AMINE-CATALYZED TANDEM AND CASCADE REACTIONS

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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]

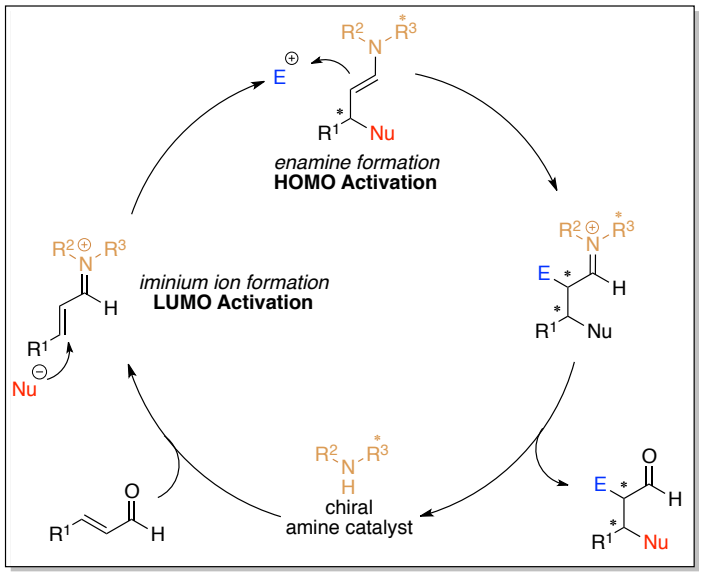


Figure 1. Catalytic cycle for a tandem reaction of an enal. R^1 = alkyl, aryl; R^2, R^3 = alkyl, H; Nu = nucleophile; E = electrophile.

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.

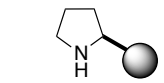
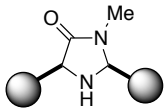
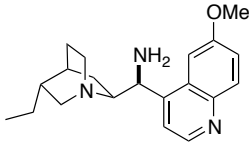
catalyst scaffold	typical activation modes	common transformations
	enamine activation of aldehydes, ketones (HOMO raising)	Aldol, Michael, Mannich, α-functionalization
	iminium activation of α,β-unsaturated aldehydes (LUMO lowering)	Michael, Diels-Alder, Friedel-Crafts
	enamine and iminium activation of enones, α-branched aldehydes	Michael, formal cycloadditions, Friedel-Crafts

Figure 2. Common amine catalyst scaffolds employed in tandem reactions.

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

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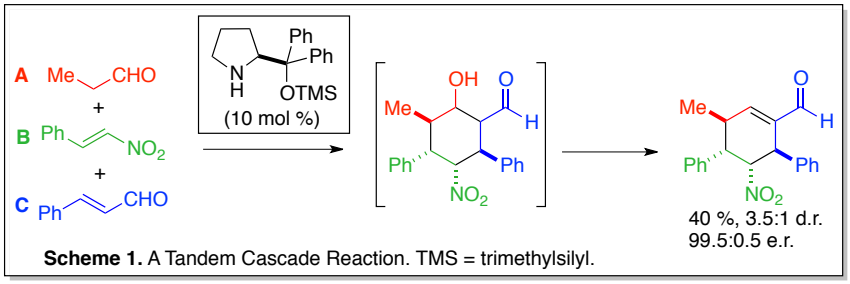
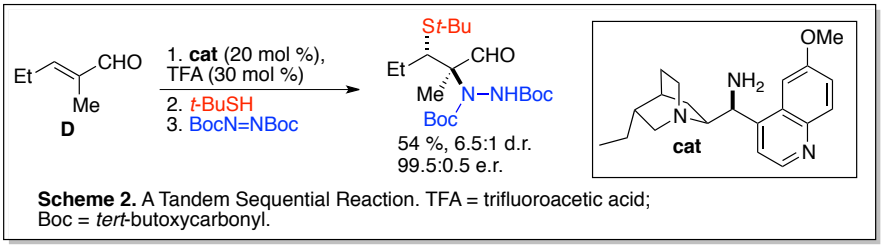


Scheme 1. A Tandem Cascade Reaction. TMS = trimethylsilyl.

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.[8] 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.[9] 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**.



Scheme 2. A Tandem Sequential Reaction. TFA = trifluoroacetic acid; Boc = *tert*-butoxycarbonyl.

CONCLUSION

Despite their relatively recent inception, aminocatalytic tandem reactions have been successfully applied in natural product syntheses. In the case of strychnine, (+)-palintantin, and α-tocopherol, tandem reactions provide the shortest and/or highest-yielding total syntheses to date.[10] The development of novel tandem cascade and tandem sequential reactions could enable new disconnection strategies.

REFERENCES

(1) Kingston, D.G.I. *Chem. Commun*. **2001**, 867.
(2) Suh, E.M.; Kishi, Y. *J. Am. Chem. Soc*. **1994**, *116*, 11205.
(3) Walji, A.M.; MacMillan, D.W.C. *Synlett* **2007**, *10*, 1477.
(4) (a) Tietze, L.F. *Chem. Rev*. **1996**, *96*, 115. (b) Denmark, S.E.; Thorarensen, A. *Chem. Rev*. **1996**, *96*, 137.
(5) (a) Lelais, G.; MacMillan, D.W.C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9748.
(6) Albrecht, L.; Jiang, H.; Jørgensen, K.A. *Angew. Chem. Int. Ed*. **2011**, *50*, 8492.
(7) Denmark, S.E.; Thorarensen, A. *Chem. Rev*. **1996**, *96*, 137.
(8) Enders, D.; Hüttl, M.R.M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.
(9) (a) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 7892. (b) Melchiorre, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 9748.
(10) (a) Jones, S.B.; Simmons, B.; Mastracchio, A.; MacMillan, D.W.C. *Nature*, **2011**, *475*, 183. (b) Hong, B.; Wu, M.; Tseng, H.; Huang, G.; Su, C.; Liao, J. *J. Org. Chem*. **2007**, *72*, 8459. (c) Liu, K.; Chougnet, A.; Woggon, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 5827.