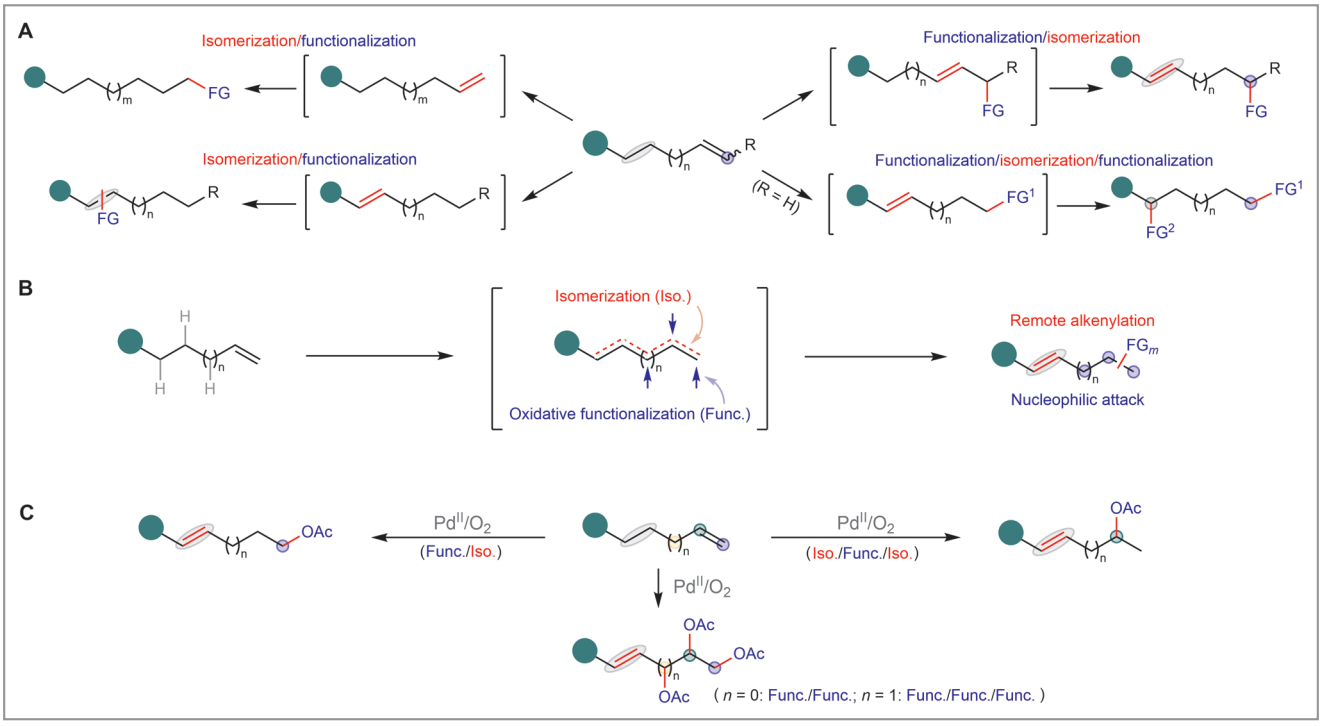
Multi-site Programmable Functionalization of Alkenes via Controllable Alkene Isomerization

Nat. Chem. **2023**, *15*, 988–997

The direct and selective functionalization of hydrocarbon chains, including their multi-functionalization, is a fundamental challenge in modern synthetic chemistry.[1,2] Conventional functionalization of C=C double bonds and C(sp^3)–H bonds provides some solutions, but site diversity remains an issue. "The merging of alkene isomerization with (oxidative) functionalization provides an ideal method for remote functionalization, which would provide more opportunities for site diversity,[3,4]" said Professor Wanbin Zhang, from Shanghai Jiao Tong University (Shanghai, P. R. of China), who added: "However, the reported functionalized sites are still limited, essentially consisting in a specific terminal position and internal site; thus new site-selective functionalization, including multi-functionalization, remains a largely unmet challenge (Scheme 1A).[3,4]" The research described in a recent article published in *Nature Chemistry* by the Zhang group provides a new solution for the diverse functionalization of flexible olefins. The authors designed a new catalytic system which controls the reaction sequence between alkene isomerization and oxidative functionalization, thus achieving multi-site programmable functionalization of terminal alkenes (involving the C=C double bond and multiple C(sp^3)–H bonds), accompanied by controllable remote alkenylation (Schemes 1B and 1C). "Specifically, aerobic oxidative 1-acetoxylation (anti-Markovnikov), 2-acetoxylation, 1,2-diacetoxylation and 1,2,3-triacetoxylation have been realized," said Professor Zhang. The authors demonstrated that this method can enable the conversion of readily available terminal olefins from petrochemical feedstocks into unsaturated alcohols and polyalcohols, and particularly into different monosaccharides and *C*-glycosides.

