

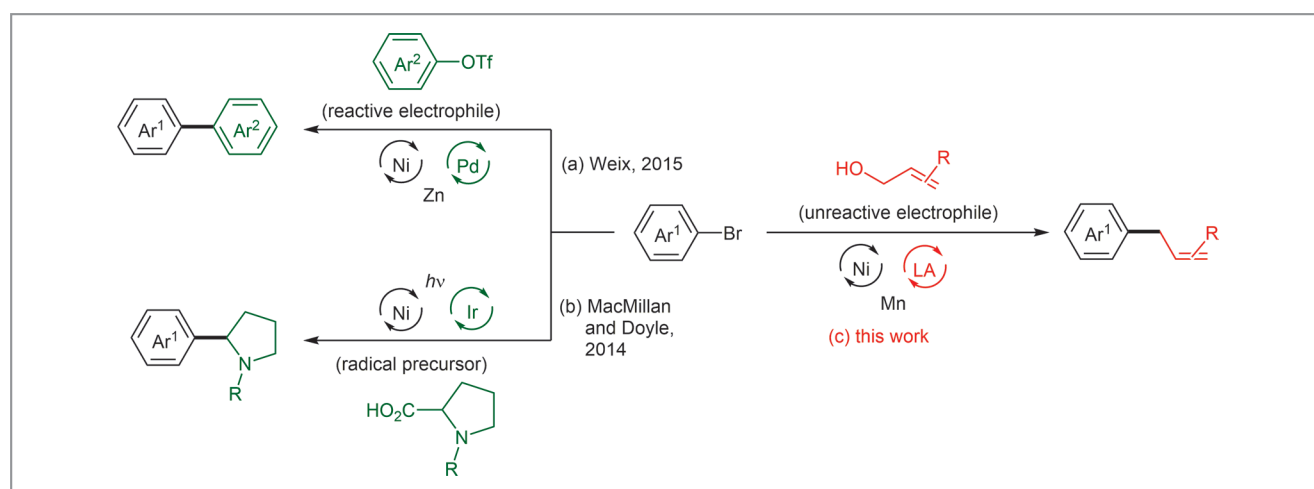
Dual Nickel and Lewis Acid Catalysis for Cross-Electrophile Coupling: The Allylation of Aryl Halides with Allylic Alcohols

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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'_3 , RB(OH)_2 , 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_2 (10 mol%), bpy (20 mol%), ZrCl_4 (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, styrene, amine, 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

