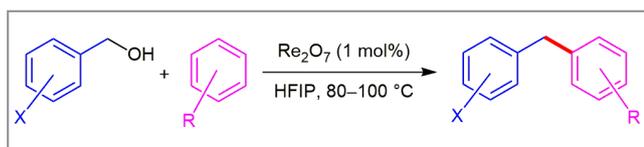


Diarylmethane Synthesis through Re_2O_7 -Catalyzed Bimolecular Dehydrative Friedel–Crafts Reactions

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First-year chemistry students learn that the OH group is a very poor leaving group and nucleophilic substitution reactions involving alcohols as electrophiles require suitable activation of the hydroxy function. In this context, transient OH group activation with an electrophilic catalyst is particularly attractive for a number of reasons, including environmental and economic ones. Dehydrative coupling reactions able to produce complex organic structures from benzylic alcohols are among the most interesting emerging options in the toolbox of modern organic synthesis.

The roots of this project lie in the work that Professor Floreancig's group at the University of Pittsburgh (USA), in conjunction with Dr. Youwei Xie of Huazhong University of Science and Technology (P. R. of China) has done on Re_2O_7 -mediated allylic alcohol transposition reactions.¹ Professor Floreancig said: "Our initial method employed electrophilic groups to trap one isomer of a mixture of transposing allylic alcohols, thereby providing a thermodynamic driving force that allowed for useful bond-forming processes. However, we noticed while using epoxide groups as electrophilic traps that increasing the level of substitution on the allylic alcohol led to an unexpected change in the product.² Further exploration revealed that the added substitution actually caused the allylic alcohol to serve as a precursor to a carbocation, causing the epoxide group to act as the nucleophile."



Scheme 1 The new dehydrative Friedel–Crafts methodology

This result allowed the authors to consider alternative reaction designs in which allylic alcohols act as precursors to electrophiles that react with appended nucleophiles to form rings.³ This was demonstrated through the development of a stereoselective dehydrative tetrahydropyran formation that proceeded through cation formation through Re_2O_7 -mediated ionizations of allylic alcohols followed by nucleophilic addition by pendent alcohols. "The applicability of this method

to complex molecule synthesis was established by its use in a cyclization reaction that delivered a late-stage intermediate in the construction of the natural product herboxidiene," explained Professor Floreancig. He continued: "We demonstrated the superiority of Re_2O_7 over Brønsted acids for allylic cation formation by comparing the efficiency of these processes with sulfonic acid catalyzed variants. This led us to postulate that the perrhenate ester, or possibly the protonated perrhenate ester, was the relevant intermediate in these reactions rather than a protonated alcohol."

Youwei Xie, who developed the early stages of the Re_2O_7 -catalyzed transformations as a graduate student and was later a postdoc in Ben List's group at the Max Planck Institute (Germany), made the connection between the dehydrative cyclization chemistry and the outstanding work being done on Lewis and Brønsted acid mediated benzylic alcohol ionization by Hall⁴ and Moran.⁵ "These processes, which were applied to diarylmethane synthesis via Friedel–Crafts reactions, were very impressive because of their ability to generate cations from electron-deficient benzylic alcohols," remarked Professor Floreancig, continuing: "Youwei postulated that the superiority of Re_2O_7 to Brønsted acids in the dehydrative cyclization reactions could be translated to benzylic alcohol ionization, leading to lower catalyst loadings and milder reaction conditions. He quickly validated his hypothesis by showing that Re_2O_7 catalyzes the dehydrative coupling of pentafluorobenzyl alcohol with *p*-xylene in hexafluoroisopropyl alcohol (HFIP, a solvent that was critical to the success of Hall's and Moran's studies) to generate the corresponding diarylmethane." The reaction proceeded with low catalyst loading (1 mol%) and provided the product in very high yield. Dr. Xie examined several additional benzene derivatives and showed that their reactivity followed an expected trend based on their nucleophilicities. He was also able to show that the reaction of *p*-methoxybenzyl alcohol with *p*-xylene could be effected with as little as 0.01 mol% Re_2O_7 . "At this point Youwei informed me of the results and asked if I would like to have a graduate student complete the study. I accepted this generous offer and Qi Qin, who had just completed the dehydrative cyclization study, continued with the project," said Professor Floreancig.

