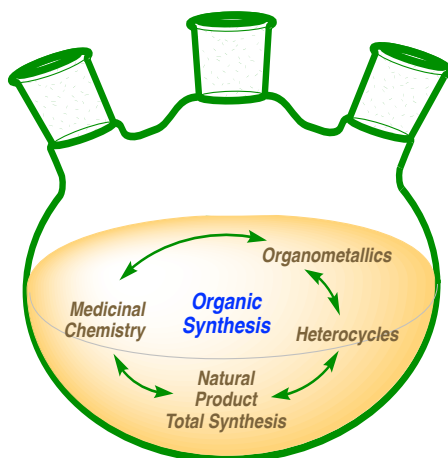


WIPF GROUP RESEARCH OVERVIEW



Program Features & Milestones Toward Ph.D.

- Projects in all areas of organic chemistry; students gain synthetic, analytical, computational & instrumental skills
- Learn how to integrate synthesis, analysis & drug discovery
- Every student can pursue 2-4 conceptually different projects
- Time to completion of PhD: 5 y
- PhD thesis requirements:
 - 3 publications (at least 1 first-author publication)
 - ability to present and discuss research results in broader context
 - chemistry knowledge covering the fundamentals of synthetic & mechanistic organic chemistry and reaction design
 - demonstrated creativity
- Group meetings cover diverse educational activities
- Extensive biological collaborations & large network of former students
- Excellent research resources: instrumentation, databases, RA support, new(ish) labs; dedicated staff
- Several GSR positions available

For a complete publication list, see our entry in Google Scholar:

<https://scholar.google.com/citations>

For current group information, see our web pages at:

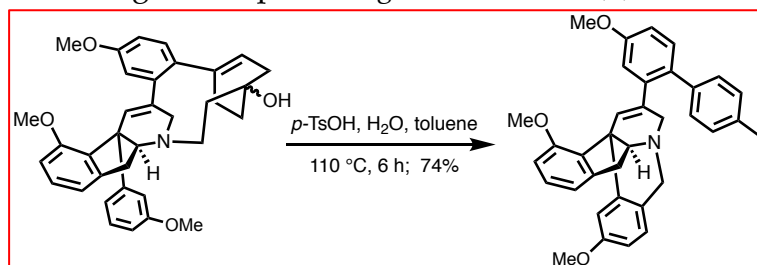
<http://ccc.chem.pitt.edu/wipf/index.html>

REPRESENTATIVE PROJECTS

Total Synthesis of Natural Products

1. "Grob-Type Fragmentation Releases Paracyclophane Ring Strain in a Late-Stage Precursor of Haouamine A." Cao, L.; Wang, C.; Wipf, P. *Org. Lett.* **2019**, 21(5), 1538-41.

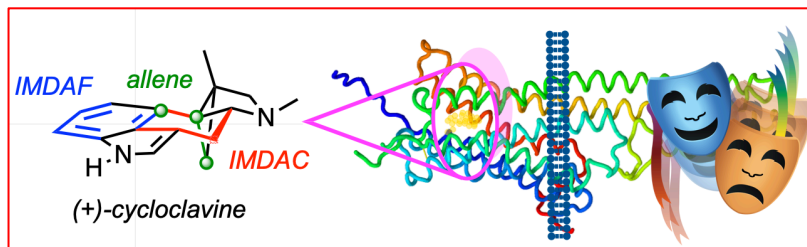
A ketene [2+2]-addition, an intramolecular aldol reaction, a Suzuki-Miyaura coupling and a chemoselective lactam reduction were used to prepare a late-stage precursor of haouamine A. Exposure to acid



led to a Grob-type fragmentation of the strained 3-aza-[7]-paracyclophane ring, followed by a tandem Pictet-Spengler reaction of the intermediate iminium ion. This cascade reaction might also be relevant for the mechanism of action of the natural product.

2. "Asymmetric Total Synthesis and Biological Evaluation of (+)-Cycloclavine." McCabe, S. R.; Wipf, P. *Synthesis* **2019**, 51(1), 213-24. Published as part of the Golden (50-year) Anniversary Issue.

The first total synthesis of natural (+)-cycloclavine uses a catalytic asymmetric cyclopropanation of allene, a regioselective Pd-catalyzed enone formation, and two

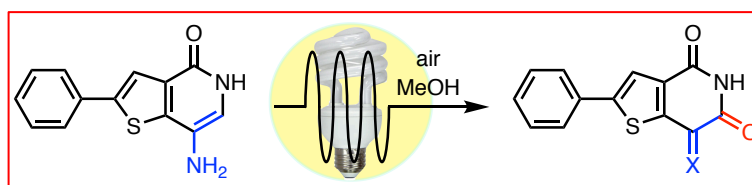


intramolecular Diels-Alder reactions for indole/ indoline annulations. The binding properties of natural (+)- and unnatural (-)-cycloclavine on 16 CNS receptors revealed significant stereospecificity and unique binding profiles in comparison to LSD, psilocin, and DMT. Differential 5-HT affinities bode well for potential therapeutic developments of clavine alkaloid scaffolds

