

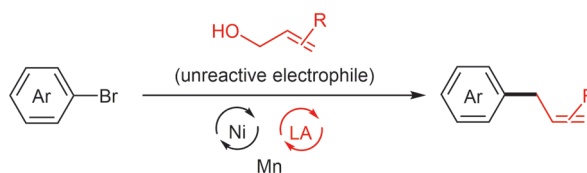
# Synform

People, Trends and Views in Chemical Synthesis

2018/05

## Dual Nickel and Lewis Acid Catalysis for Cross-Electrophile Coupling: The Allylation of Aryl Halides with Allylic Alcohols

Highlighted article by X.-G. Jia, P. Guo, J. Duan, X.-Z. Shu



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## Dear Readers,

I am afraid this is not going to be a long editorial because today (and yesterday too) I have been dealing with one of those colds that make you fear that the nose – and everything next to it – may be about to explode in a huge bang. I am really trying hard to write something that makes sense on this laptop, but the tears in my eyes and the reiterated sneezing are making me feel as if the words I am typing are floating in a fish tank... so no, this is definitely going to be a short editorial... OK, let's start with the first contribution to this May issue then, which is about the new method for preparing chiral 1,2-amino tertiary alcohols designed by S. Malcolmson (USA). The second article is a Young Career Focus interview with the emerging organofluorine chemist T. Poisson (France), which is followed by the new method developed by X.-Z. Shu (P. R. of China) for introducing an allyl group on aryl halides using allylic alcohols and a dual Ni/Lewis acid catalyst. Finally, more organofluorine chemistry is presented with the trifluoromethylation strategy based on the use of anionic borazine- $\text{CF}_3^-$  adducts introduced by N. Szymczak (USA). Yay, I guess I've managed to write a few lines...

Enjoy your reading! Aaa-choo...



### Contact

If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

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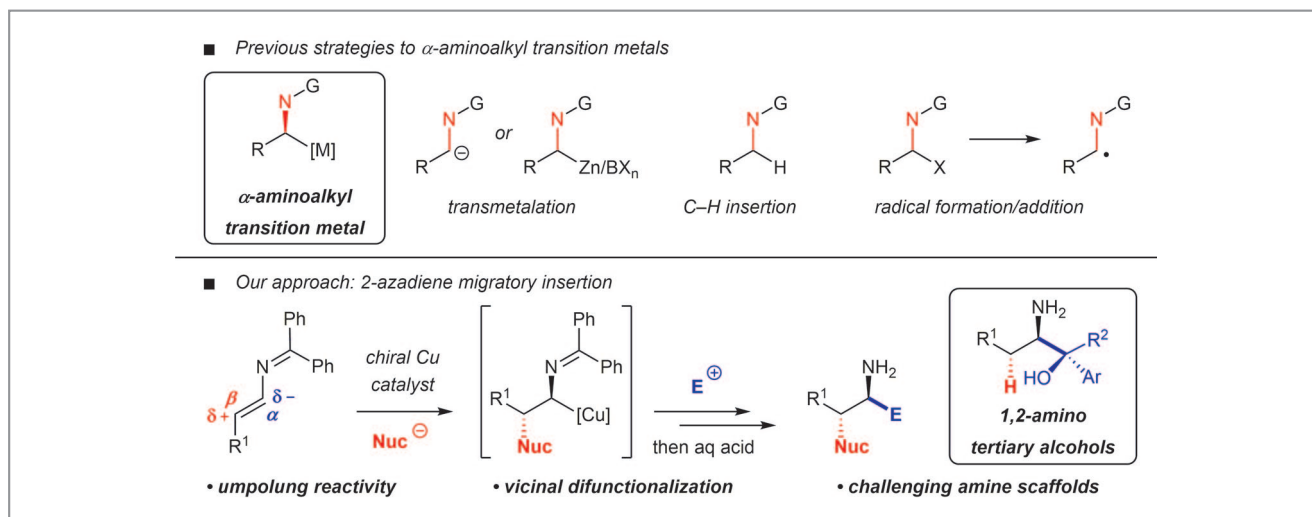
## 2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones

*J. Am. Chem. Soc.* **2018**, *140*, 598–601

The development of methods for the enantioselective construction of amines is an important objective in synthetic chemistry, and C–C bond-forming reactions are a critical subset, as highly functionalized molecules may be assembled quickly by the union of two complex fragments. One common tactic utilizes stereoselective nucleophile additions to electrophilic imines; however, there are several families of amines that are not easily prepared in this manner. 1,2-Amino alcohols are one class that are difficult to access via this normal polarity C–C bond formation. In particular, 1,2-amino *tertiary* alcohols have almost never succumbed to catalytic enantioselective synthesis.

The lab of Professor Steven Malcolmson at Duke University (Durham, USA) envisioned that 1,2-amino tertiary alcohols could be prepared if a nucleophilic  $\alpha$ -aminoalkyl transition metal intermediate could be generated and added to a ketone electrophile (reverse polarity strategy). Professor Malcolmson explained: “Several means of forming such a species are known, including transmetalation, C–H functionalization, and metal recombination with an in situ generated  $\alpha$ -aminoalkyl radical (Scheme 1). However, few of these transformations are

enantioselective and none of these approaches generates an intermediate capable of ketone addition.” Fifth-year graduate student Kangnan Li said: “We have thus developed an unconventional method to access  $\alpha$ -aminoalkyl transition metal species through migratory insertion of 2-azadienes, which then enantioselectively react with ketones to prepare unprecedented 1,2-amino tertiary alcohols.” Previously, 2-azadienes had only sporadically been utilized in synthesis and never for catalytic enantioselective chemistry for preparing chiral amines. Kangnan also pointed out: “Employing 2-azadienes opens up a way to access more complicated downstream amine-containing molecules, as the general reaction platform allows for the vicinal difunctionalization of the N-substituted alkene.” Thus, a Cu catalyst may promote the addition of a range of nucleophiles to the N- $\beta$ -position of the azadiene and subsequent trapping of the resulting aza-allyl copper intermediate with several classes of electrophiles at the N- $\alpha$ -position, formally umpolung of an enamine. Hydrolysis of the product’s imine then delivers the free primary amine. “In this first proof of concept, hydride plays the role of nucleophile in Cu-catalyzed reductive couplings with ketones,” said Professor Malcolmson.



