

Unlocking the Friedel–Crafts Arylation of Primary Aliphatic Alcohols and Epoxides Driven by Hexafluoroisopropanol

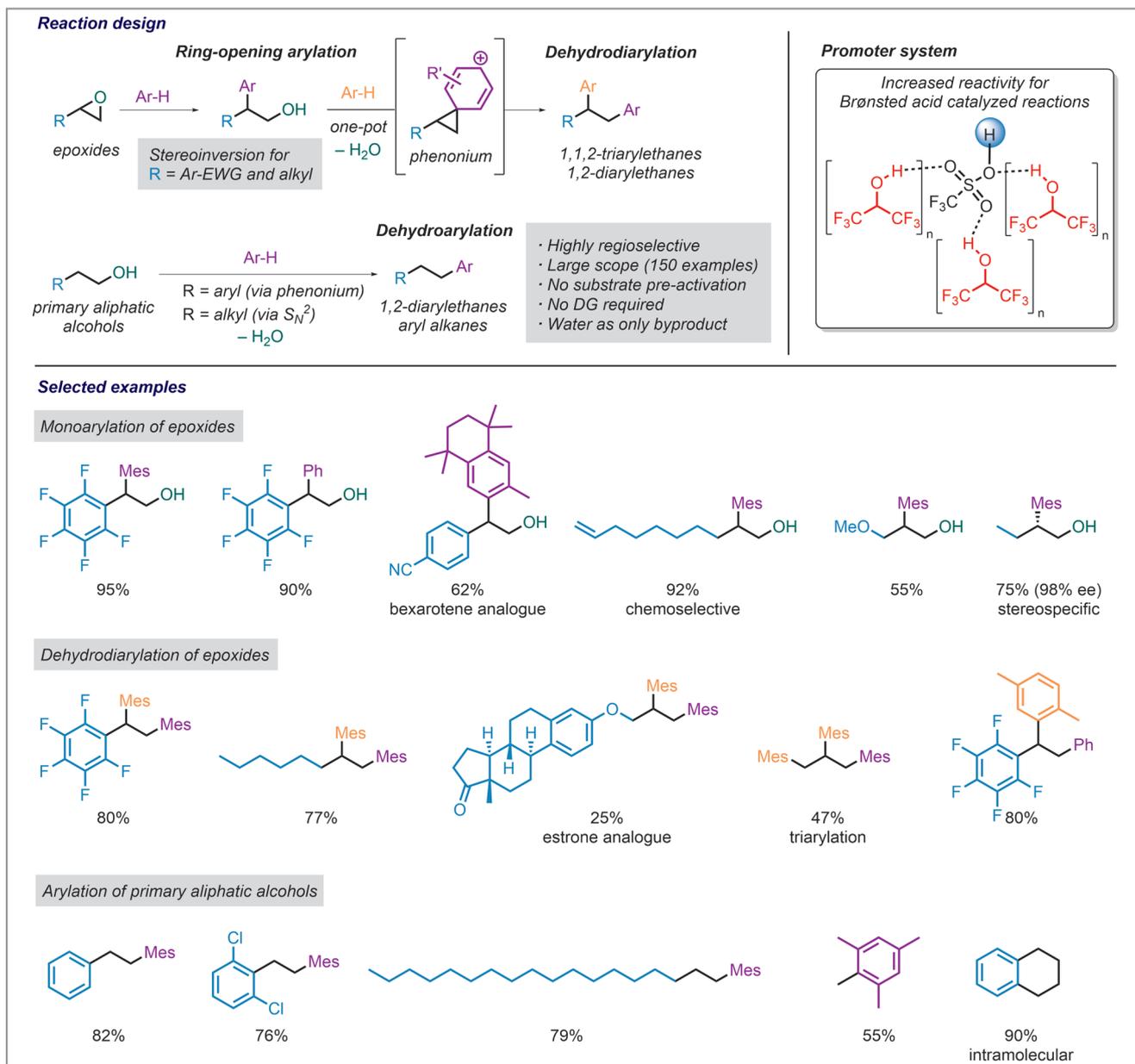
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The Friedel–Crafts alkylation is an important way to form C_{sp^2} – C_{sp^3} bonds. Traditionally, the reaction starts from alkyl halides and uses a stoichiometric quantity of a Lewis acid such as aluminium trichloride. However, alkyl halides are usually prepared from alcohols. Using alcohols directly in the Friedel–Crafts reaction removes the steps and reagents needed for the pre-activation of the alcohol and eliminates the associated waste. Direct Friedel–Crafts reactions starting from alcohols date back to the 1940s, but they were initially limited to tertiary aliphatic alcohols and were carried out with large excesses of Brønsted acids as the promoters, which were often used directly as solvent. Over the subsequent 70 years, the Friedel–Crafts reaction with alcohols was eventually extended to other substitution patterns, such as benzylic, allylic, and propargylic alcohols, otherwise known as π -activated alcohols. Chemists also started to realize that the reaction could be achieved with catalytic quantities of a Lewis or Brønsted acid promoter. However, highly electronically deactivated π -activated alcohols and primary aliphatic alcohols have always remained challenging due to the difficulty (or impossibility) of forming a carbocation intermediate from such substrates. In 2017, the group of Prof. Joseph Moran at the University of Strasbourg (France) found that the combination of catalytic quantities of the strong Brønsted acid TfOH and the solvent hexafluoroisopropanol (HFIP) was an excellent promoter system for direct Friedel–Crafts reactions of electronically deactivated benzylic¹ and propargylic alcohols.² “What is important to understand is that HFIP is not innocent here. Its capacity to generate H-bond networks is a key factor to significantly harness the acidity of the promoter system and activate rather challenging substrates,” said Professor Moran. He added: “We then became excited about the prospects of using this catalytic system to enable direct Friedel–Crafts reactions of primary aliphatic alcohols longer than two carbons, which had been a longstanding challenge in the field. Primary aliphatic carbocations are too unstable, so the reaction needs to operate through an S_N^2 -type mechanism, which is not so easy, because competing carbocation rearrangements lead to undesired branched products,” he explained.