Heterocyclic & Medicinal Chemistry

1. "In-Flow Photooxygenation of Aminothienopyridinones Generates Iminopyridinedione PTP4A3 Phosphatase Inhibitors." Tasker, N. R.; Rastelli, E. J.; Blanco, I. K.;

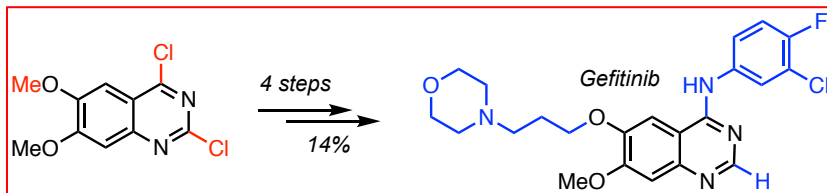
Burnett, J. C.; Sharlow, E. R.; Lazo, J. S.; Wipf, P. *Org. Biomol. Chem.* **2019**, 17, 2448. A continuous flow photooxygenation of 7-



aminothieno[3,2-c]pyridin-4(5H)-ones to produce 7-iminothieno[3,2-c]pyridine-4,6(5H,7H)-diones has been developed, utilizing ambient air as the sole reactant. N-H Imines are formed as the major products, and excellent functional group tolerance and conversion on gram-scale without the need for chromatographic purification allow for facile late-stage diversification of the aminothienopyridinone scaffold. Several analogs

exhibit potent *in vitro* inhibition of the cancer-associated protein tyrosine phosphatase PTP4A3, and the SAR supports an exploratory docking model.

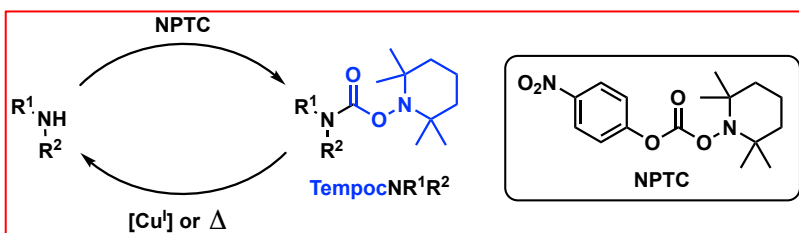
- "A New Synthesis of Gefitinib." Maskrey, T. S.; Kristufek, T.; LaPorte, M. G.; Nyalapatla, P. R.; Wipf, P. *Synlett* **2019**, 30(4), 471-6. Published as part of the Pearl (30-year) Anniversary Issue. A four-step synthesis of the FDA approved anticancer agent Gefitinib was developed starting with 2,4-dichloro-6,7-



dimethoxyquinazoline. Reaction temperatures were in the 0-55 °C range, and chromatographic purifications were avoided. The ionic liquid [TMAH][Al₂Cl₇] was utilized to mono-demethylate the dimethoxyquinazoline core. In the final step, a selective dehalogenation was employed to provide Gefitinib in 14% overall yield on multi-gram scale.

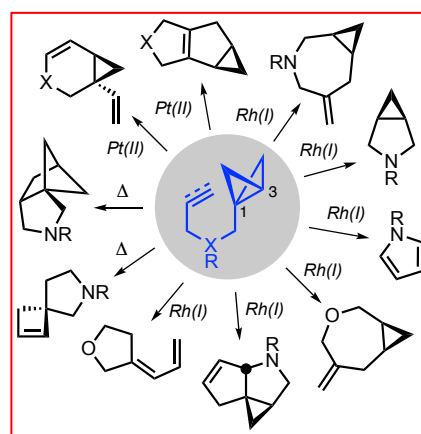
Synthetic Methods & Catalysis

- "2,2,6,6-Tetramethylpiperidin-1-yloxycarbonyl: A Protecting Group for Primary, Secondary, and Heterocyclic Amines." Lizza, J. R.; Bremerich, M.; McCabe, S. R.; Wipf, P. *Org. Lett.* **2018**, 20(21), 6760-4. The



Tempoc protecting group is readily introduced by the reaction of amines with a new acyl transfer reagent, NPTC. Tempoc has a reactivity profile that complements the commonly used Boc and Cbz protecting groups. Deprotection can be achieved under mild reductive conditions with *in-situ* generated catalytic Cu(I). This reagent is now commercially available from Millipore Sigma.

- "Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes." Walczak, M. A.; Krainz, T.; Wipf, P. *Acc. Chem. Res.* **2015**, 48, 1149. Mechanistically as well as synthetically, bicyclo[1.1.0]butanes represent one of the most fascinating classes of organic compounds. They offer a unique blend of compact size (4 carbon atoms), high reactivity (strain energy of 66 kcal/mol), and mechanistic pathway diversity that can be harvested for the rapid assembly of complex scaffolds. The C(1)-C(3) bond combines the electronic features of both σ - and π -bonds with facile homolytic and heterolytic bond dissociation properties, and thereby readily engages pericyclic, transition metal mediated, nucleophilic, and electrophilic pathways as well as radical acceptor and donor substrates. Our metal-



Our metal-

catalyzed and thermal ring transformations of bicyclo[1.1.0]butanes suggest many additional strategies for new reaction discoveries, accessing a wide variety of novel cyclic frameworks from relatively simple starting materials. In addition, there is considerable potential for future applications in natural products, medicinal, and diversity-oriented synthesis based on the wealth of mechanistic pathways available to these strained small-ring carbocycles.

