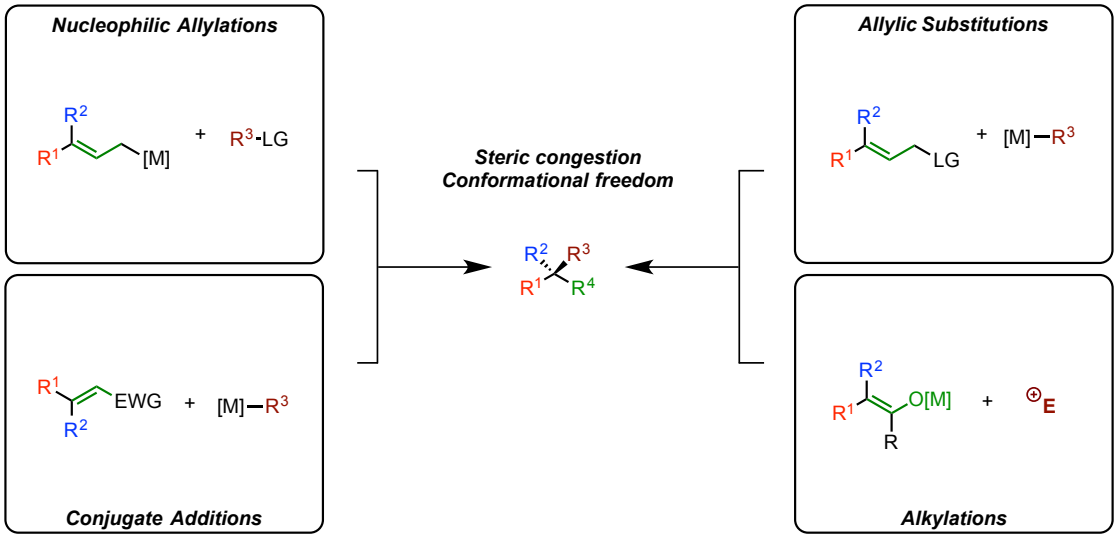
CATALYTIC ASYMMETRIC CONSTRUCTION OF QUATERNARY CENTERS IN ACYCLIC SYSTEMS

Reported by Summer D. Laffoon November 1, 2016

INTRODUCTION

Quaternary carbons are highly prevalent in pharmaceuticals and natural products, yet their enantioselective installation represents a significant challenge in organic synthesis. Much of the work in this field has focused on generating quaternary centers in cyclic systems; however, these methods are largely ineffective for acyclic systems due to the added conformational freedom in the transition state.[1] To address this challenge, several strategies have been devised. These methods include nucleophilic allylations, allylic substitutions, conjugate additions, and alkylations (Scheme 1).

Scheme 1. Various strategies toward quaternary centers in acyclic systems



NUCLEOPHILIC ALLYLATIONS

Nucleophilic allylations employ allylic organometallic reagents as prochiral nucleophiles for the formation of quaternary centers. The introduction of chirality at the metal center engenders an enantio- and diastereoselective transformation when the reaction proceeds through a closed transition state.[2]

ALLYLIC SUBSTITUTIONS

Complementary to nucleophilic allylations, allylic substitutions involve an electrophilic allyl species in combination with a nucleophile to yield quaternary centers. Most examples employ trisubstituted olefins bearing an allylic leaving group as prochiral electrophiles for incoming carbon nucleophiles. The primary examples of this technique employ copper catalysts and various organometallic reagents.[3] In theory, metal π-allyl species could serve as competent electrophiles for the formation of quaternary centers; however, this strategy is difficult to employ in acyclic systems. Nonetheless, there do exist highly selective methods that react through this pathway.[4]

CONJUGATE ADDITIONS

Enantioselective conjugate addition (ECA) reactions represent an effective means for installing quaternary centers at the β- or γ-position with respect to an electron-withdrawing group. General ECA methodologies often fail to directly translate into routes for accessing quaternary carbons. Chiral catalysts that have been optimized to yield tertiary centers can distinguish between carbon and hydrogen substituents on an olefin, but often fail to distinguish between two carbon substituents which are sterically more similar. Quaternary centers at the β-position can be accessed *via* ECA with trisubstituted resonance-stabilized olefins and carbon nucleophiles.[5] To construct a quaternary center at the γ-position, acidified tertiary centers serve as prochiral nucleophiles for ECA.[6]

ALKYLATIONS

Enolate alkylations are a powerful means of inducing chirality in a variety of products; however, this approach becomes markedly more difficult when building quaternary centers since the geometry of trisubstituted enolates is often difficult to control. Enolates can be used as nucleophiles for building quaternary centers if the enolate geometry does not affect the stereochemical outcome[7] or if one enolate isomer reacts more readily than the other and the two isomers are in equilibrium.[8] Enolate surrogates offer an attractive approach to generating aldol-type products with high selectivities.[9] In addition to these strategies, the geometry of *in situ* generated enolates can be controlled by a chiral catalyst.[10]

CONCLUSION

Quaternary stereogenic centers in acyclic systems cannot typically be generated through general asymmetric methodologies. Catalytic methods for the formation of these centers have therefore been a topic of significant interest in recent years. In addition to the primary strategies outlined above, future work may involve transition metal-mediated transformations that provide access to quaternary centers in chemical environments orthogonal to what has been traditionally described.

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