Professor Zhang remarked: "In fact, the study began as early as in 2013, when Zhengxing Wu (the first author of the title article) was still a doctoral student in my group. At that



Scheme 1 Remote functionalization of alkenes

  • Published online: November 15, 2023 • DOI: 10.1055/s-0040-1720615

time, he was focusing on the aerobic oxidative difunctionalization of conjugated dienes, which was a good method for obtaining multifunctional compounds, because of the presence of an easily convertible double bond in the functionalized product. Considering that the preparation of conjugated dienes is not easy, and our group has accumulated experience in the oxidative functionalization of mono-alkenes, we discussed whether it was possible to obtain the product identical to that resulting from the difunctionalization of conjugated dienes from readily available unactivated mono-alkenes." Dr. Wu recalled: "In the preliminary reaction design, we initiated the process with an easily monitored terminal alkene, namely 5-phenylpent-1-ene. The reaction was designed to proceed through tandem oxidative acetoxylation to afford the 1,2-difunctionalized products while preserving the double bond. These reactions were then conducted using palladium as the catalyst, acetic acid as the nucleophile, and oxygen as the oxidant. Interestingly, after exploring various reaction conditions, we did not obtain the desired 1,2-diacetoxylated product; instead, we observed a small number of 1- and 2-acetoxylated products, accompanied by the isomerization of the double bond to the conjugated position with the phenyl group. Additionally, we also observed that changing the acidity of the sodium acetate/acetic acid buffer had a significant impact on the ratio of 1- and 2-acetoxylated products, although the ratio was not particularly high (3:1~1:2). We realized that this is a very interesting phenomenon, so the reaction mechanism was studied further. Through the mechanism studies, we learned that both 1-acetoxylation and 2-acetoxylation involve alkene isomerization and oxidative functionalization (the oxidative functionalization is facilitated by $Pd^{II}X_2$, while alkene isomerization is facilitated by *in situ* generated Pd^{II}–H species). The distinct reaction sequence between alkene isomerization and oxidative functionalization leads to the formation of different 1- and 2-acetoxylated products." At that point, after further discussions, the authors had a breakthrough idea: "Drawing inspiration from computer programming languages using 0 and 1, we thought that if we can precisely control the sequence of alkene isomerization and oxidative functionalization, similarly to programming commands, the diversity of functionalized sites could, in theory, be significantly enriched." While the idea was promising and offered rich possibilities, finding a suitable catalytic system to precisely control the reaction sequence turned out to be extremely challenging. After more than a year of exploration (until 2015), the research had successfully achieved 1-acetoxylation with good yield and selectivity; however, further significant progress could not be achieved regarding the control of the reaction sequence. On the other hand, Zhengxing Wu began preparing for his doctoral graduation. Hence, it was agreed that the research would be temporarily placed in stand-by, for more systematic development when the timing was appropriate.

Dr. Wu remained in Professor Zhang's group as an assistant research fellow after graduating in 2017, and then the study was resumed. "Some things cannot be expected to be accomplished overnight; after pausing for some time, we may gain new perspectives and ideas when we look back," said Professor Zhang. Indeed, after in-depth analysis of the body of data accumulated from the past, the authors realized that many factors can simultaneously affect the rate of alkene isomerization and oxidative functionalization in the catalytic reaction, which makes it difficult to design suitable reaction conditions. Professor Zhang continued: "To make progress, we needed to simplify the problem and identify the main conflicting elements. This would help us gain a clear direction to move forward." Dr. Wu recalled: "After thorough considerations, we came to the conclusion that alkene isomerization is more challenging to control compared to oxidative functionalization. To address this, we simplified the rate of oxidative functionalization to be constant, while the focus shifted to controlling alkene isomerization, which was deemed to be the key challenge in solving the problem." Furthermore, the authors broke down the control of alkene isomerization on the hydrocarbon chain into two parts: alkene isomerization before oxidative functionalization, and alkene isomerization after oxidative functionalization. This rationalization allowed for a more systematic approach to tackle the challenge of controlling the reaction sequence. After finalizing the research idea, Professor Zhang and co-authors conducted a comprehensive analysis of the impact of various factors on alkene isomerization based on existing literature. They also designed a series of experiments to observe the influence of different factors on the two types of alkene isomerization. "One year later, we had made significant progress and essentially determined that the alkene isomerization before oxidative functionalization could be primarily controlled by the stability of the Pd(II)–H species in the catalytic system," recalls Professor Zhang. This stability was found to be influenced by the acidity of the reaction system (Scheme 2A, top).[5,6] The isomerization after oxidative functionalization, enabled by Pd(II)–H, was found to be predominantly controlled by Pd(II)–H coordination with the alkene chain and the rotation of the coordinating bond. These processes were found to be influenced by the synergistic coordinating effects of the amide solvent and chloride ion (Scheme 2A, bottom).[7–10] "By utilizing the aforementioned factors to control the reaction sequence, as of 2019, we achieved 1-acetoxylation (anti-Markovnikov), 2-acetoxylation, 1,2-diacetoxylation, and even 1,2,3-triacetoxylation of alkenes," said

