α-C–H Functionalization of π-Bonds Using Iron Complexes: Catalytic Hydroxyalkylation of Alkynes and Alkenes

The α-functionalization of alkynes and alkenes with aldehydes reported in this study from the group of Professor Yiming Wang from the University of Pittsburgh (USA) is based on stoichiometric reactions of cationic alkene-iron π-complexes originally investigated by Myron Rosenblum and his research group in the 1970s. In particular, Rosenblum and co-workers observed that (i) cationic alkene complexes of cyclopenta-dienyliron dicarbonyl were strongly acidic, with α-protons undergoing quantitative deprotonation using triethylamine as the base; and (ii) the resulting δ-allyliron complexes were good nucleophiles.[1] Subsequent studies revealed that these allyliron complexes are transition-metal analogues of allyl-stannanes, having similar nucleophilicity[2] and reacting via an open-transition state S_E2' pathway.[3,4] However, the propargyl-ic functionalization of alkynes was not investigated in detail in these, nor in subsequent, studies.

Nevertheless, given this reactivity, the Wang group posited that it would be possible to develop a catalytic functionalization of the α-position of nonpolarized C–C multiple bonds using the general catalytic cycle, shown in Scheme 1 for alkyne substrates. "We observed that this would be a redox-

neutral process using electrophilic reagents for functionalization," explained Professor Wang. He continued: "We chose to investigate C–C bond formation using this process, since allylic (and propargylic) functionalization reactions that introduce carbon-based substituents (rather than heteroatoms) at the α-position are comparatively rare. Moreover, we wanted to focus our attention on alkynes rather than alkenes, since most known methods for allylic functionalization tend not to extend well to the corresponding propargylic functionalization reaction or result in other types of reactivity when applied to alkyne substrates,[5,6] while other reported transformations lead to the concomitant reduction or functionalization of the triple bond.[7,8]"

Professor Wang pointed out: "Zhang and co-workers have designed gold catalysts for alkyne-to-diene isomerization[9] and propargylic C–H functionalization,[10] but there are some important differences between our system and the Zhang system. In our system, (i) the base is external rather than being built into the ligand; (ii) the reaction halts at the homoprop-argylic alcohol without subsequent metal-catalyzed cyclization of the initially formed product; and (iii) in some cases, alkenes can also be used as substrates."

The authors attribute the relative rarity of C–C bond-forming propargylic functionalization reactions to the incompatibility of many potential nucleophilic carbon sources with the oxidizing conditions typically employed for the installation of heteroatoms by C–H functionalization, but also to the more challenging energetics for the formal removal of H[·] or H[–] from the propargylic position, as compared to the analogous allylic position, as evidenced by bond dissociation energy (BDE) and hydride ion affinity (HIA) data, shown for typical alkenes and alkynes in Figure 1.[11] "Given these considerations, we felt that a redox-neutral process that effects C–H functionalization through the removal of proton (H^{+}) may be able to overcome these challenges," said Professor Wang.