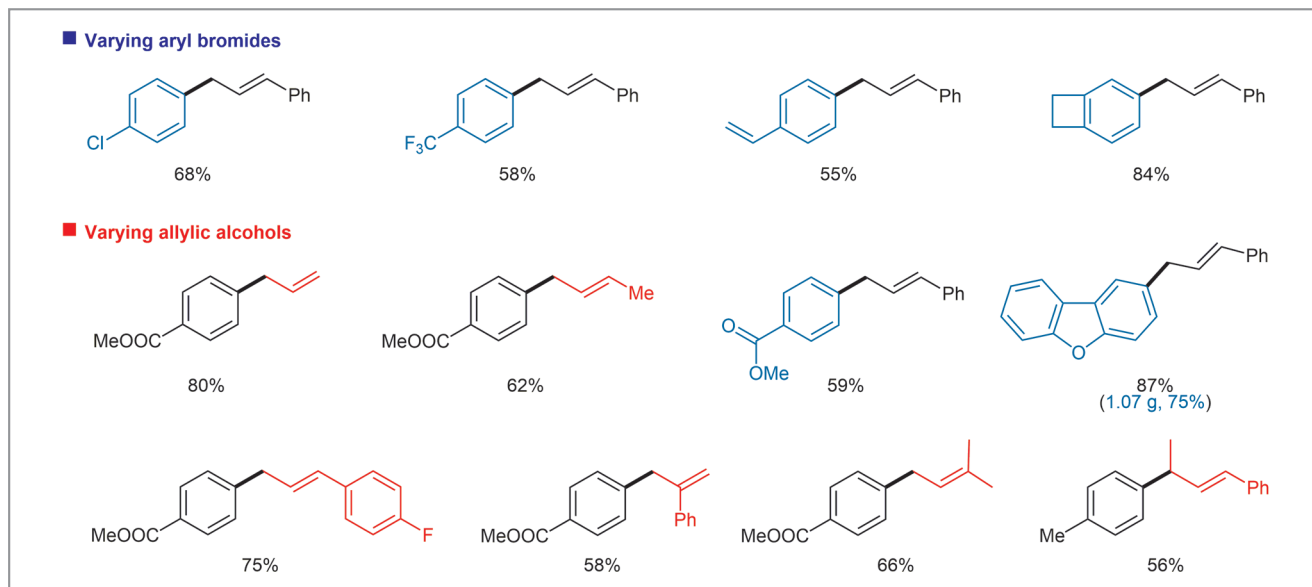


Figure 1 Selected examples of products obtained from different aryl bromides and allylic alcohols

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 π -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 Ni⁰, which is

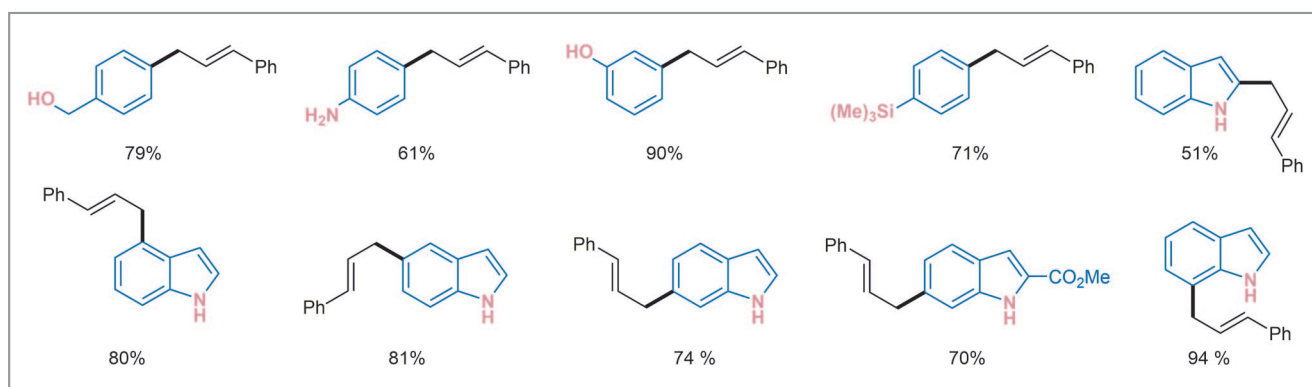


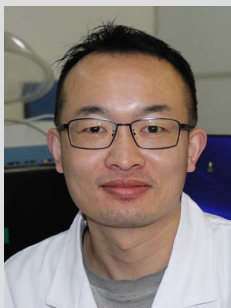
Figure 2 Chemoselective allylation of Ar–Br having nucleophilic functions

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 $(\text{bpy})\text{Ni}^0(\text{cod})$. 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.”

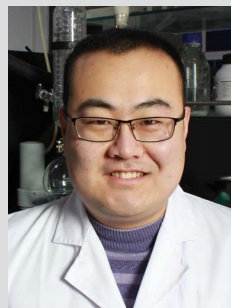
Matthew Fenske

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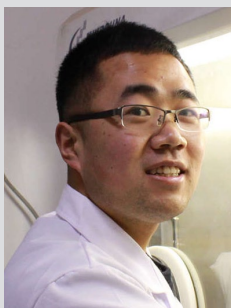
X.-G. Jia

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.



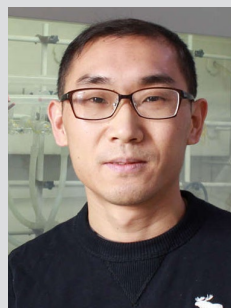
J. Duan

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.