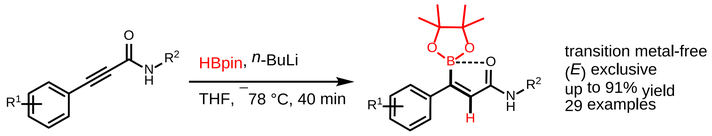
Virginia Tech Department of Chemistry

Organic Synthesis and Medicinal Chemistry

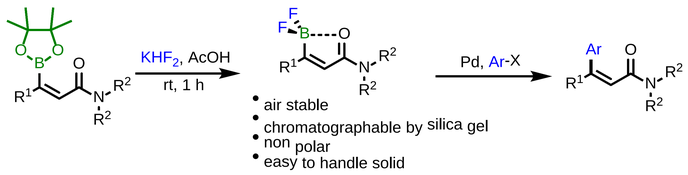
Stereoselective Borylations and Silylation

Goal: develop sustainable, cost effective, and environmentally friendly reactions

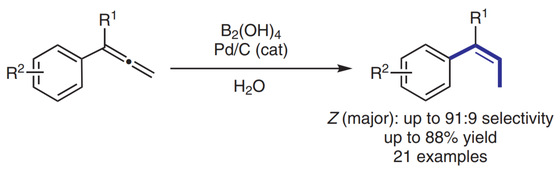
trans-Hydroboration of Propiolamides



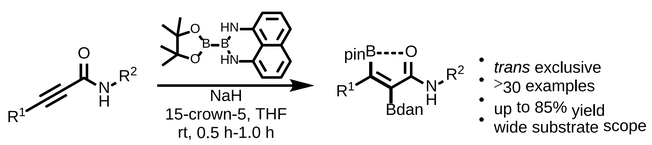
Route to Air and Moisture Stable β-Difluoroboryl Acrylamides



Regioselective Diboron-Mediated Semireduction of Terminal Allenes

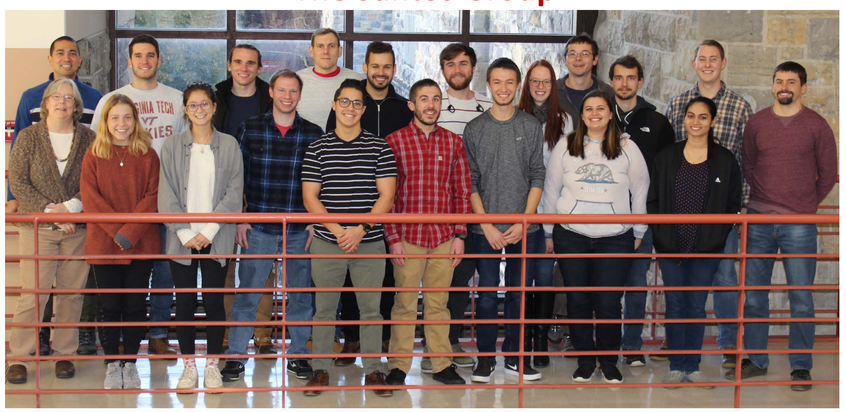


Transition Metal-free Diboration of Alkynamides with Mixed Diboron



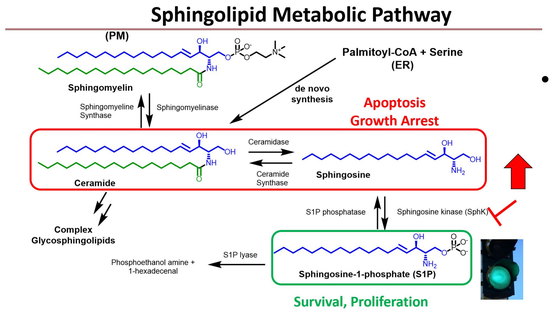
Eur. J. Org. Chem. **2020**, *in press.* http://dx.doi.org/10.1002/ejoc.202000128; *Org. Lett.* **2019**, *21*, 8053; *Org. Lett.* **2019**, *21*, 6795; *Tetrahedron*, **2019**, *75*, 2113; *Synthesis*, **2019**, *51*, 4619; *J. Org. Chem.* **2018**, 83, 10436;. *Angew. Chem. Int. Ed.* **2017**, *56*, 5111; *J. Org. Chem.* **2016**, *81*, 4269; *Org. Lett.* **2016**, *18*, 2443; *Synthesis,* **2015**, *47*, 2242; *ACS Catal.*, **2015**, *5*, 2172; *Angew. Chem. Int. Ed.* **2014**, 53, 4154; *Org. Lett.* **2012**, *14*, 1918; *Org. Lett.* **2012**, 14, 2090; *J. Org. Chem.* **2011**, *76*, 3997; *J. Org. Chem*; **2011**, *76*, 3571; *Chem. Commun.* **2011**, *47*, 424; *Org. Lett.* **2009**, 11, 3478.

The Santos Group

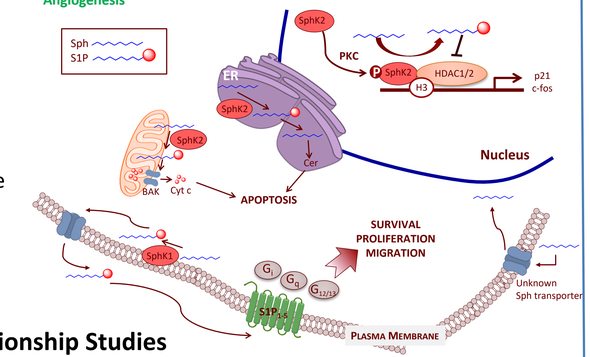


Drugging the Sphingosine-1-phosphate Pathway

Goal: develop drugs to target cancer, fibrosis, sickle cell disease, and Alzheimer's disease