"Our initial attempts to implement the proposed catalytic cycle focused on the use of trityl cation (E–LG = CPh$_3$[+]BF$_4$[–]) as a model (or, perhaps 'toy') electrophile for the development of a proof-of-concept reaction and for initial exploration of reactivity," continued Professor Wang. After verifying that the reaction could be achieved stoichiometrically, the challenge, taken up by postdoctoral researcher Dr. Yidong Wang, was to
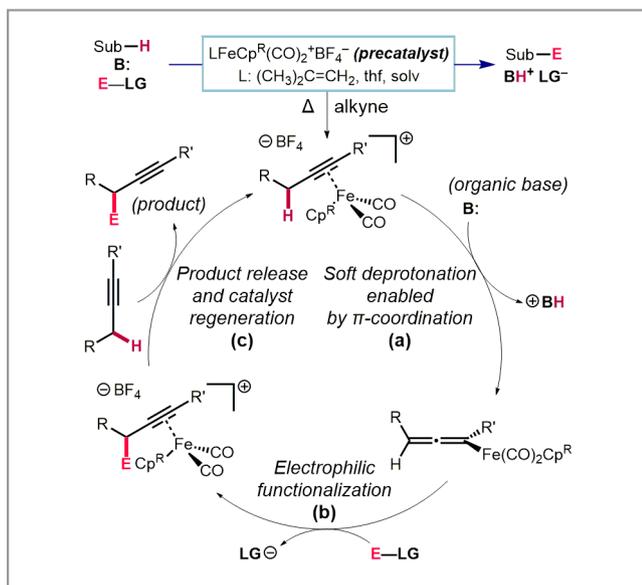
Scheme 1 Balanced equation and proposed catalytic cycle
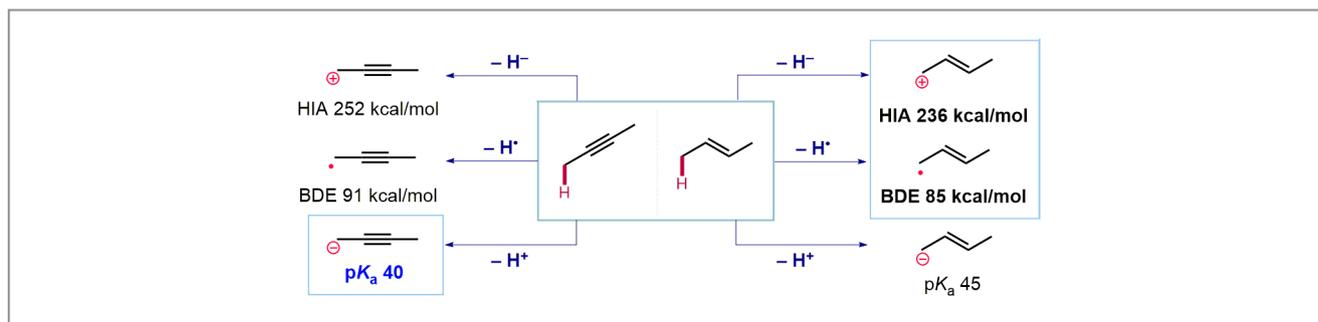
Figure 1 Comparative energetics of allylic and propargylic C–H activation

find a set of conditions wherein all three steps of the catalytic cycle are compatible (Scheme 2). Using 3-hexyne as the model alkyne and [CpFe(CO)$_2$(3-hexyne)]$^+$BF$_4^-$ (Cp = C$_5$H$_5$) as the catalyst, a variety of bases were screened, including hindered secondary and tertiary alkylamines, tertiary anilines, hindered amidines (DBU) and guanidines (Barton's base), and Proton Sponge. However, Dr. Wang found that 2,6-dimethyl-substituted pyridines (collidine and lutidine) were uniquely successful, giving an initial hit of 14% yield (the rest gave < 2%). "Another crucial observation that Dr. Wang made was that the more hindered and electron-rich [Cp*Fe(CO)$_2$ (3-hexyne)]$^+$BF4$^-$ (Cp* = C$_5$Me$_5$) was particularly successful," said Professor Wang. In addition to disfavoring amine-deactivation of the cationic catalyst, subsequent kinetic experiments revealed that steps (b) and (c) of the catalytic cycle were also accelerated (results yet to be published).
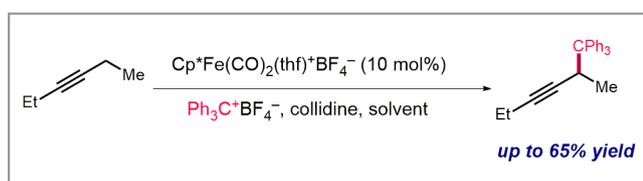

Scheme 2 Preliminary catalysis

"Using these findings, we sought to develop a more challenging but practically useful coupling of aldehydes and alkynes (Scheme 3)," said Professor Wang. He continued: "An additional parameter to consider was the nature of the Lewis acid used to activate the carbonyl group of the alkyne. It was found that BF$_3$·OEt$_2$ was particularly effective in this regard, although certain silyl triflates also gave some coupling product. A re-optimization of the base revealed that tetramethylpiperidine (TMPH) was superior to the hindered pyridine bases. It was found that toluene was the optimal solvent for this process, although chlorinated solvents like dichloroethane or benzotrifluoride were also good choices. During the course of scope exploration (Scheme 4), it was found that the addition of catalytic zinc bistriflimide (Zn(NTf$_2$)$_2$) as an auxiliary Lewis acid, presumably for carbonyl activation, was beneficial for less reactive aldehyde substrates."

The scope of the process was then fully investigated by graduate students Jin Zhu, Austin Durham, and undergraduate Haley Lindberg. "A variety of electron-poor aryl aldehydes were competent substrates, as were some moderately electron-rich aryl aldehydes," explained Professor Wang. The group found that functional groups including a diaryl ketone, esters, pinacol esters, and tertiary sulfonamides, and aryl chlorides and bromides, including a 2,6-dichlorinated aldehyde, were tolerated. Similarly, α,β-unsaturated aldehydes, and other non-enolizable aldehydes, were also useful substrates. A somewhat narrower range of substituted aryl methyl alkynes were found to react efficiently, as did higher aryl alkyl alkynes. However, the latter class of substrates gave mixtures of diastereomers, generally with little diastereocontrol.