Mr. Qin's initial objectives were to explore the reactivity of a number of benzylic alcohols that incorporate electron-

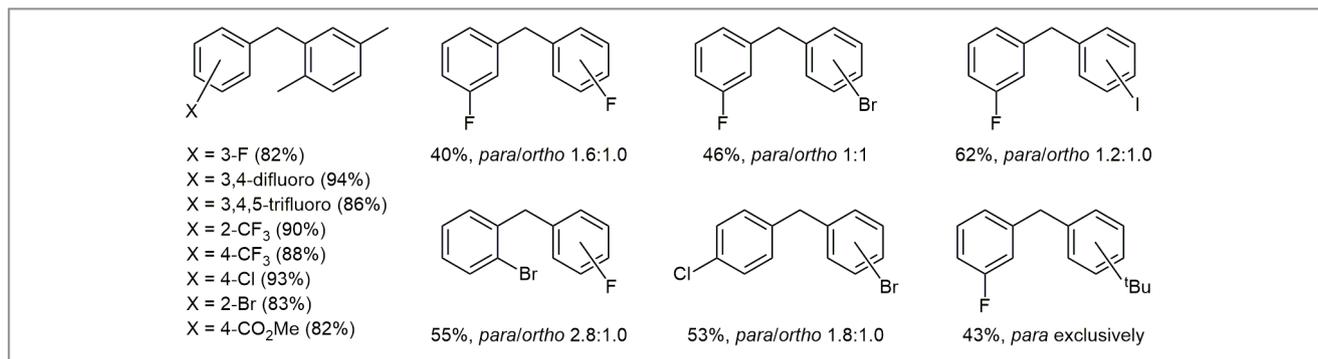


Figure 1 Reaction scope and regioselectivity

withdrawing groups. Professor Floreancig explained: “While he did not complete a formal Hammett plot, he was able to use Hammett parameters to show which substrates would be reactive. He also showed that certain halogenated arenes could act as nucleophiles. This will be valuable for efforts in which the products can be further diversified through cross-coupling chemistry or – in case of drug candidates – prevented from metabolic destruction by fluorine incorporation.” During this study, Mr. Qin discovered that Re₂O₇·SiO₂ could be used as an alternative to crystalline Re₂O₇ with only a modest reduction in rate for most substrates. This agent, simply prepared by stirring Re₂O₇ and SiO₂ in Et₂O followed by solvent evaporation, was useful for measuring the quantities of catalyst to be used in these low-loading experiments and provided superior handling properties during a humid Pittsburgh summer. Very reasonable concerns arose in the initial review of this paper as to whether Re₂O₇·SiO₂ is a distinct catalyst or simply an agent that releases Re₂O₇. “Qi addressed this issue by heating Re₂O₇·SiO₂ in HFIP then filtering the solids. The filtrate was observed to be catalytically active, indicating that Re₂O₇·SiO₂ acts by releasing Re₂O₇ into solution,” said Professor Floreancig.

Lowering the catalyst loading became Mr. Qin’s next objective. He observed that 0.1 mol% loading of Re₂O₇·SiO₂ was sufficient for promoting ionization of moderately deactivated systems, such as *m*-fluorobenzyl alcohol, but was not effective for the ionization of highly deactivated alcohols, such as *p*-trifluoromethylbenzyl alcohol. The catalyst loading to ionize activated alcohols, however, could be lowered significantly. “*p*-Methoxybenzyl alcohol couples with mesitylene in the presence of just 0.0033 mol% Re₂O₇·SiO₂. Moreover, the concentration of this reaction could be increased to 2.5 M without consequence, and to 5.0 M with only a minimal impact on reaction efficiency” said Professor Floreancig. He continued: “This is significant because it improves the process with respect to cost and environmental impact. HFIP, despite showing

extremely useful properties, is somewhat expensive. We attributed the drop in efficiency at 5.0 M to a change in solvent properties since the relative volume of HFIP is much lower when the substrate concentrations are increased. This led us to examine the role of and need for HFIP in these processes. Qi showed that pure HFIP is required for reactions of unreactive substrates while mixtures of HFIP and 1,2-dichloroethane (DCE) can be used for more reactive substrates.” This is consistent with the high polarity of HFIP being required to generate unstable carbocation intermediates. However, the reaction with *p*-methoxybenzyl alcohol in pure DCE provided bis-*p*-methoxybenzyl ether as a significant by-product. “This suggests that HFIP plays the additional role of suppressing the nucleophilicity of the alcohols through hydrogen bonding,” explained Professor Floreancig.

He continued: “These reactions generate water as the sole by-product, and Re₂O₇ is an anhydride. Therefore, Mr. Qin explored the possibility that perrhenic acid is the active agent in these reactions. This work showed that HOREO₃ can serve as a suitable alternative to Re₂O₇ or Re₂O₇·SiO₂ for these reactions. This result was significant because HOREO₃ is less expensive than Re₂O₇ while being equally reactive and can be handled as readily as Re₂O₇·SiO₂. However, this also led to questions as to whether the reactions proceeded through a perrhenate ester, as initially proposed, or simply through Brønsted acid catalysis.”

