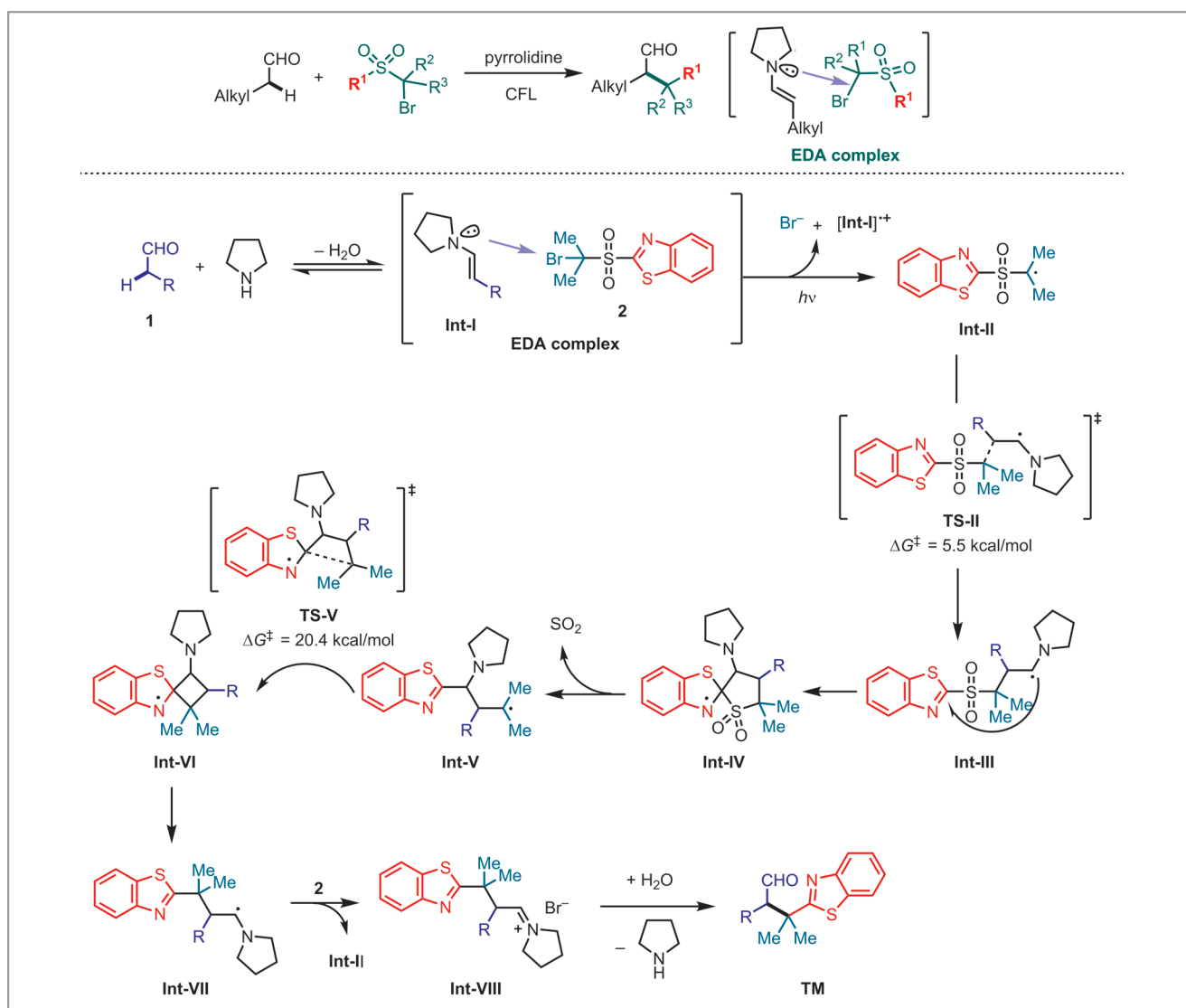


Radical-Mediated α -*tert*-Alkylation of Aldehydes by Consecutive 1,4- and 1,3-(Benzo)thiazolyl Migrations