"Somewhat surprisingly, it was found that dialkyl alkynes were generally poor substrates, although previous α-tritylation of these substrates was successful, and the stoichiometric hydroxyalkylation with an aryl aldehyde in the presence of BF$_3$·OEt$_2$ was also successful," remarked Professor Wang. He continued: "In certain cases, useful yields of the coupling product could still be obtained by using a higher loading of iron catalyst. Finally, we were pleased to find that these conditions were somewhat transferrable to terminal alkenes. For instance, 1-octene could be functionalized in 40% yield using the current conditions."

The group is currently conducting investigations into improved catalysts for faster reactions and higher turnover numbers. "Kinetic studies and *in situ* spectroscopic studies are being conducted to gain insight into the catalyst deactivation process and reasons behind the scope limitations," said
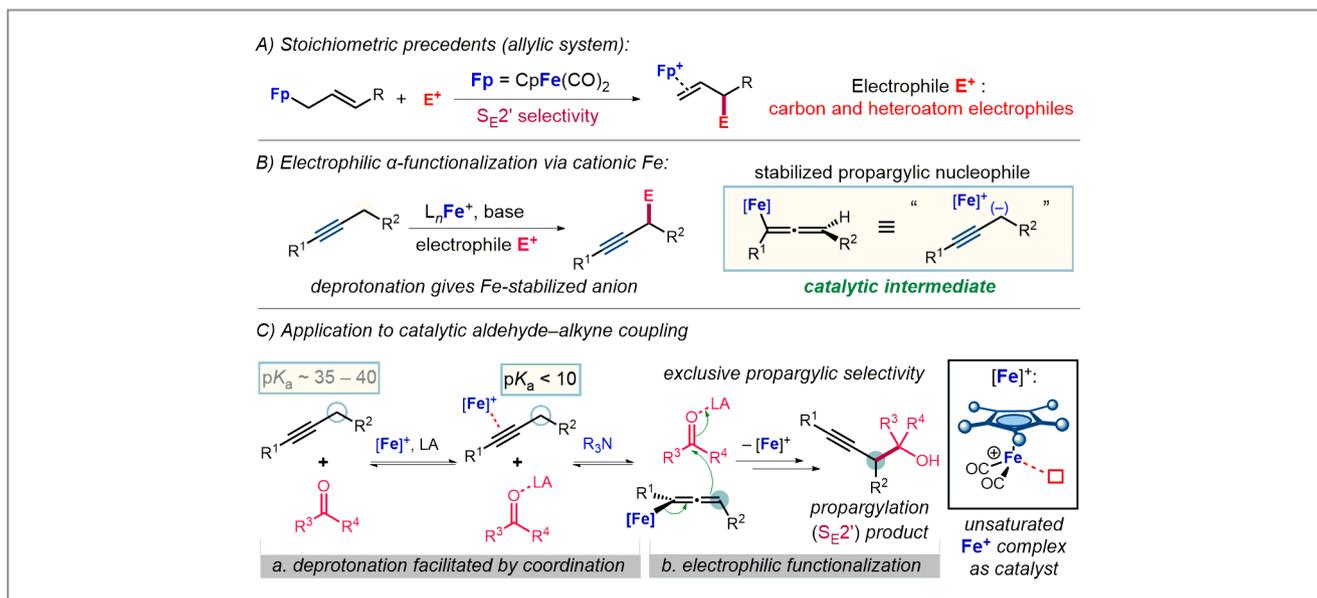
Scheme 3 Propargylic nucleophiles in catalytic alkyne-aldehyde coupling
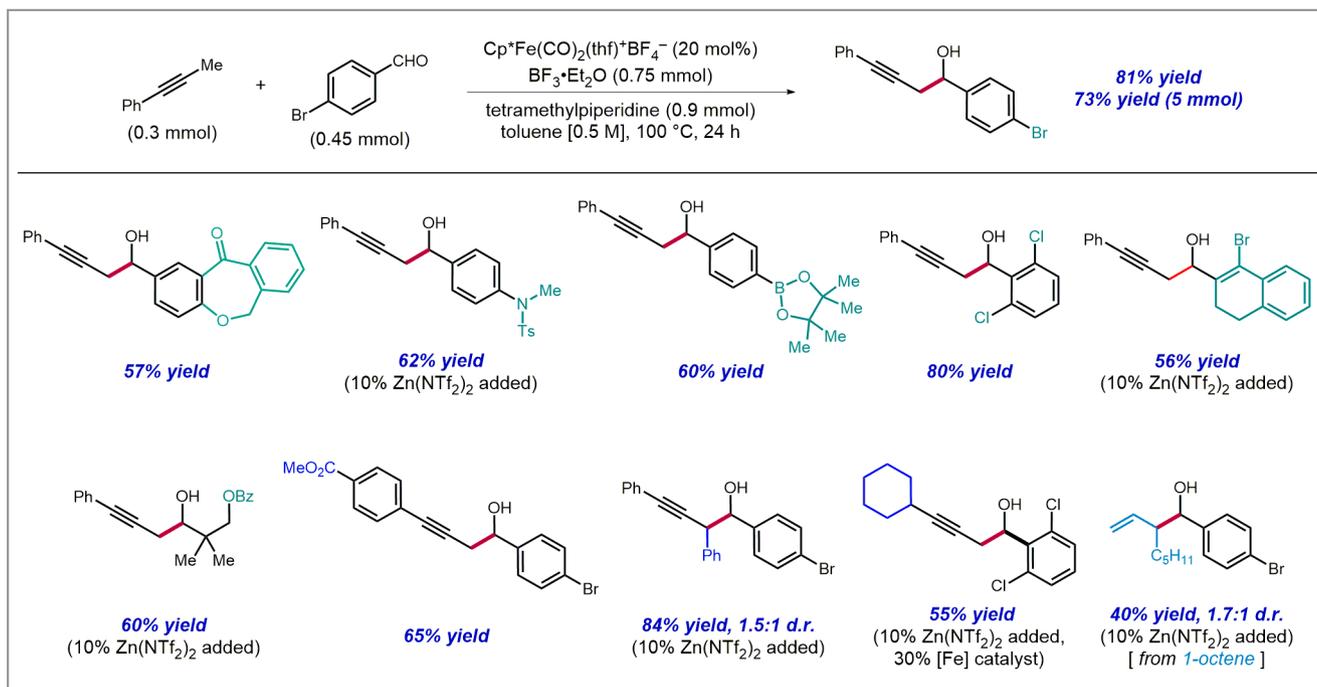
Scheme 4 Reaction conditions and selected scope