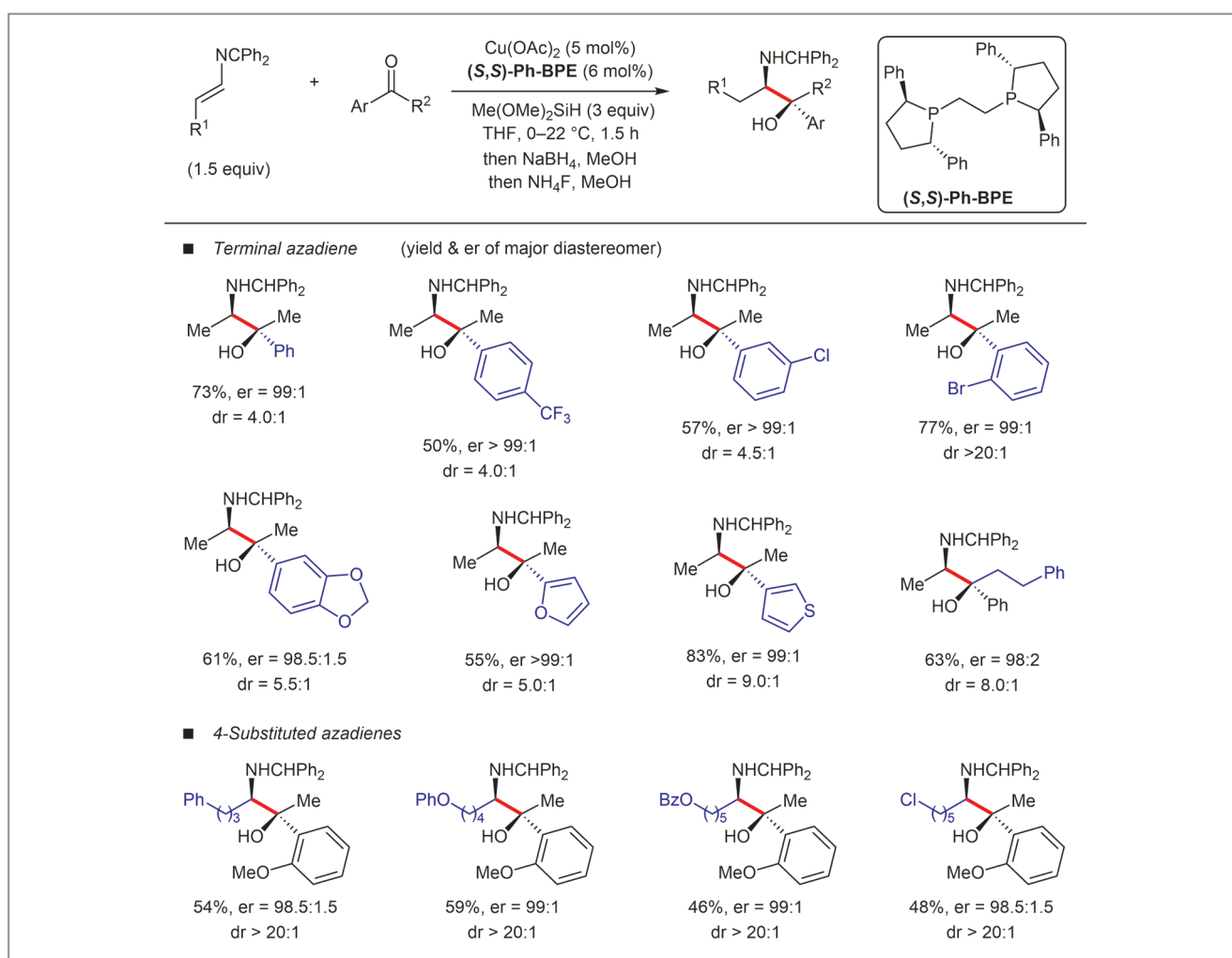
**Scheme 1** 2-Azadiene migratory insertion versus other strategies for forming  $\alpha$ -aminoalkyl transition metals

He continued: “We discovered that the desired reductive coupling reaction could be promoted only by a Cu catalyst bearing Ph-BPE as the chiral ligand (Scheme 2). Under the established optimized conditions, the terminal azadiene ( $R^1 = H$ ) undergoes addition to a range of aryl and heteroaryl ketones. Enantioselectivity is uniformly high but diastereoselectivity is modest in most cases. Still, after reductive and desilylative workup, the major diastereomer of the amino alcohol products could be isolated in good yields. Notably, we found that *ortho* substitution on the aromatic ring or larger alkyl substituents of the ketone ( $R^2$ ) lead to higher diastereoselectivity.”

Additionally, the group established that 4-substituted 2-azadienes were also competent partners in the three-component couplings with several functional groups tolerated

within the substituent. As postdoctoral researcher Dr. Xinxin Shao pointed out: “Critical to the success with substituted azadienes was finding multiple useful methods for preparing them.” Professor Malcolmson added: “In the end, we found two protocols that worked well: 1) a cross-coupling approach, developed in the Liebeskind laboratory, and 2) a Horner–Wadsworth–Emmons reaction, which afforded a separable *E/Z* mixture of stereoisomers.”

However, several limitations of the reaction are apparent. Dr. Shao commented: “Although this work provides a method to prepare chiral 1,2-amino tertiary alcohols with vicinal stereogenic centers, the ketone scope is limited. Dialkyl ketones and electron-deficient ketones are major challenges.” The authors believe that this can be attributed to a chemoselectivity issue: in some cases, the ketone undergoes reduction



**Scheme 2** Selected substrate scope for 2-azadiene–ketone reductive couplings

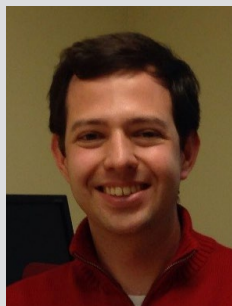
instead of the desired reductive coupling. Electron-poor acetophenones also suffer from this competing side reaction, contributing to somewhat lower yields. Contrastingly, more sterically hindered ketones, such as those with *ortho*-substituted aromatic rings lead to higher quantities of the 1,2-amino alcohols. Dr. Shao also explained: “Substituted azadienes are also less reactive, which leads to more ketone reduction.” As a result, only sterically hindered ketones may currently undergo reductive coupling with 4-substituted azadienes (Scheme 2).

“Our future efforts will focus on the Cu-catalyzed addition of other types of nucleophiles to azadienes for multicompo-

nent couplings as well as trapping the  $\alpha$ -aminoalkyl Cu intermediate with myriad classes of electrophiles,” said Professor Malcolmson, echoed by Kangnan Li who concluded: “Although methods with 2-azadienes are still limited, their ease of preparation and the general reaction illustrated by the reductive coupling with ketones will likely promote increased research interest in this class of reagents.”

*Matthew Fenske*

### About the authors



Prof. S. Malcolmson

**Steven Malcolmson** grew up in Boston, Massachusetts (USA) and graduated with a bachelor's degree in chemistry from Boston University (USA) in 2004. After graduate work with Professor Amir Hoveyda at Boston College (USA), where he developed new Mo catalysts and methods for olefin metathesis as part of a collaborative project with Professor Richard Schrock at MIT (USA), Steve moved to Harvard Medical School (USA), studying natural product biosynthesis with Professor Christopher Walsh as an NIH postdoctoral fellow. He began his independent career as an assistant professor at Duke University (USA) in 2013. His research interests include developing new enantioselective transition-metal-catalyzed reactions and investigating their reaction mechanisms.