Very Recent & Highly Collaborative Publications

- **"ETHE1 and MOCS1 Deficiencies: Disruption of Mitochondrial Bioenergetics, Dynamics, Redox Homeostasis and Endoplasmic Reticulum-Mitochondria Crosstalk in Patient Fibroblasts."** Grings, M.; Seminotti, B.; Karunanidhi, A.; Ghaloul-Gonzalez, L.; Mohsen, A.-W.; Wipf, P.; Palmfeldt, J.; Vockley, J.; Leipnitz, G. *Sci. Rep.* **2019**, 9(1), 12651.
- **"Tapping the Therapeutic Potential of Protein Tyrosine Phosphatase 4A with Small Molecule Inhibitors."** Tasker, N. R.; Rastelli, E. J.; Burnett, J. C.; Sharlow, E. R.; Lazo, J. S.; Wipf, P. *Bioorg. Med. Chem. Lett.* **2019**, 29(16), 2008-2015.
- **"Synthesis and Optimization of Kv7 (KCNQ) Potassium Channel Agonists: The Role of Fluorines in Potency and Selectivity."** Liu, R.; Tzounopoulos, T.; Wipf, P. *ACS Med. Chem. Lett.* **2019**, 10(6), 935-941.
- **"Amelioration of Amyotrophic Lateral Sclerosis in Sod1(G93a) Mice by M2 Microglia from Transplanted Marrow."** Epperly, M. W.; Fisher, R.; Zhang, X.; Hou, W.; Shields, D.; Francicola, D.; Wang, H.; Thermoziar, S.; Henderson, A.; Greenberger, J. S.; Rigatti, L.; Watkins, S.; Bayir, H.; Donnelly, C.; Wipf, P. *In Vivo* **2019**, 33(3), 675-688.
- **"Mitochondrial Energetics Is Impaired in Very Long-Chain Acyl-Coa Dehydrogenase Deficiency and Can Be Rescued by Treatment with Mitochondria-Targeted Electron Scavengers."** Seminotti, B.; Leipnitz, G.; Karunanidhi, A.; Kochersperger, C.; Roginskaya, V. Y.; Basu, S.; Wang, Y.; Wipf, P.; Van Houten, B.; Mohsen, A.-W.; Vockley, J. *Hum. Mol. Genet.* **2019**, 28(6), 928-941.
- **"Ferroptosis as a Novel Therapeutic Target for Friedreich's Ataxia."** Coticelli, M. G.; Xia, S.; Lin, D.; Lee, T.; Terrab, L.; Wipf, P.; Huryn, D. M.; Wilson, R. B. *J. Pharmacol. Exp. Ther.* **2019**, 369(1), 47-54.
- **"Synthesis and Evaluation of Esterified Hsp70 Agonists in Cellular Models of Protein Aggregation and Folding."** Chiang, A. N.; Liang, M.; Dominguez-Meijide, A.; Masaracchia, C.; Goekeler-Fried, J. L.; Mazzone, C. S.; Newhouse, D. W.; Yates, M. E.; Manos-Turvey, A.; Needham, P. G.; Outeiro, T. F.; Wipf, P.; Brodsky, J. L. *Bioorg. Med. Chem.* **2019**, 27(1), 79-91.
- **"Mitochondria Are a Substrate of Cellular Memory."** Cheikhi, A.; Wallace, C.; St Croix, C.; Cohen, C.; Tang, W.-Y.; Wipf, P.; Benos, P. V.; Ambrosio, F.; Barchowsky, A. *Free Radical Biol. Med.* **2019**, 130, 528-541.
- **"Hsp70 Binds to the Androgen Receptor N-Terminal Domain and Modulates the Receptor Function in Prostate Cancer Cells."** Dong, J.; Wu, Z.; Wang, D.; Pascal, L. E.; Nelson, J. B.; Wipf, P.; Wang, Z. *Mol. Cancer Ther.* **2019**, 18(1), 39-50.
- **"Continuous One Year Oral Administration of the Radiation Mitigator, MMS350, after Total-Body Irradiation, Restores Bone Marrow Stromal Cell Proliferative Capacity and Reduces Senescence in Fanconi Anemia (Fanca(-/-)) Mice."** Sivananthan, A.; Shields, D.; Fisher, R.; Hou, W.; Zhang, X.; Francicola, D.; Epperly, M. W.; Greenberger, J. S.; Wipf, P. *Radiat. Res.* **2019**, 191(2), 139-153.