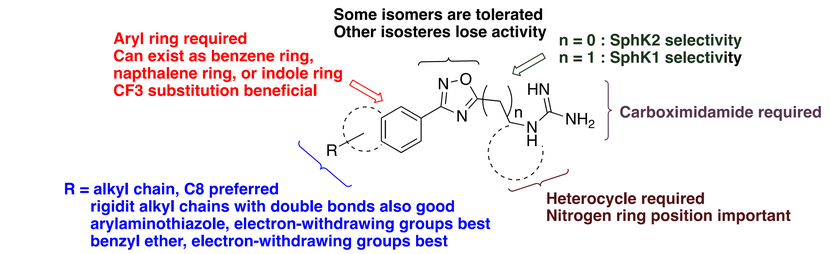
- Inhibition of sphingosine metabolism to S1P results in accumulation of sphingosine and, as a result, signals for growth arrest and apoptosis.



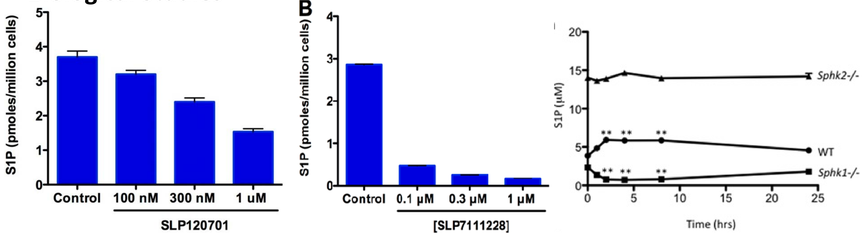
- S1P functions primarily as an extracellular ligand for its GPCRs $S1P_{1\text{-}5}$ to promote cell growth and proliferation.

spns2/
mfsd2b

Structure-Activity Relationship Studies



Biological Studies



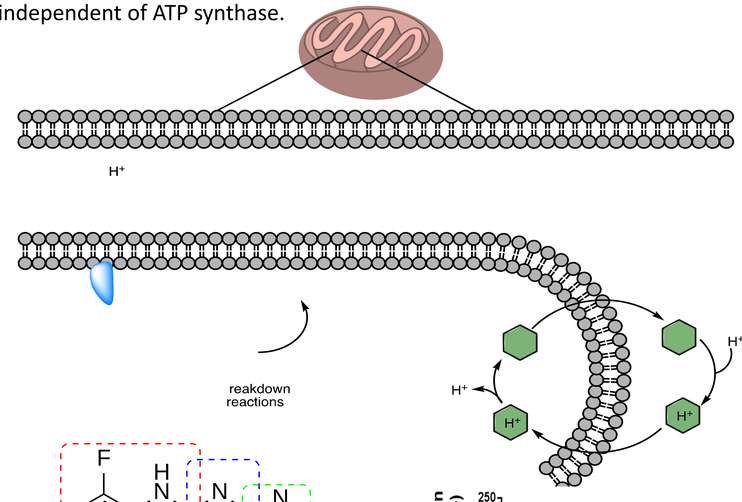
- SphK1 and SphK2 inhibition decreases S1P levels in cells
- SphK2 inhibition increases S1P levels in mice

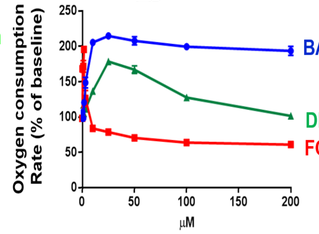
J. Med. Chem. **2015**, *58* , 1879; *Bioorg. Med. Chem. Lett*, **2015**, *25*, 4956; *J. Pharm. Exp. Ther.* **2015**, *355*, 23–31; *ACS Med. Chem. Lett.* **2016**, *7*, 229; *ACS J. Chem. Inf. Model.*, **2019**, *59*, 2339; *J. Med. Chem.* **2020**, 63, 1178; *Biochem. J. 2020*, doi.org/10.1042/BCJ20190730

Medicinal Chemistry of Mitochondrial Uncouplers

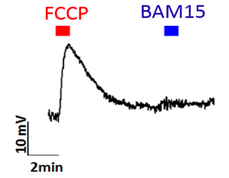
Goal: develop drugs to treat obesity, type 2 diabetes, NASH and age-related diseases

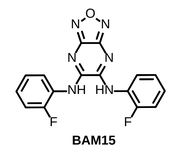
- Mitochondrial uncouplers leak protons into mitochondrial matrix, independent of ATP synthase.

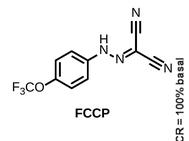


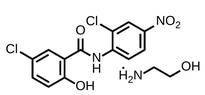


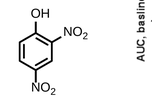
- New class mitochondrial uncouplers
  - Unrelated to DNP structure
- Lack off-target activity
- Orally bioavailable and bioactive
- Broad safety window (hERG, AMES negative)
- Reverse obesity
- Decrease liver steatosis, fibrosis, and injury
- range of self-limiting activity

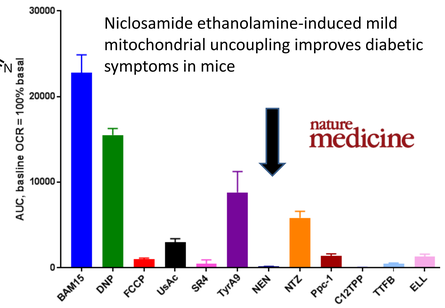












Mol. Met. **2014**, *3*, 114; *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4858; *J. Med. Chem.* **2018,** *61*, 4641. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127057; *J. Med. Chem.* **2020**, *63*, 2511.

Funding Sources

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