Professor Wang, who concluded: "Improved catalysts will be applied to a variety of carbon and heteroatom electrophiles currently being explored. Ligands with bulky, chiral groups are also being investigated for the development of stereocontrolled C–H functionalization processes."
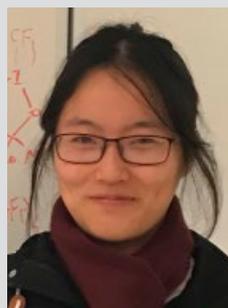
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Yidong Wang was born in 1990 in Zhejiang Province (P. R. of China). He obtained his BSc degree at Northeast Normal University (P. R. of China) under the supervision of Prof. Xihe Bi in 2012. Then he moved to East China Normal University (P. R. of China) to begin his PhD studies. In 2017, he obtained his PhD under the supervision of Prof. Junliang Zhang. After that, he joined Prof. Yiming Wang's group as a postdoctoral researcher and focused on C–H bond activation of unsaturated bond catalyzed by iron(II).

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Jin Zhu was born and grew up in Jiangsu (P. R. of China). She graduated from Nanjing University (P. R. of China) with a BA degree in chemistry in 2018, where she studied in the group of Prof. Shaolin Zhu for her undergraduate thesis. Now, she is carrying out doctoral research in the Wang group at the University of Pittsburgh (USA).

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Austin Durham was born and grew up in Harrisburg, Pennsylvania (USA). He received his Bachelor's degree at Hamilton College in New York (USA) where he worked under Professor Emeritus Robin Kinnel. He is currently conducting his PhD research on the use of iron catalysis for novel transformations under Dr. Yiming Wang at the University of Pittsburgh (USA).

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H. Lindberg

Yiming Wang was born in Shanghai (P. R. of China), and grew up in Boulder, CO (USA). He graduated with an AB/AM degree from Harvard University (USA) in 2008 after conducting research in the group of Prof. Andrew Myers. After obtaining his PhD under the supervision of Prof. Dean Toste at UC Berkeley (USA) in 2013, he was an NIH Postdoctoral Fellow in the laboratory of Prof. Stephen Buchwald at MIT (USA) before joining the Department of Chemistry at the University of Pittsburgh (USA) in the fall of 2017.

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