JACS Au 2024, 4, 2108–2114

The direct alkylation of aliphatic aldehydes in the α -position represents a common strategy for the preparation of complex functionalized aldehydes, which are present in numerous natural products and functional molecules. The precedents are mainly limited to the incorporation of primary and secondary

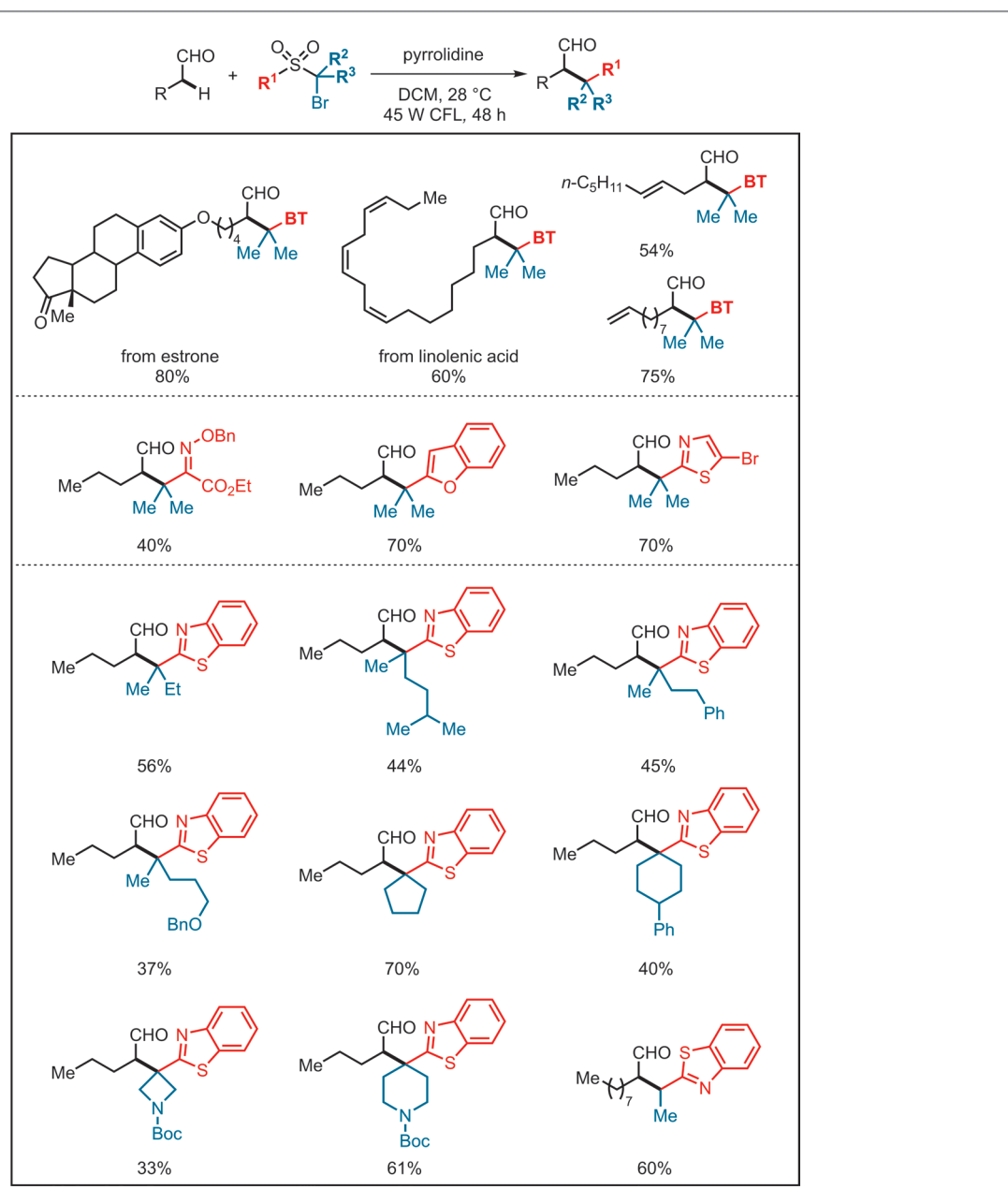
alkyl groups by electrophilic alkylation, while the *tert*-alkylation of aldehydes remains challenging due to steric hindrance and halide elimination often occurring with tertiary alkyl halides. A recent article in *JACS Au* from the groups of Professor Chen Zhu at Shanghai Jiao Tong University and Professor



