Borazine-CF_3^- Adducts for Rapid, Room Temperature, and Broad Scope Trifluoromethylation

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The trifluoromethyl functional group (CF_3) is now routinely applied in drug discovery because it can increase the lipophilicity and metabolic stability of bioactive compounds.[1,2] Professor Nathaniel Szymczak from the University of Michigan (Ann Arbor, USA) said: "The introduction of this alkyl group presents unique challenges, compared to other alkyl groups, because reagents that are analogous to organolithium and organomagnesium compounds do not exist for CF_3 analogues. As a matter of fact, Mg- and $LiCF_3$ reagents spontaneously eliminate fluoride, with enough energy released to be considered explosive.[3,4] This inherent instability has hindered progress in the development of new trifluoromethylation methodologies; indeed, ninety years passed between the first nucleophilic methylations[5] and the first efficient nucleophilic trifluoromethylations."[6] The group of Professor Szymczak recently designed a new approach to CF_3^- reagents from an industrial waste gas.[7] "One of the most appealing sources of the CF_3 functional group that might be used as a synthon in trifluoromethylation methodologies is fluoroform (HCF_3), which is a waste product of the Teflon industry and unfortunately underused," said Professor Szymczak, who envisioned a design approach conceptually related to heterolytic H_2 activation and transfer using acidic and basic groups, an area that his group has previously worked in. He noted: "There are strong parallels between the small molecules H_2 and HCF_3, and we thought that a combination of acids and bases might induce the ideal properties to fluoroform; these principles have been demonstrated with Frustrated Lewis Pair chemistry for H_2 activation."

To approach the problem rationally, the Michigan team needed a scale of CF_3^- affinity for Lewis acids in order to identify a favorable Lewis acidity regime for both CF_3^- stabilization and release. According to Professor Szymczak, if the Lewis acidity of the stabilizer is too high, CF_3^- would bind too tightly and not transfer to substrates. If it is too weak, CF_3^- may not bind at all or the resulting adduct may decompose at room temperature. Using DFT to calculate the CF_3 binding affinity of over 40 Lewis acids, the authors of this work were able to narrow in on an ideal regime where the Lewis acid additive provides just enough stabilization to keep CF_3^- from decomposing, yet reactive enough to be used as a reagent. "The best Lewis acid, hexamethylborazine [$B_3N_3(CH_3)_6$], appears in many chemistry textbooks as an 'inorganic benzene' yet has few applications as a reagent in organic synthesis," said Professor Szymczak, whose lab had previous experience working with borazines for energy-storage related projects: "The very challenge we had been facing in our previous investigations with borazines – delivering anionic nucleophiles – suggested they might be perfect candidates for CF_3^- generation/capture/release experiments because they are very weak Lewis acids," he added. Professor Szymczak and co-workers found that using the borazine Lewis acid facilitated the preparation of highly nucleophilic CF_3^- transfer reagents from HCF_3 in quantitative yield at room temperature. They used this strategy to prepare widely used reagents for nucleophilic ($SiMe_3CF_3$), radical (KSO_2CF_3), and electrophilic (Togni I) trifluoromethylation reagents from HCF_3 and a low-cost base, with complete regeneration and recycling of the borazine stabilizer after CF_3 transfer. Professor Szymczak noted, "We are working to commercialize the borazine and borazine-CF_3^- reagent, which we hope will broaden its use."

The Michigan-based team showed that the borazine-CF_3^- reagent exhibits high nucleophilicity and reacts with weak electrophiles, such as benzophenone, 1000 times faster than previously reported $B(OMe)_3$-CF_3^- adducts. They also showed that normally challenging transmetalation reactions occurred rapidly at room temperature, enabling the synthesis of Pd(II)-, Cu(I)-, Ag(I)-, Zn(II)-, and Au(I)-CF_3 complexes. Graduate student Jacob Geri noted: "This should open the door to catalytic cross-coupling applications. The unique reactivity of our HCF_3-derived reagent inspired us to explore new electrophiles which had not been well-represented in reactions with CF_3^- sources, namely arene electrophiles. Trifluoromethylation of electron-deficient arenes and heteroarenes is challenging because cross-coupling methodologies rarely work well for CF_3 transfer." The group discovered that their CF_3^- transfer reagent was able to efficiently trifluoromethylate nitrobenzene and nitropyridine in direct substitution reactions and could be used to dearomatize unsubstituted pyrimidine and triazine substrates in high yield and selectivity. The dearomatized intermediates could be captured with electrophiles, or alternatively oxidized to produce aromatic products. Professor Szymczak remarked: "Overall, we demonstrated four distinct types of new metal-free aromatic trifluoromethylation