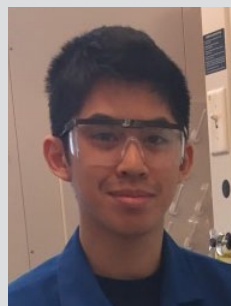
K. Li

**Kangnan Li** was born and raised in Chongqing (P. R. of China). He obtained his bachelor's degree in chemical physics from the University of Science and Technology of China (Anhui, P. R. of China) in 2013, where he carried out undergraduate research under the supervision of Professor LiuZhu Gong. He then joined the Malcolmson group in 2013 at Duke University (USA) as a graduate student and has been working on developing methods for the  $\alpha$ -functionalization of amines.



Dr. X. Shao

**Xinxin Shao** was born in Zhejiang (P. R. of China) and graduated from Northwest University (P. R. of China) in 2010. He then completed his Ph.D. at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) under the supervision of Professors Long Lu and Qilong Shen in 2015. After a year as an SIOC postdoctoral fellow with Professor Dean Toste at UC Berkeley (USA), studying gold(III) chemistry, he joined the Malcolmson group at Duke University (USA) as a postdoctoral researcher in early 2017. His research interests are focused on enantioselective transformations of 2-azadienes to furnish useful molecules.



L. Tseng

**Luke Tseng** was raised in Houston, Texas (USA) and received a bachelor's degree in chemistry from Duke University (USA) in 2017. He is currently a first-year medical student at Columbia University (USA).

## Young Career Focus: Dr. Thomas Poisson (INSA-Rouen, France)

**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. Thomas Poisson (INSA-Rouen, France).

### Biographical Sketch



Dr. T. Poisson

**Dr. Thomas Poisson** received his Ph.D. in 2008 from the University of Rouen (France) under the mentorship of Dr. Vincent Levacher, working on the development of new catalytic enantioselective protonation reactions. Then, he joined the group of Professor Shū Kobayashi as a JSPS postdoctoral fellow, working on asymmetric catalysis by using alkaline earth metal complexes (2008–2010, Tokyo University, Japan). In 2010, he joined the group of Professor Magnus Rueping (RWTH Aachen University, Germany) as a postdoctoral fellow working on the design of new photocatalyzed reactions. In September 2011, he was appointed as an Assistant Professor at INSA-Rouen (France), within the group of 'Fluorinated Biomolecules Synthesis'. In 2015, he defended his habilitation and was elected as a Distinguished Junior Fellow of the French Chemical Society (SCF). He received the Young Lecturer Prize (Prix Jeune Enseignant-Chercheur) from the Organic Chemistry Division of the SCF in 2016. In 2017, he received the Thieme Chemistry Journals Award and was nominated Junior Member of the 'Institut Universitaire de France' (IUF).

### INTERVIEW

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

**Dr. T. Poisson** Our current research interest is dedicated to the development of new methods to build up fluorinated molecules. We have a strong interest in introducing functionalized fluorinated motifs that can be readily modified or that are considered as bioisosters of important functional groups. With that aim, we are focusing on the use of copper or other transition metals to promote or catalyze these transformations. We are also interested in the design of new glycomimetics and in the development of methods to build up chiral fluorinated building blocks.

**SYNFORM** *When did you get interested in synthesis?*

**Dr. T. Poisson** I have been interested in chemistry since high school, but my passion for organic chemistry started during my second year at university. At that time, I really understood the power of organic chemistry and chemical synthesis. I realized that organic synthesis was like a Lego game (my favorite toy when I was a child). The fact that chemists can build any molecule and can imagine and design original reactions to get them was fascinating. Then, my passion grew thanks to the wonderful teachers and mentors I met during my education. They had a tremendous impact on my career.

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

**Dr. T. Poisson** In my opinion, organic chemistry and particularly organic synthesis is a central science. So, I am pretty confident about the future of organic chemistry; it will continue to play a pivotal role. However, although many impressive achievements have appeared in the last 70 years, organic chemists still need to pursue their efforts. Indeed, societal concerns have changed over the last 30 years. Nowadays, glo-

bal warming and aging populations are probably the biggest issues we face. So, we still have a lot of challenges to overcome. For chemists, one of the most important tasks is to make our science more sustainable. With that aim, I believe that the control of selectivity and the development of catalytic and/or green processes will play an important role and will stimulate the community to find original and elegant solutions. I believe our field can contribute to make our planet great again.

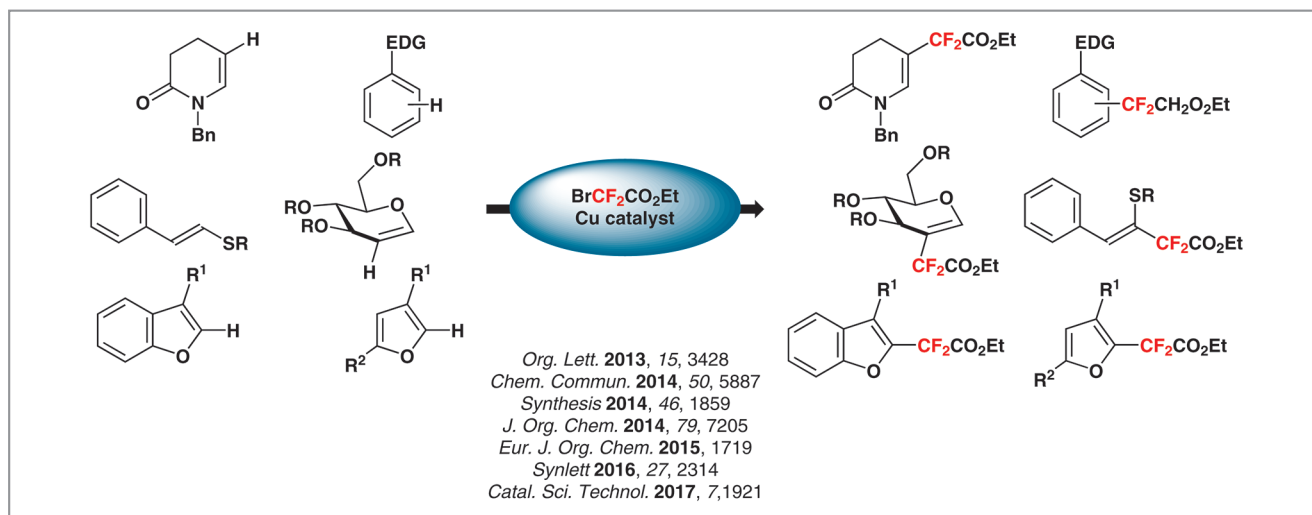
**SYNFORM** Your research group is active in the area of organofluorine chemistry. Could you tell us more about your research and its aims?

