AMINE-CATALYZED TANDEM AND CASCADE REACTIONS

Reported by Spencer Eggen

December 3, 2012

INTRODUCTION

Complex molecule synthesis has advanced tremendously in recent decades. Previously inconceivable synthetic feats such as the total synthesis of taxol\(^1\) and palytoxin\(^2\) are now a reality. However, these syntheses rely on ‘stop-and-go’ synthesis, in which individual chemical transformations are performed as discrete steps and each step is punctuated by isolation and purification. One disadvantage to this approach is that it is time-consuming and requires a significant amount of resources that will not be incorporated into the final product (chromatography solvents, drying agents, etc.).\(^3\) Tandem reactions offer a potential remedy by enabling the sequential formation of two or more bonds in a single reaction medium, wherein subsequent reaction(s) occur as a consequence of functionality formed in a prior step.\(^4\)

One means of initiating tandem reactions of carbonyl-containing substrates is through iminium-enamine activation (Figure 1), a process particularly suited to amine catalysts for two reasons: (1) one catalyst is able to perform both enamine and iminium activation\(^5\) and (2) amines are compatible with a number of other reagents including Hantsch esters, electrophilic halogen sources, and other organocatalysts.\(^6\) A sampling of amine catalysts is provided in Figure 2.

TANDEM CASCADE REACTIONS

Amine-catalyzed tandem reactions are divided into two categories: tandem cascade reactions and tandem sequential reactions.\(^7\) In tandem cascade reactions, the two bond-forming
processes occur without the agency of additional reagents and the intermediate is not isolable. Scheme 1 illustrates a tandem cascade Michael/Michael/aldol annulation reaction, resulting in a highly functionalized cyclohexenecarbaldehyde. Many of these processes utilize secondary amines as catalysts, which often limits the reaction scope to β-substituted enals such as C (Scheme 1).

**TANDEM SEQUENTIAL REACTIONS**

Tandem sequential reactions require an additional component for the second bond formation to occur; the intermediate may or may not be isolable. As illustrated in Scheme 2, these processes can effect the vicinal difunctionalization of enals through iminium-enamine activation. The use of primary amine catalysts increases substrate scope relative to that of the tandem cascade reactions, enabling functionalization of enals, enones, and α,β-disubstituted enals such as D.

**CONCLUSION**

Despite their relatively recent inception, aminocatalytic tandem reactions have been successfully applied in natural product syntheses. In the case of strychnine, (+)-palintatin, and α-tocopherol, tandem reactions provide the shortest and/or highest-yielding total syntheses to date. The development of novel tandem cascade and tandem sequential reactions could enable new disconnection strategies.

**REFERENCES**