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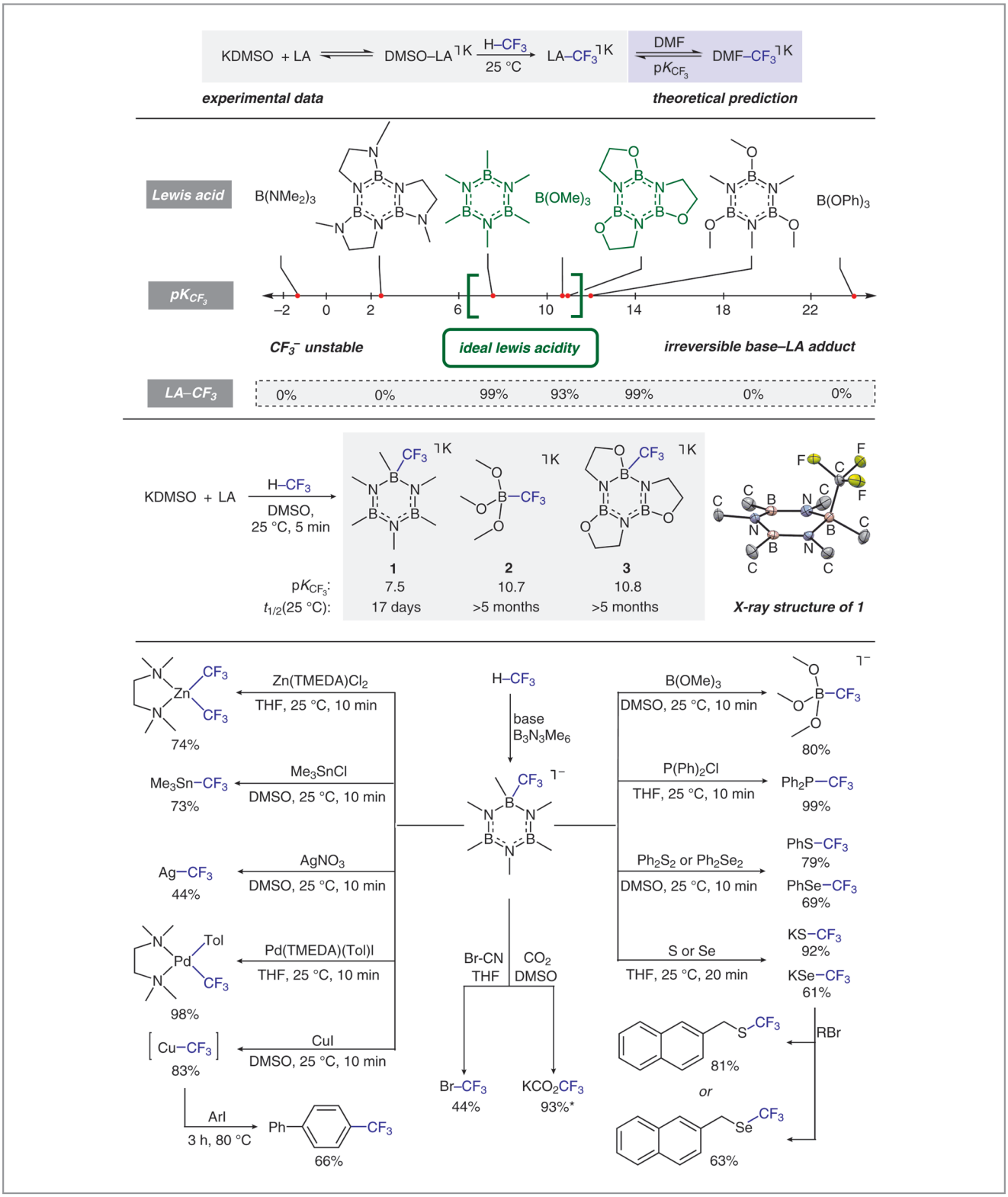
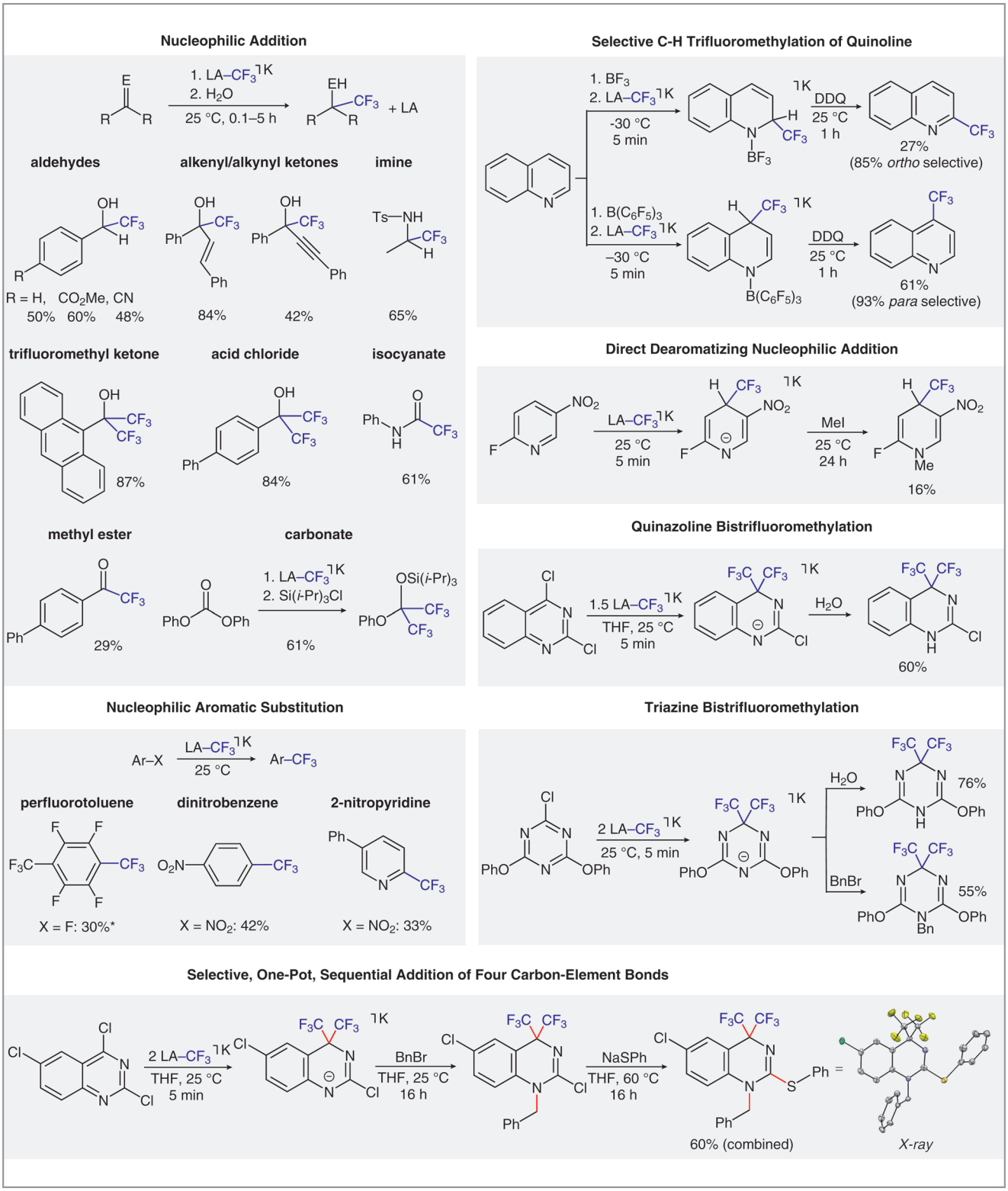