**Dr. T. Poisson** Organofluorine chemistry is an important research area nowadays. The impact of the fluorine atom on molecules is quite impressive, particularly on bioactive ones. As a result, a plethora of marketed molecules have a fluorine atom or a fluorinated group in their structure. Therefore, organofluorine chemistry plays a key role in the discovery of drugs and agrochemicals. When we started our research program at the end of 2011, we paid attention to underexplored fluorinated motifs, particularly those bearing a functional group. At that time, we noticed that most reports were focusing on the introduction of the  $\text{CF}_3$  group or the fluorine atom. In the meantime, new drugs with original fluorinated motifs (e.g. Zioptan<sup>®</sup>) appeared. So, we tried to bring our modest contribution to that field by developing new methods to access compounds bearing either emergent fluorinated groups or bioisosters of important biological function, like phosphate for instance.

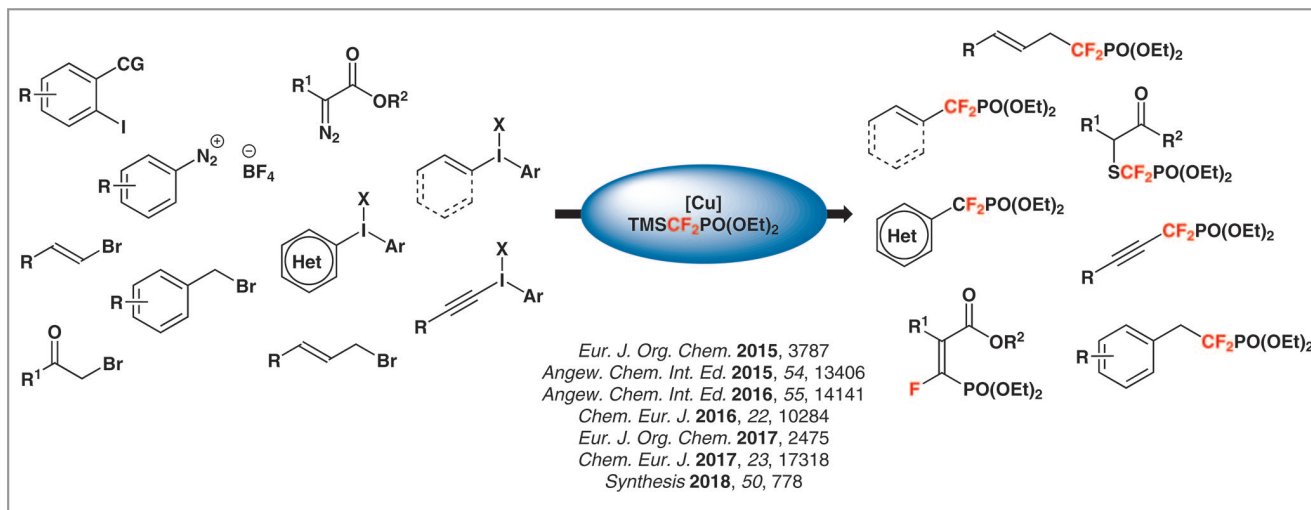
**SYNFORM** What is your most important scientific achievement to date and why?

**Dr. T. Poisson** So far, our research program is still young, so this is a very difficult question. I am tempted to say that it still lies in the future. So far, our most important paper is the first communication we published in the area of copper catalysis (*Org. Lett.* **2013**, *15*, 3428). This paper was a milestone in our program. Most of our current research projects result from this important paper. Indeed, the method we developed to functionalize glycals with a  $\text{CF}_2\text{CO}_2\text{Et}$  group showed us the power of copper as a transition metal for the introduction of a fluorinated motif. Since then, we have been focusing our efforts on copper-based methodologies to build up fluorinated molecules. For us, copper is a fascinating metal and it has many advantages compared to other transition metals (particularly its cost!). However, it is also a very difficult guy to work with! It can exist in four oxidation states and reaction mechanisms are often tricky to determine, but that is what makes it so attractive and motivates us.

*Matthew Farnok*



Scheme 1



Scheme 2



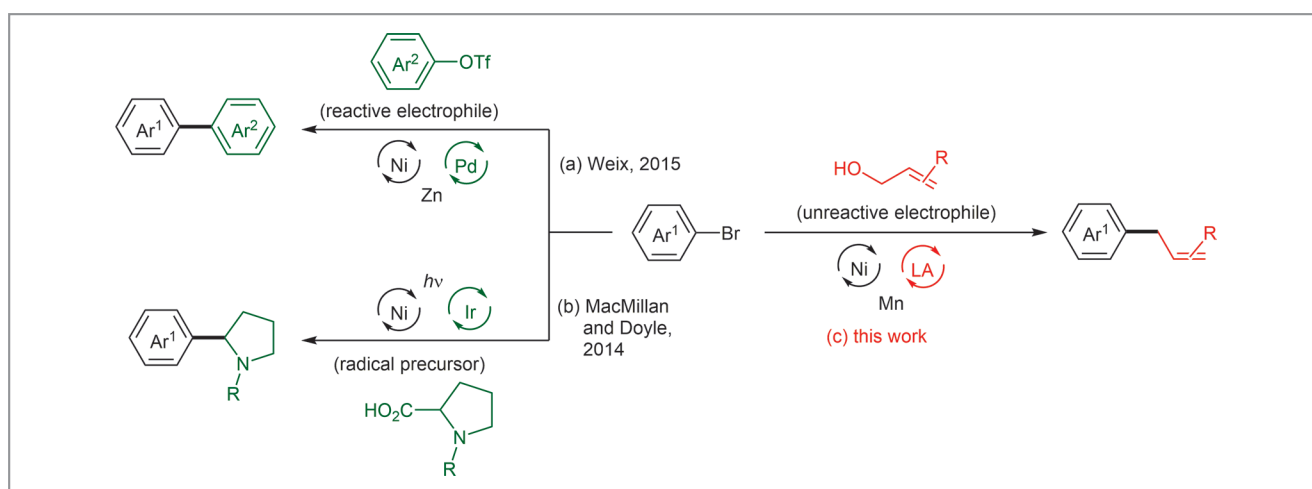
# Dual Nickel and Lewis Acid Catalysis for Cross-Electrophile Coupling: The Allylation of Aryl Halides with Allylic Alcohols

