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Regio- and Enantioselective Vinylogous Functionalization of *α,β*-Unsaturated Aldehydes Using Dienamine Catalysis

One of the greatest challenges in synthetic organic chemistry is to achieve highly selective organic transformations. There is much more emphasis on enantioselective reactions due to the increasing demand for the single enantiomer drugs. Organocatalytic chemo-, regio- and enantioselective reactions are found to be very much attractive because of avoiding tedious separation procedures to obtain pure products and is environmental-friendly. The enamine activation has been greatly studied for the selective *α*-functionalization of aldehydes and ketones utilizing distinctive electrophiles and subsequently applied in the synthesis of biologically active natural products. Comparatively, asymmetric vinylogous functionalization of *α,β*-unsaturated aldehyde using dienamine catalysis is one of the important yet less explored areas of amine catalyzed reactions. Mostly the dienamine intermediates that have been utilized in enantioselective pericyclic reactions and are relatively less explored in nucleophilic addition/substitution reactions.

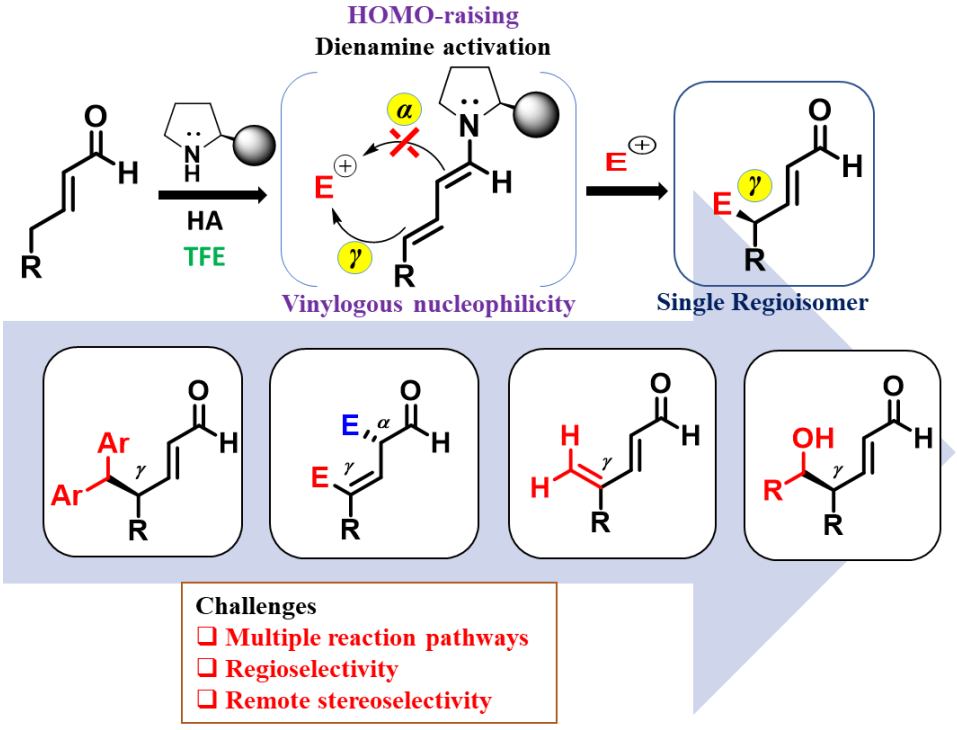

Figure 1. Dienamine activation for the vinylogous processes: challenges and scope.

The dienamine intermediate was first demonstrated for the γ-amination of α,β-unsaturated aldehydes and the high regio- and enantioselectivities were attributed to a proposed [4+2] cycloaddition mechanism. However, achieving high regio- and enantioselectivities were found to be difficult with other S_N-type electrophiles. The main reason behind this is the multiple reaction pathways, the formation of a mixture of regioisomers, and complexity in controlling the stereoselectivity at the remote γ-position (Figure 1). The prime objective of this thesis is to overcome the challenges associated with the dienamine catalysis and the development of novel organocatalytic methodologies for regio- and enantioselective vinylogous functionalization of α,β-unsaturated aldehydes and the detailed experimental studies, mechanistic insight and application. The products of vinylogous remote functionalization of α,β-unsaturated aldehydes importantly, have free α and β reactive centres which could be further functionalized in a cascade fashion, and thus can be manipulated orthogonally for synthesis of challenging and potentially useful chiral building blocks.

The entire thesis work has been divided into the following five chapters. In chapter 2, a methodology for the highly regio- and enantioselective γ-alkylation of linear α,β-unsaturated aldehyde using dienamine activation is described. Further, we have demonstrated the use of TFE (trifluoroethanol) as a co-solvent to achieve excellent regioselectivity in the γ-alkylated products while an in-situ kinetic resolution has contributed to the product enantioselectivity.

In chapter 3, we disclose the experimental evidence obtained to understand the role of TFE in regioselective γ-alkylation. During the detailed mechanistic investigation of the dienamine catalysed γ-functionalization of α,β-unsaturated aldehydes, we have understood the formation of a new dienamine intermediate from the γ-functionalized products. Therefore, we have envisaged a further reaction of this product dienamine intermediate with another electrophile to achieve a cascade α,γ-double functionalization.

In chapter 4, we have shown a new method for the regio- and enantioselective cascade double alkylation of α,β-unsaturated aldehydes. After successful regioselective γ-alkylation with S_N-type electrophiles, another S_N-type electrophile was added to functionalize the α-position. The substrate scope for the cascade α,γ-dialkylation α,β-unsaturated aldehydes with different electrophiles has resulted in the dialkylated products up to 70% yield and up to 99% *ee*. The formation of α,γ-dialkylated products not only confirms the γ-alkylated dienamine intermediate formation but also provides a new route for the selective double functionalization of α,β-unsaturated aldehydes.

In continuation of our interest to achieve a highly regioselective vinylogous γ-functionalization, we further envisaged a γ-hydroxymethylation of α,β-unsaturated aldehydes via the vinylogous aldol reaction using formaldehyde.

In chapter 5, an organocatalytic methodology for the remote regioselective γ-methylenation of α,β-unsaturated aldehydes under mild reaction conditions is demonstrated. An excellent γ-selectivity has been obtained with a variety of α,β-unsaturated aldehydes in the presence of TFE as a co-solvent. This organocatalytic direct γ-methylenation is successfully applied for a short synthesis of α-triticene (an antifungal agent). γ-Methylenated products have been further transformed into synthetically important building blocks. The reaction of crotonaldehyde with formaldehyde has led to unusual double γ-functionalized products. A vinylogous Mannich-type reaction mechanism is proposed for the γ-methylenation of α,β-unsaturated aldehydes based on the experimental evidence. We have also developed highly regio and enantioselective vinylogous γ-hydroxymethylation of α,β-unsaturated aldehydes using phenylglyoxal. We have optimized the reaction condition for the γ-hydroxymethylation of 2-decenal in 92% *ee* and *dr* > 20:1. Upon further exploration of the reaction of phenylglyoxal with β-substituted α,β-unsaturated aldehydes, we have observed a lactol intermediate which has been *in situ* transformed into a chiral dihydroxy cyclopentene carbaldehyde via vinylogous double cascade annulation reaction. The dynamic kinetic resolution was observed during the transformation of lactol to cyclopentene carbaldehyde obtained in 57% yield, 76% *ee* and >20:1 *dr*.