KDMSO + LA
DMSO–LA
H–CF3
25 °C
LA–CF3
DMF
pKCF3
DMF–CF3
experimental data
theoretical prediction
Lewis acid
B(NMe2)3
B(OMe)3
B(OPh)3
pKCF3
–2
0
2
6
10
14
18
22
CF3– unstable
ideal lewis acidity
irreversible base–LA adduct
LA–CF3
0%
0%
99%
93%
99%
0%
0%
KDMSO + LA
H–CF3
DMSO,
25 °C, 5 min
1
2
3
pKCF3:
7.5
10.7
10.8
t1/2(25 °C):
17 days
>5 months
>5 months
X-ray structure of 1
Zn(TMEDA)Cl2
THF, 25 °C, 10 min
74%
Me3SnCl
DMSO, 25 °C, 10 min
Me3Sn–CF3
73%
AgNO3
DMSO, 25 °C, 10 min
Ag–CF3
44%
Pd(TMEDA)(Tol)I
THF, 25 °C, 10 min
98%
CuI
DMSO, 25 °C, 10 min
83%
ArI
3 h, 80 °C
66%
H–CF3
base
B3N3Me6
Br-CN
THF
CO2
DMSO
Br–CF3
44%
KCO2CF3
93%*
B(OMe)3
DMSO, 25 °C, 10 min
80%
P(Ph)2Cl
THF, 25 °C, 10 min
Ph2P–CF3
99%
Ph2S2 or Ph2Se2
DMSO, 25 °C, 10 min
PhS–CF3
79%
PhSe–CF3
69%
S or Se
THF, 25 °C, 20 min
KS–CF3
92%
KSe–CF3
61%
RBr
81%
or
63%