*Chem. Sci.* **2018**, *9*, 640–645

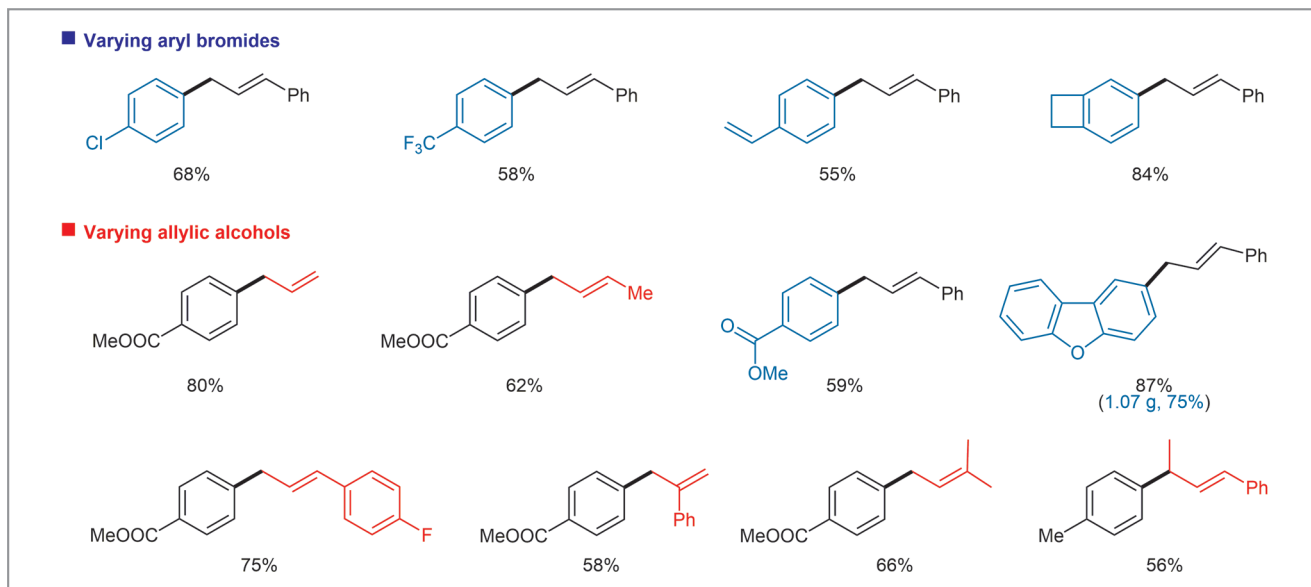
Cross-electrophile coupling provides an attractive approach to combine two different bench-stable electrophiles (aryl/alkyl halides, etc.), avoiding the use of air- and/or moisture-sensitive organometallic reagents (RMgX, RZnX, RSnR<sub>3</sub>, RB(OH)<sub>2</sub>, etc.). Thus, it is an interesting alternative to classic cross-coupling reactions, offering a unique opportunity to discover new reactivity and selectivity within this field of organic synthesis. However, control of selectivity for the cross-product is very difficult, which has restricted the widespread use of this versatile method severely. The strategy described in a recent article from the lab of Professor Xing-Zhong Shu at Lanzhou University (P. R. of China) provides a practical solution for overcoming this selectivity challenge in the cross-electrophile coupling of unreactive C–O/N electrophiles. According to Professor Shu, this strategy is complementary to cooperative catalysis developed by Weix for the cross-electrophile coupling of aryl bromides with aryl triflates, and McMillan for the coupling of aryl bromides with carboxylic acids (Scheme 1). “The design principle is based on the concept of tuning the activation energy of relatively inert C–O/N bonds with catalytic amounts of Lewis acid (LA), which then can be coupled with other electrophiles by Ni catalysis,” explained Professor Shu. “In this work, it has been used for the allylation reaction of Ar–Br with allylic alcohols.”

Allyl arenes are ubiquitous motifs in various biologically active natural products. The selective synthesis of these compounds has been achieved by the coupling reaction of aryl halides with allyl metals, the allylation reaction of aryl metals with allylic substrates, and the reductive allylation reaction of Ar–Br with allylic acetate. Professor Shu remarked: “While these reactions are powerful, they require pre-activation of at least one reactant. Our method achieves direct allylation of Ar–Br with allylic alcohols, providing a convenient approach to allyl arenes from feedstocks.”

The reaction was initially investigated by Xue-Gong Jia, who found that almost all the Ar–Br substrate was converted into unwanted Ar–Ar and no desired product was observed in the absence of a LA. “Addition of catalytic amounts of LA significantly improved the selectivity for the allyl arene,” explained Mr. Jia. Finally, he found that the use of Ni(dppp)Cl<sub>2</sub> (10 mol%), bpy (20 mol%), ZrCl<sub>4</sub> (10 mol%) and Mn (3.0 equiv) in DMA gave the best result. The reaction tolerates a broad substrate scope of electron-rich, electron-poor and sterically hindered aryl bromides. Functional groups such as fluoride, chloride, ester, ketone, as well as a strained ring were accommodated and remained intact. The reaction could be scaled up to gram scale and gave the desired product in a good yield. Professor Shu remarked: “Besides aryl bromides, a



**Scheme 1** Dual catalysis to address the selectivity challenge in cross-electrophile coupling



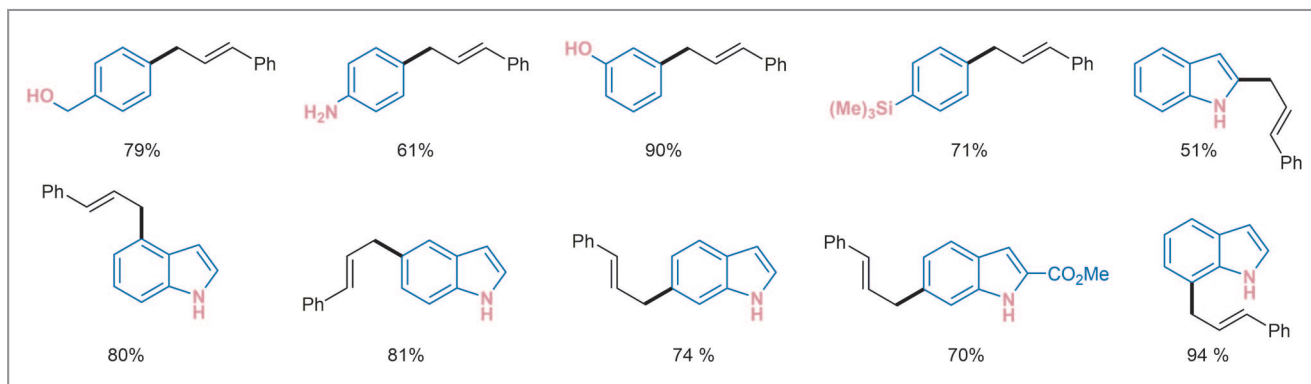
**Figure 1** Selected examples of products obtained from different aryl bromides and allylic alcohols

wide range of primary, secondary and tertiary allylic alcohols were successfully applied and, in most cases, gave linear *E*-products selectively (Figure 1). Prenylated arenes are found in many bioactive compounds, and their synthesis generally requires prenyl-metal species. Such a structure, however, could be efficiently constructed here from isoprenyl alcohol."

The chemoselective allylation of Ar–Br in the presence of nucleophilic functions was investigated by Peng Guo (Figure 2). While the existing allylation reactions with allylic alcohols are efficient for allylating nucleophiles, this reaction is highly selective for electrophiles even in the presence of nucleophiles. "A broad range of nucleophilic aryl bromides were selectively allylated, leaving alcohol, amine, phenol, indole and silane

intact," explained Professor Shu. He continued: "Further, our approach provides direct access to C2-, C4-, C5-, C6- and C7-allylated indoles, being well complementary to prior methods for N1- and C3-allylated products."

