* (7747), 223–228. 9-0982 https://doi.org/10.1038/s41586-019-0982-0
40. Shine, H. J.; Silber, J. J. Ion Radicals. XXII. Reaction of Thianthrenium Perchlorate (C12H8S2. ClO4-) with Aromatics. *The Journal of Organic Chemistry* **1971**, *36* (20), 2923–2926. https://doi.org/10.1021/jo00819a002
41. Bray, M.-A.; Singh, S.; Han, H.; Davis, C. T.; Borgeson, B.; Hartland, C.; Kost-Alimova, M.; Gustafsdottir, S. M.; Gibson, C. C.; Carpenter, A. E. Cell Painting, a High-Content Image-Based Assay for Morphological Profiling Using Multiplexed Fluorescent Dyes. *Nature protocols* **2016**, *11* (9), 1757–1774. https://doi.org/10.1038/nprot.2016.105
42. Svenningsen, E. B.; Poulsen, T. B. Establishing Cell Painting in a Smaller Chemical Biology Lab - A Report from the Frontier. *Bioorg Med Chem* **2019**, *27* (12), 2609–2615. https://doi.org/10.1016/j.bmc.2019.03.052
43. Bagheri, N.; Carpenter, A. E.; Lundberg, E.; Plant, A. L.; Horwitz, R. The New Era of Quantitative Cell Imaging—Challenges and Opportunities. *Molecular Cell* **2022**, *82* (2), 241–247. https://doi.org/10.1016/j.molcel.2021.12.024

44. Garcia, M. B.; Singh, M.; Miller, E.; Neuenswander, S.; Douglas, J.; Boskovic, Z. Twisted Intramolecular Charge-Transfer State Addition to Electron-Poor Olefins. *J. Org. Chem.* **2024**. https://doi.org/10.1021/acs.joc.3c02521
45. Mayo, P. D.; Takeshita, H. Photochemical Syntheses: 6. the Formation of Heptandiones from Acetylacetone and Alkenes. *Can. J. Chem.* **1963**, *41* (2), 440–449. https://doi.org/10.1139/v63-061
46. Grabowski, Z. R.; Dobkowski, J. Twisted Intramolecular Charge Transfer (TICT) Excited States: Energy and Molecular Structure. *Pure and Applied Chemistry* **1983**, *55* (2), 245–252. https://doi.org/10.1351/pac198855020245
47. Singh, M.; Gaskins, B.; Johnson, D.R.; Elles, C.G.; Boskovic, Z. Synthesis of Cycloheptatriene-Containing Azetidine Lactones. *The Journal of Organic Chemistry* **2022** *87* (22), 15001-15010. DOI: https://doi.org/10.1021/acs.joc.2c00367
48. Bajusz, D.; Rácz, A.; Héberger, K. Why Is Tanimoto Index an Appropriate Choice for Fingerprint-Based Similarity Calculations? *Journal of Cheminformatics* **2015**, *7* (1), 20. https://doi.org/10.1186/s13321-015-0069-3

Author's Biography

Zarko Boskovic obtained his undergraduate degree from the University of Niš, Serbia, where he performed research on mathematical chemistry with Ivan Gutman and on the isolation and analysis of secondary metabolites with Gordana Stojanović. He earned his PhD from the UCSB Chemistry department under the guidance of Bruce H. Lipshutz working primarily on copper hydride-initiated reactions, catalysis, and stereoselective synthetic organic methods. He was then a postdoctoral researcher in Stuart L. Schreiber's lab at the Broad Institute of MIT and Harvard where he worked on delineating molecular mechanism of action of several screening hits, and on the design of new synthetic pathways for diverse collections of complex small molecules. He joined the faculty of the Department of Medicinal Chemistry at the University of Kansas in 2018.