Scheme 1


Nucleophilic Addition
1. LA–CF3 ⁊K
2. H2O
25 °C, 0.1–5 h
+ LA
aldehydes
alkenyl/alkynyl ketones
imine
R = H, CO2Me, CN
50% 60% 48%
84%
42%
65%
trifluoromethyl ketone
acid chloride
isocyanate
87%
84%
61%
methyl ester
carbonate
29%
1. LA–CF3 ⁊K
2. Si(i-Pr)3Cl
61%
Nucleophilic Aromatic Substitution
Ar–X
LA–CF3 ⁊K
25 °C
Ar–CF3
perfluorotoluene
dinitrobenzene
2-nitropyridine
X = F: 30%*
X = NO2: 42%
X = NO2: 33%
Selective C-H Trifluoromethylation of Quinoline
1. BF3
2. LA–CF3 ⁊K
-30 °C
5 min
DDQ
25 °C
1 h
27%
(85% ortho selective)
1. B(C6F5)3
2. LA–CF3 ⁊K
–30 °C
5 min
DDQ
25 °C
1 h
61%
(93% para selective)
Direct Dearomatizing Nucleophilic Addition
LA–CF3 ⁊K
25 °C
5 min
MeI
25 °C
24 h
16%
Quinazoline Bistrifluoromethylation
1.5 LA–CF3 ⁊K
THF, 25 °C
5 min
H2O
60%
Triazine Bistrifluoromethylation
2 LA–CF3 ⁊K
25 °C, 5 min
H2O
76%
BnBr
55%
Selective, One-Pot, Sequential Addition of Four Carbon-Element Bonds
2 LA–CF3 ⁊K
THF, 25 °C
5 min
BnBr
THF, 25 °C
16 h
NaSPh
THF, 60 °C
16 h
60% (combined)
X-ray

Scheme 2

reactions with electron-deficient arenes and heteroarenes via substitution of aryl fluoride, chloride, and nitro groups." Finally, the potent nucleophilicity of the reagent was showcased with a new geminal bistrifluoromethylation reaction. The authors showed that their synthetic method is selective for a single C–Cl bond in the presence of three available C–Cl bonds and co-author Michael Wade Wolfe noted: "This offers complementary reactivity profiles with currently used methods."