While classic allylation reactions are generally proposed to proceed through a  $\pi$ -allyl metal intermediate, this reaction might start with an arylnickel intermediate, which then reacts with allylic alcohols. In order to gain insight into the mechanism of this process, several experiments were investigated by Xue-Gong Jia and Jicheng Duan. Professor Shu explained that the study of the relative reactivity of two electrophiles revealed that Ar–Br was much more reactive than allylic alcohol towards the initial oxidative addition to Ni<sup>0</sup>, which is



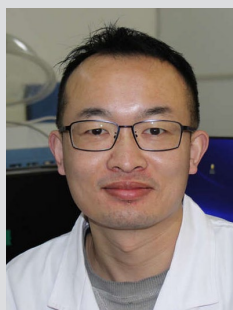
**Figure 2** Chemoselective allylation of Ar–Br having nucleophilic functions

consistent with a mechanism in which  $\text{Ar-Ni}^{\text{II}}(\text{L})\text{Br}$  serves as an intermediate. On the other hand, the initial rate of reaction with complex  $\text{Ar-Ni}^{\text{II}}(\text{bpy})\text{Br}$  was faster than that of reaction with pre-catalyst  $(\text{bpy})\text{Ni}^{\text{0}}(\text{cod})$ . According to Professor Shu, this result further indicates that  $\text{Ar-Ni}^{\text{II}}(\text{L})\text{Br}$  is likely the key intermediate in this reaction. "Such a distinctive mechanism should lead to the unique selectivity of this transformation," he said.

Professor Shu concluded: "I expect that this method will have broad applications in the field of allylation reactions, and furthermore, the strategy can be used for the cross-coupling of various electrophiles."

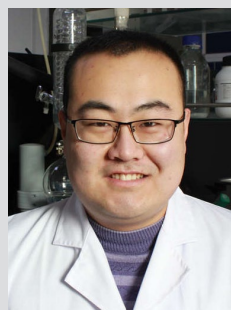
*Matthew Fenwick*

### About the authors



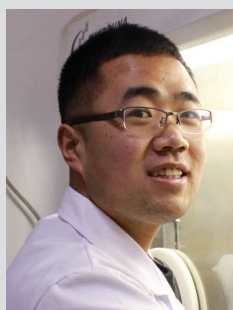
X.-G. Jia

**Xue-Gong Jia** received his B.S. degree from Central South University (P. R. of China) and his M.S. degree from Jiangxi Normal University (P. R. of China). In the summer of 2015, he moved to Lanzhou University (P. R. of China) to pursue his Ph.D. under the guidance of Professor Xing-Zhong Shu. His current research mainly focuses on the cross-electrophile coupling.



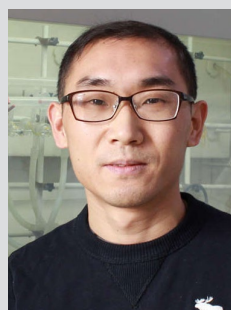
J. Duan

**Jicheng Duan** was born and raised in Shandong (P. R. of China). He received his B.S. degree in chemistry from Liaocheng University (P. R. of China) in 2015. He then started his graduate studies in organic chemistry at Lanzhou University (P. R. of China) under the supervision of Professor Xing-Zhong Shu. His current research focuses on cross-electrophile coupling and enantioselective catalysis.



P. Guo

**Peng Guo** was born and grew up in Gansu (P. R. of China). He received his B.S. degree in chemistry from Beihua University (P. R. of China). In 2015, he started his graduate studies in organic chemistry with Professor Xing-Zhong Shu at Lanzhou University (P. R. of China). His current research focuses on base metal catalysis.



Prof. X.-Z. Shu

**Xing-Zhong Shu** was born and grew up in Zhejiang (P. R. of China). He obtained his B.S. degree from Shaoxing University (P. R. of China) and Ph.D. degree from Lanzhou University (P. R. of China), working with Professor Yong-Min Liang. Upon completion of his graduate work, he moved to the University of Wisconsin–Madison (USA) to carry out postdoctoral research with Professor Weiping Tang. In the summer of 2012, he joined Professor F. Dean Toste's group at the University of California, Berkeley (USA) as a postdoctoral researcher. He began his independent career at Lanzhou University (P. R. of China) in 2015 and was granted by "1000-plan for the young talent". Professor Shu's team is interested in novel synthetic organic methodology, including cross-electrophile coupling, base metal catalysis and enantioselective catalysis.

## Borazine- $\text{CF}_3^-$ Adducts for Rapid, Room Temperature, and Broad Scope Trifluoromethylation

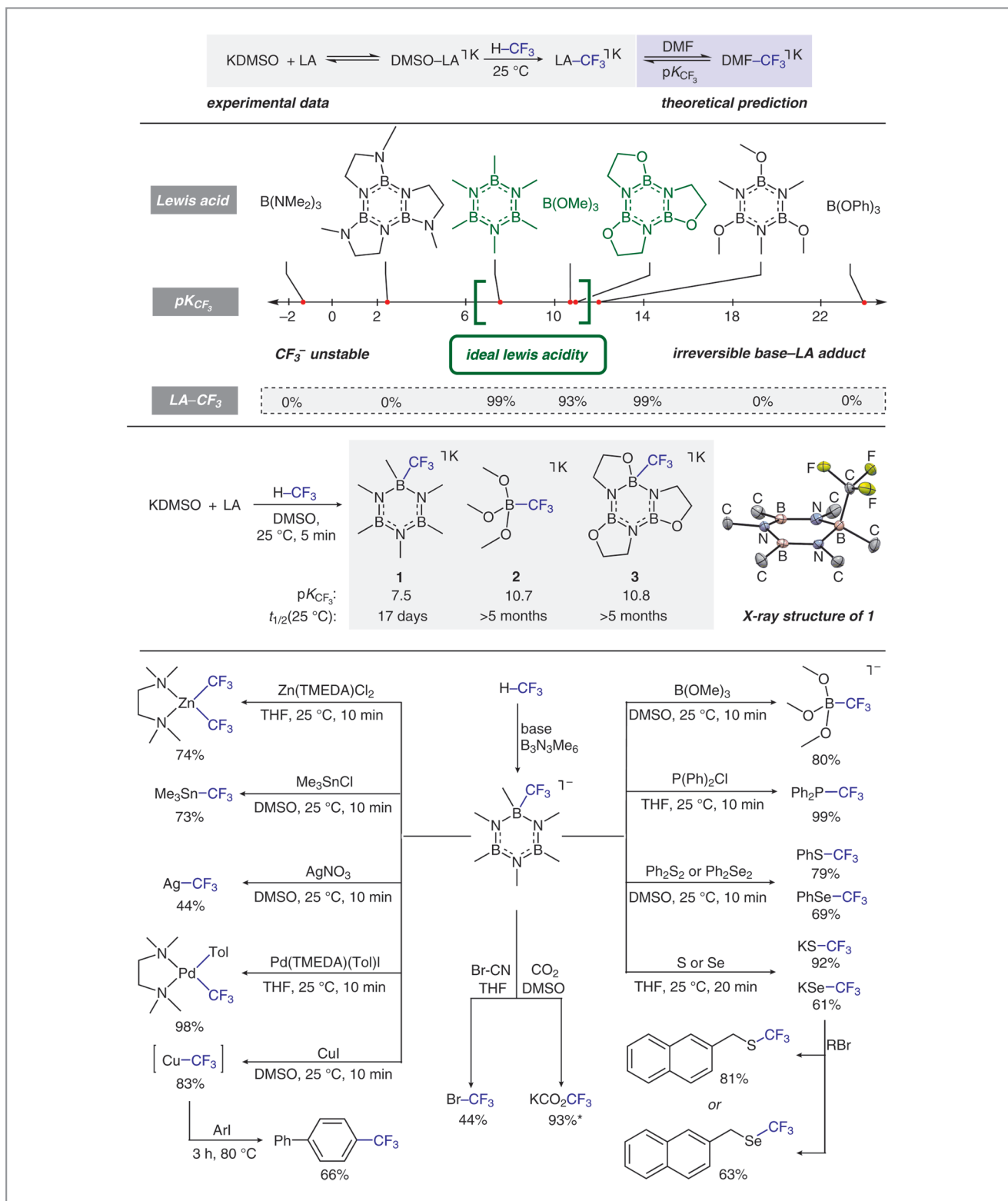
*Angew. Chem. Int. Ed.* **2018**, *57*, 1–7