Scheme 1 Radical *tert*-alkylation of the α -position of aldehydes

Xiao-Song Xue at Shanghai Institute of Organic Chemistry (both P. R. of China) describes a novel radical cascade for the elusive *tert*-alkylation of aldehydes, leading to structurally diverse aldehydes. “Initially, the reaction of pyrrolidine and aldehyde generates an enamine intermediate, which interacts with the strategically designed sulfone reagent to form an electron donor–acceptor (EDA) complex, which in turn produces a

radical species that triggers the ensuing consecutive 1,4- and 1,3-functional group migrations (Scheme 1),” explained Professor Zhu. Professor Xue continued: “Consecutive functional group migrations, especially the 1,3-group migration via four-membered cyclic transition state, are uncommon. However, our density functional theory (DFT) calculations revealed that such a process has a feasible barrier of 20.4 kcal/mol under



Scheme 2 Product diversity and reaction scope

the used experimental conditions. Compared with the three-membered cyclic transition state in a competing pathway, the lower strain arising from its four-ring transition state makes the proposed mechanism kinetically favored.”

The process entails the formation of an EDA intermediate through the interaction of enamines with bifunctional reagents, followed by a single electron transfer and subsequent 1,4-heteroaryl migration. “Remarkably, it also includes an atypical 1,3-heteroaryl group migration,” added Professor Zhu. “This innovative mechanism enables the concurrent incorporation of heterocycles and bulky alkyl groups at the α -position of the aldehyde. Furthermore, this protocol exhibits excellent functional group compatibility. Additionally, the resultant products can be further transformed into more valuable compounds, such as alcohols, amines, carboxylic acids, olefins, and alkynes.”

The Zhu group has a long-term interest in radical-mediated functional group migration reactions, which have been successfully applied to the difunctionalization of various alkenes and alkynes (*Acc. Chem. Res.* **2020**, *53*, 1620–1636). “Differently from previous contributions, this report targeted the difunctionalization of enamines,” Professor Zhu explained, continuing: “Surprisingly, the reaction did not afford the multi-substituted aliphatic amines via routine 1,4-benzothiazolyl intermediate, as expected. Instead, it resulted in the serendipitous finding of the unusual 1,3-benzothiazolyl migration.”

What particularly stands out with this method are the mild reaction conditions and broad product diversity. “The reaction proceeds under photochemical conditions and works with a broad range of aliphatic aldehydes (Scheme 2),” said Professor Zhu. He added: “It is worth noting that when the substrate contains olefinic fragments, the reaction exclusively targets the right α -position, and the olefin remains unaltered, thus demonstrating excellent chemoselectivity. Complex natural product aldehyde derivatives can also be effectively modified. Furthermore, varying the alkylating agents allows for diverse alkylation modifications, including heterocycles and even oxime esters. Chain alkyl groups, cyclic alkyl groups, and alkyl groups containing heteroatoms have been successfully applied in this reaction. Secondary alkyl groups are also well-suited for this process.”

Professors Zhu and Xue remarked that this process represents a useful approach to achieve α -site alkylation of aldehydes, characterized by excellent functional group compatibility and a broad substrate scope. “Looking forward, we aim to use catalytic conditions instead of the current stoichiometric pyrrolone, and to design chiral amines for the asymmetric alkylation reaction,” they concluded.

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