The team also discovered the importance of the countercation identity in these anionic reagents. Replacing potassium with a less Lewis acidic cation, cesium, increased the thermal stability of the reagent by 25-fold. Parallel to this observation, the addition of five equivalents of exogenous potassium accelerated the reaction rate of CF_3 transfer to benzaldehyde by 40-fold. Professor Szymczak noted: "The new regent may be considered as an inverted analogue to the widely used Ruppert–Prakash reagent ($TMSCF_3$). $TMSCF_3$ is activated by bases, whereas the borazine-CF_3^- reagent is activated by acids – this opens up distinct avenues that we hope will expand substrate scope for trifluoromethylation."

In the future, the group hopes to apply their methodology to the stabilization of other reactive fluoroalkyl anions. "We are currently exploring a host of new, previously unused 1-H fluoroalkane feedstocks for nucleophilic fluoroalkylation. While our initial efforts have demonstrated that small changes to fluoroalkyl anion structure lead to significant changes in stability and reactivity, we are rapidly learning how to design Lewis acid platforms for their reversible capture and release," remarked Professor Szymczak. "1-H fluoroalkanes are ideal precursors due to their wide availability. In the end, our ultimate goal is to make nucleophilic fluoroalkylation as simple and general as the Grignard reaction."

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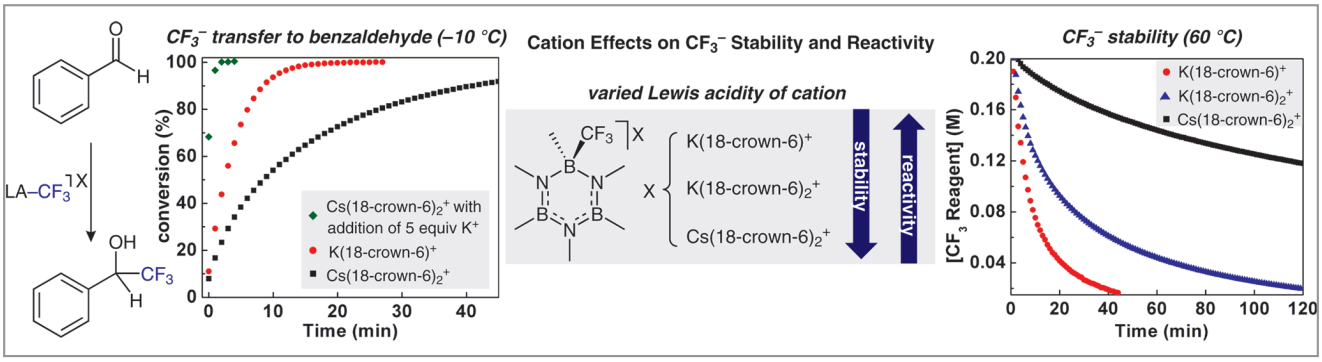

Scheme 3

About the authors

Prof. N. K. Szymczak

Nathaniel K. Szymczak pursued doctoral research under the direction of Professor David Tyler at the University of Oregon (USA). He then worked in the laboratories of Professor Jonas Peters at the Massachusetts Institute of Technology (USA) and the California Institute of Technology (USA). In 2010, Professor Szymczak joined the faculty at the University of Michigan (USA) where his research program focuses on developing new approaches to use acidic and basic groups to regulate small molecule binding, activation, and catalysis.

J. B. Geri

Jacob Geri graduated from Stetson University (USA) in 2012 after working under Professor John York for three years, where he used DFT calculations to model organometallic reactions. His work focuses on using non-traditional Lewis acid/base pairs to activate small molecules in both applied organic methodologies and fundamental inorganic chemistry. Through these efforts, he has developed new nitrile hydroboration catalysts that employ metal–ligand cooperativity to mediate H–B cleavage, selective methods for N_2 activation and protonation using reduced iron centers and organic Lewis acids, and a new class of HCF_3-derived nucleophilic trifluoromethylation reagents which use a recyclable Lewis acid stabilizer.

M. M. Wade Wolfe

Michael Wade Wolfe developed a passion for organometallic chemistry and physical organic chemistry methods while working under Professor Huw Davies at Emory University (USA). After graduating in 2016, he began working in the Szymczak lab at the University of Michigan (USA). His work has focused on unraveling the mechanism of CF_3^- transfer from borazine-CF_3^- reagents, the development of next-generation reagents, and exploring new types of metal-mediated fluoroalkylation reactions.

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