“We had initially assumed that the reaction proceeded through a perrhenate ester since the pK_a values of HOREO₃ and TfOH, the acid used in Moran’s studies,⁵ differ by nearly 13, but the two agents are comparable at promoting the reactions,” said Professor Floreancig, who pointed out that other Brønsted acids that have pK_a values that are similar to HOREO₃, such as TFA and *p*-TsOH, are not nearly as effective at promoting the reactions. “The possibility exists, however, that an anomalous acidity enhancement is observed for HOREO₃ in

HFIP and none of our prior experiments could disprove that hypothesis,” said Professor Floreancig, who explained: “We addressed this initially by comparing the catalytic potencies of Re_2O_7 , HReO_3 , and TfOH in the coupling of *p*-trifluorobenzyl alcohol with *p*-xylene. We observed similar reaction rates with 1 mol% Re_2O_7 , 2 mol% HReO_3 , and 10 mol% TfOH . Lowering the loading of TfOH to 2 mol% resulted in a much slower reaction. Thus, if HReO_3 acts as a Brønsted acid then the HFIP enhancement must provide >13 orders of magnitude in potency. The remarkable nature of this conclusion still does not invalidate the Brønsted acid hypothesis. We addressed this through comparing the reactivity of the alcohols, which can act through protonation or perrhenate ester formation, with acetate analogues, which can react only through protonation since the acyl group blocks perrhenate ester formation. TfOH catalyzes Friedel–Crafts alkylation reactions with the alcohols and the acetates, but Re_2O_7 and HReO_3 only promote reactions with the alcohols.” This study finally dispelled the notion that HReO_3 acts solely as a Brønsted acid and supported the intermediacy of the perrhenate ester, though reactions could indeed proceed through a protonated perrhenate ester intermediate. Notably, the reactions between the acetate substrates in the presence of TfOH , while effective, proceeded slightly more slowly than the reactions of the corresponding alcohols despite the greater nucleofugacity of acetic acid in comparison to H_2O . This – according to the authors – indicates an additional role of HFIP as a desiccant in these reactions.

Professor Floreancig believes that this study is significant for multiple reasons. “From a practical perspective the use of HReO_3 as an agent for alcohol ionization provides a mild yet powerful approach to the formation of potent and important electrophiles. From a mechanistic perspective, the validation of a perrhenate or protonated perrhenate ester provides a new intermediate that can be generated in situ from readily available precursors.” Professor Floreancig concluded: “The use of perrhenate esters as progenitors to cationic intermediates should be considered as an alternative for processes that utilize strong acids to initiate ionization or that employ leaving groups that must be generated in a distinct step from an alcohol precursor.”



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About the authors



Prof. P. Floreancig

Paul Floreancig received his B.S. degree in chemistry from Indiana University (USA) in 1986. He moved to Yale University (USA) where he earned an M.S. degree while working for Professor Fred Ziegler. After spending two years at Eli Lilly (USA) he left for Stanford University (USA), where he earned his PhD in 1997 with Professor Paul Wender while working on the total synthesis of paclitaxel. After two years as an NIH postdoc-

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Dr. Y. Xie

Youwei Xie received his B.Sc. degree from Jilin University (P. R. of China) in 2006. He moved to the USA and received his M.Sc. degree under the guidance of Prof. Tewodros Asefa from Syracuse University (USA), and moved to the University of Pittsburgh (USA) to earn his PhD under the guidance of Prof. Paul Floreancig. In 2015, he became a Humboldt post-doctoral fellow at the Max-Planck-Institut für Kohlenforschung (Germany)

with Prof. Benjamin List. In early 2018, he joined the faculty at Huazhong University of Science and Technology (HUST, P. R. of China) where he is a professor in the School of Chemistry and Chemical Engineering.



Q. Qin

Qi Qin was born in Shanxi (P. R. of China). He received his B.S. degree in pharmaceutical science from Peking University Health Science Center (P. R. of China) in 2011, and his M.S. degree in chemical biology at the same school in 2013 under the guidance of Dr. Xin-shan Ye investigating stereoselective glycosylation based on pre-activation of thioglycosides. He then joined Dr. Paul Floreancig's group at the University of Pittsburgh (USA) as

a graduate student. His main research is centered around the synthesis of oxygen-based heterocycles and diarylmethane scaffolds through the use of Re_2O_7 catalysis.