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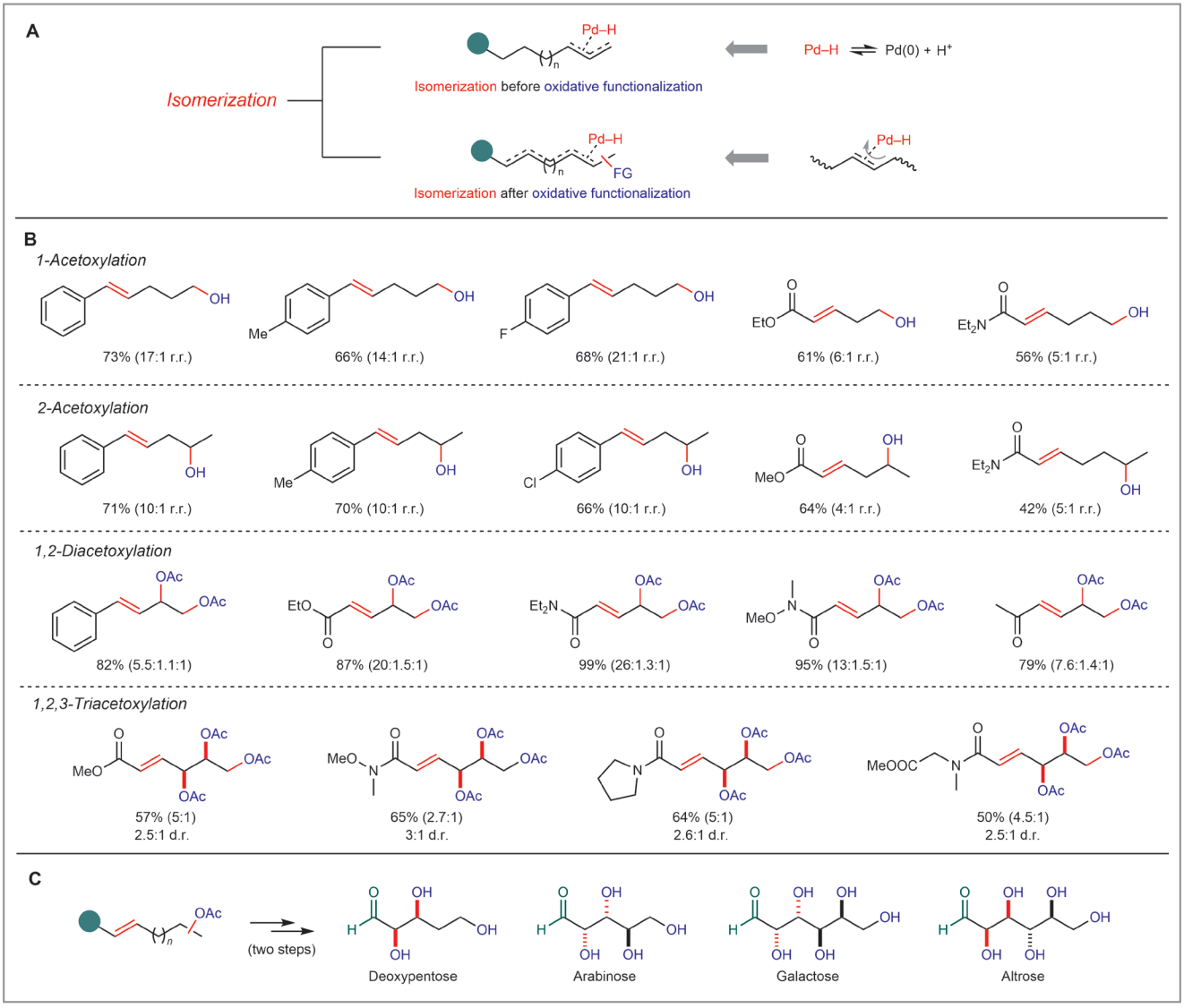
Professor Zhang. "These transformations were accompanied by controllable remote alkenylation as shown in Scheme 2B. Notably, for the 1,2,3-triacetoxylation, five sequential site activations on the hydrocarbon chain (one C=C double bond and three C(sp^3)–H bonds) in a one-step reaction was achieved." In the following year, the authors of this study continued to deepen their understanding of the mechanism and further expanded the method's scope. "After successfully achieving further dihydroxylation of the unsaturated bond in our catalytic product, we came to the realization that this could be a promising approach to constructing sugars," Professor Zhang remarked. "Based on this, one of the most efficient syntheses of pentose and hexose sugars (including some rare ones) with different configurations was achieved via a two-step route from the catalytic products (Scheme 2C)."

Professor Zhang concluded: "The study period was quite extensive, and we encountered countless difficulties throughout the research process. There were even moments when the idea of giving up halfway was contemplated. However, fortunately, we persevered and overcame the challenges. This methodology allows for the diverse functionalization of flexible olefins, which has the potential to efficiently produce compounds that are needed in medicinal chemistry and materials science. We firmly believe that the controllable



Scheme 2 Selected catalytic products of aerobic oxidative acetoxylations and their application

 Synform **2023/12**, A202–A206 • Published online: November 15, 2023 • DOI: 10.1055/s-0040-1720615

reaction sequence strategy still holds significant potential for exploring new functionalized sites on the hydrocarbon chain. With this in mind, we are committed to continuing our efforts in this direction and further advancing these developments."

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