At the same time, Dr. David Leboeuf, who was then working at the University Paris-Saclay (France), had been exploring how Lewis and Brønsted acid catalysts in HFIP could push the

boundaries of classic synthetic transformations such as the hydroarylation of highly deactivated styrenes³ and halofunctionalization of unactivated alkenes,⁴ making similar observations as Prof. Moran regarding the role of HFIP. “I started to think about whether the TfOH/HFIP system might enable Friedel–Crafts reactions of electronically deactivated epoxides and aliphatic epoxides, which were classically excluded from Friedel–Crafts methodologies. Rather than compete against each other on these closely related problems within the same country, we decided to align our forces,” said Dr. Leboeuf, who moved to Strasbourg in 2019. He continued: “The interesting thing about merging these two projects is that the product of a Friedel–Crafts reaction of an epoxide is a primary alcohol, so solving both problems at the same time allowed us to develop sequential Friedel–Crafts reactions starting from epoxides, where two different arenes can be introduced into the molecule in a single experiment.”

In the end, the team was able to show that primary aliphatic alcohols and electronically deactivated epoxides could undergo Friedel–Crafts reactions with a variety of arenes under very similar conditions (5–10 mol% TfOH in HFIP) – only the temperature varied. The researchers found that electronically deactivated epoxides, such as pentafluorophenylstyrene oxide, react at 0–40 °C, and undergo stereochemical inversion upon opening for most substrates. Primary phenylethanol react at 60 °C because of their ability to react through a phenonium ion intermediate. Simple primary aliphatic alcohols that must react through a direct S_N^2 reaction require higher temperatures of 140 °C in a sealed tube. “As anticipated, we could combine the epoxide and alcohol reactions in one pot to directly access complex arylated scaffolds from epoxides,” remarked Prof. Moran. The overall reaction schemes and selected examples are shown in Scheme 1. However, epoxides and primary aliphatic alcohols weren't the only substrates that ended up undergoing Friedel–Crafts reactions under these conditions. “The conditions turned out to be compatible with secondary and tertiary aliphatic alcohols, oxetanes, isochromans, and aziridines as electrophiles,” explained Dr. Leboeuf. “This is as close as you can get right now to general conditions for the Friedel–Crafts reaction without stoichiometric pre-activation,” he added, continuing: “Yet Joseph and I both often get the criticism that HFIP is expensive



Scheme 1 Friedel–Crafts reactions of electronically deactivated epoxides and primary aliphatic alcohols without stoichiometric activating agents

and corrosive. However, based on the simplicity of our system and the fact that those reactions cannot be accomplished in traditional solvents with existing catalysts, the reward is greater.”

Of course, great research does not happen without a great team. “The lion’s share of the credit must go to the co-workers who did the experiments, especially to PhD student Shaofei Zhang, who did the bulk of the work, and to postdoctoral fel-

low Dr. Marie Vayer, who helped push it over the line,” said Dr. Leboeuf. Professor Moran added: “The work also relied on preliminary results generated by two previous PhD students and an MSc intern, all of whom are co-authors on the paper. We’re also grateful to Prof. Chris Rowley at Carleton University (Canada) and his PhD student Nazanin Rezajooei for their help with DFT calculations.”

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About the authors



Prof. J. Moran

Joseph Moran is a professor and group leader at ISIS, a joint institute of the University of Strasbourg (France) and the CNRS. After completing his PhD in organic chemistry (André Beauchemin, University of Ottawa, Canada), he took postdoctoral positions in chemical biology (John Pezacki, NRC Canada) and transition-metal catalysis (Michael Krische, University of Texas at Austin, USA). He moved to France as an assistant professor in 2012 and was promoted to full professor in 2018. His research interests include prebiotic systems chemistry, supramolecular catalysis, and the use of vibrational strong coupling in organic chemistry.



Dr. D. Leboeuf

David Leboeuf is an associate professor at the University of Strasbourg (ISIS) in France. He earned a PhD in 2009 at the Université Pierre et Marie Curie (France), where he explored new transition-metal-catalyzed cyclizations with Max Malacria. He then moved to the University of Rochester (USA) with Alison J. Frontier to investigate abnormal Nazarov electrocyclizations (2010–2012). After a second postdoctoral stay at the Institut Català d'Investigació Química (ICIQ, Spain) with Antonio M. Echavarren, developing new gold catalysts (2012–2013), he was appointed by the CNRS as assistant professor in 2013 at the Université Paris-Saclay (France). In 2019, he joined ISIS (UNISTRA), where he is currently developing new simple synthetic methods featuring supramolecular chemistry, cultivating the use of HFIP in synthesis.