The trifluoromethyl functional group ( $\text{CF}_3$ ) is now routinely applied in drug discovery because it can increase the lipophilicity and metabolic stability of bioactive compounds.<sup>1,2</sup> 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  $\text{CF}_3$  analogues. As a matter of fact,  $\text{Mg-}$  and  $\text{LiCF}_3$  reagents spontaneously eliminate fluoride, with enough energy released to be considered explosive.<sup>3,4</sup> This inherent instability has hindered progress in the development of new trifluoromethylation methodologies; indeed, ninety years passed between the first nucleophilic methylations<sup>5</sup> and the first efficient nucleophilic trifluoromethylations.”<sup>6</sup> The group of Professor Szymczak recently designed a new approach to  $\text{CF}_3^-$  reagents from an industrial waste gas.<sup>7</sup> “One of the most appealing sources of the  $\text{CF}_3$  functional group that might be used as a synthon in trifluoromethylation methodologies is fluoroform ( $\text{HCF}_3$ ), which is a waste product of the Teflon industry and unfortunately underused,” said Professor Szymczak, who envisioned a design approach conceptually related to heterolytic  $\text{H}_2$  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  $\text{H}_2$  and  $\text{HCF}_3$ , 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  $\text{H}_2$  activation.”

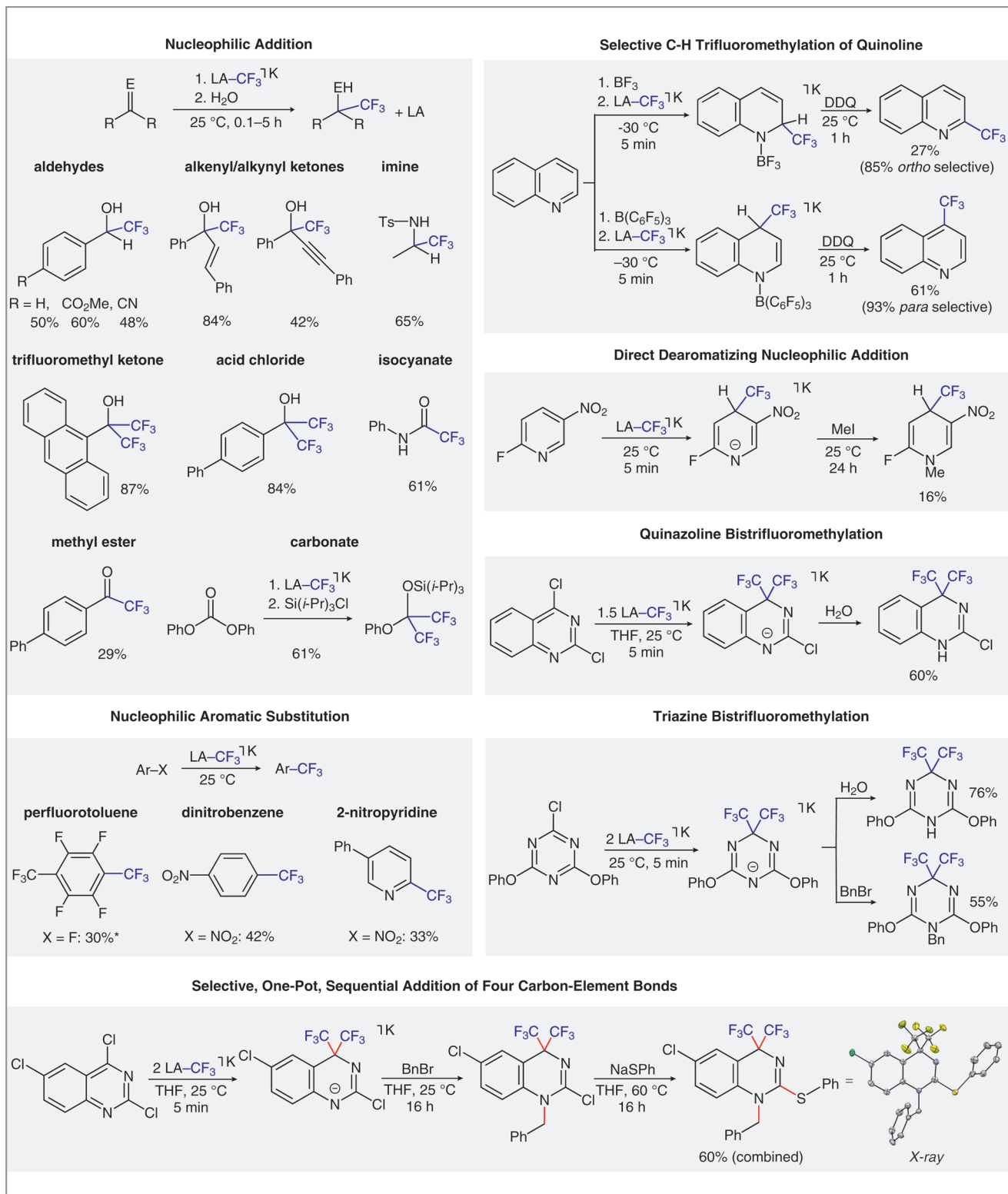
To approach the problem rationally, the Michigan team needed a scale of  $\text{CF}_3^-$  affinity for Lewis acids in order to identify a favorable Lewis acidity regime for both  $\text{CF}_3^-$  stabilization and release. According to Professor Szymczak, if the Lewis acidity of the stabilizer is too high,  $\text{CF}_3^-$  would bind too tightly and not transfer to substrates. If it is too weak,  $\text{CF}_3^-$  may not bind at all or the resulting adduct may decompose at room temperature. Using DFT to calculate the  $\text{CF}_3$  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  $\text{CF}_3^-$  from decomposing, yet reactive enough to be used as a reagent. “The best Lewis acid, hexamethylborazine [ $\text{B}_3\text{N}_3(\text{CH}_3)_6$ ], 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  $\text{CF}_3^-$  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  $\text{CF}_3^-$  transfer reagents from  $\text{HCF}_3$  in quantitative yield at room temperature. They used this strategy to prepare widely used reagents for nucleophilic ( $\text{SiMe}_3\text{CF}_3$ ), radical ( $\text{KSO}_2\text{CF}_3$ ), and electrophilic (Togni I) trifluoromethylation reagents from  $\text{HCF}_3$  and a low-cost base, with complete regeneration and recycling of the borazine stabilizer after  $\text{CF}_3$  transfer. Professor Szymczak noted, “We are working to commercialize the borazine and borazine- $\text{CF}_3^-$  reagent, which we hope will broaden its use.”

The Michigan-based team showed that the borazine- $\text{CF}_3^-$  reagent exhibits high nucleophilicity and reacts with weak electrophiles, such as benzophenone, 1000 times faster than previously reported  $\text{B}(\text{OMe})_3\text{-CF}_3^-$  adducts. They also showed that normally challenging transmetalation reactions occurred rapidly at room temperature, enabling the synthesis of  $\text{Pd}(\text{II})^-$ ,  $\text{Cu}(\text{I})^-$ ,  $\text{Ag}(\text{I})^-$ ,  $\text{Zn}(\text{II})^-$ , and  $\text{Au}(\text{I})\text{-CF}_3$  complexes. Graduate student Jacob Geri noted: “This should open the door to catalytic cross-coupling applications. The unique reactivity of our  $\text{HCF}_3$ -derived reagent inspired us to explore new electrophiles which had not been well-represented in reactions with  $\text{CF}_3^-$  sources, namely arene electrophiles. Trifluoromethylation of electron-deficient arenes and heteroarenes is challenging because cross-coupling methodologies rarely work well for  $\text{CF}_3$  transfer.” The group discovered that their  $\text{CF}_3^-$  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



Scheme 1



Scheme 2

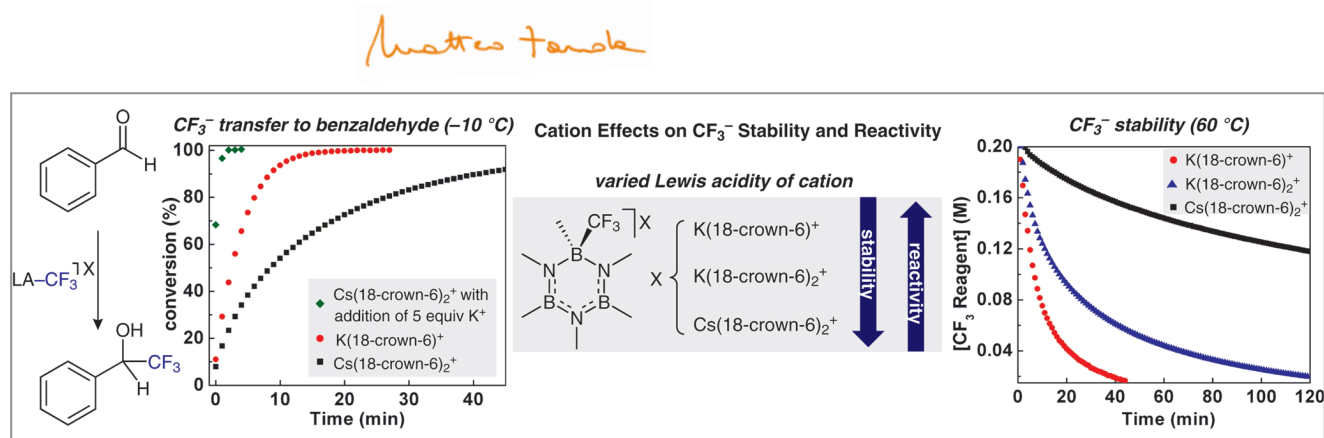
reactions with electron-deficient arenes and heteroarenes via substitution of aryl fluoride, chloride, and nitro groups.” Finally, the potent nucleophilicity of the reagent was showcased with a new geminal bistrifluoromethylation reaction. The authors showed that their synthetic method is selective for 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 counterion 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  $\text{CF}_3^-$  transfer to benzaldehyde by 40-fold. Professor Szymczak noted: “The new reagent may be considered as an inverted analogue to the widely used Ruppert–Prakash reagent ( $\text{TMSCF}_3$ ).  $\text{TMSCF}_3$  is activated by bases, whereas the borazine- $\text{CF}_3^-$  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.”

## REFERENCES

- (1) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur *Chem. Soc. Rev.* **2008**, *37*, 320.
- (2) H. L. Yale *J. Med. Chem.* **1958**, *1*, 121.
- (3) A. Lishchynskiy, F. M. Miloserdov, E. Martin, J. Benet-Buchholz, E. C. Escudero-Adán, A. I. Konovalov, V. V. Grushin *Angew. Chem. Int. Ed.* **2015**, *54*, 15289.
- (4) G. K. S. Prakash, F. Wang, Z. Zhang, R. Haiges, M. Rahm, K. O. Christe, T. Mathew, G. A. Olah *Angew. Chem. Int. Ed.* **2014**, *53*, 11575.
- (5) V. Grignard *Compt. rend. Hebd. Séances Acad. Sci* **1900**, *130*, 1322.
- (6) G. K. S. Prakash, R. Krishnamurti, G. A. Olah *J. Am. Chem. Soc.* **1989**, *111*, 393.
- (7) J. B. Geri, N. K. Szymczak *J. Am. Chem. Soc.* **2017**, *139*, 9811.



Scheme 3

## About the authors



Prof. N. K. Szymczak

to use acidic and basic groups to regulate small molecule binding, activation, and catalysis.



J. B. Geri

Through these efforts, he has developed new nitrile hydroboration catalysts that employ metal–ligand cooperativity to mediate H–B cleavage, selective methods for N<sub>2</sub> activation and protonation using reduced iron centers and organic Lewis acids, and a new class of HCF<sub>3</sub>-derived nucleophilic trifluoromethylation reagents which use a recyclable Lewis acid stabilizer.

**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



M. M. Wade Wolfe

and exploring new types of metal-mediated fluoroalkylation reactions.

**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<sub>3</sub><sup>-</sup> transfer from borazine-CF<sub>3</sub><sup>-</sup> reagents, the development of next-generation reagents,



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(by P. Barrio and co-workers)

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