Organic Chemistry
Current Research

Frink, Organic Chem Curr Res 2013, 2:3
DOI: 10.4172/2161-0401.1000e127

Editorial Open Access

Enzyme Initiated Cascade Reactions

Cannatelli MD and Ragauskas AJ*

School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, 30332, USA

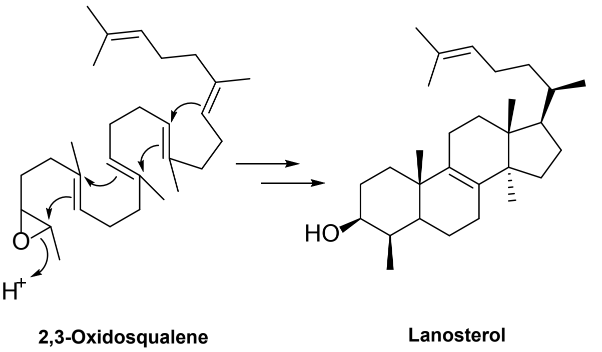
As many sectors within the chemical industry move towards greener and more sustainable processes, the incorporation of biotechnology into existing operations has become more widespread. With regards to the field of organic synthesis, enzymes (nature's catalysts) are being increasingly employed to carry out chemical transformations, both in the lab and at an industrial scale, for the preparation of valuable products [1]. Compared to traditional chemical approaches, enzymes come with the advantages of being relatively inexpensive, renewable, and the ability to operate efficiently in aqueous solvents under mild conditions. Furthermore, with advances in molecular biology and protein characterization, the possibility of being able to tailor an enzyme to meet its desired need is becoming a reality.

Cascade (or domino) reactions are a class of reaction wherebya series of individual transformations take place consecutively via the formation of highly reactive intermediates. Due to their dynamic nature, cascade reactions are able to produce products that would be difficult to obtain otherwise via a one-step process. One of the most well-known examples of a cascade reaction occurs within the cholesterol biosynthetic pathway whereby a series of intramolecular cyclizations, followed by methyl and hydride migrations, drives the conversion of 2,3-oxidosqualene into lanosterol (Scheme 1).

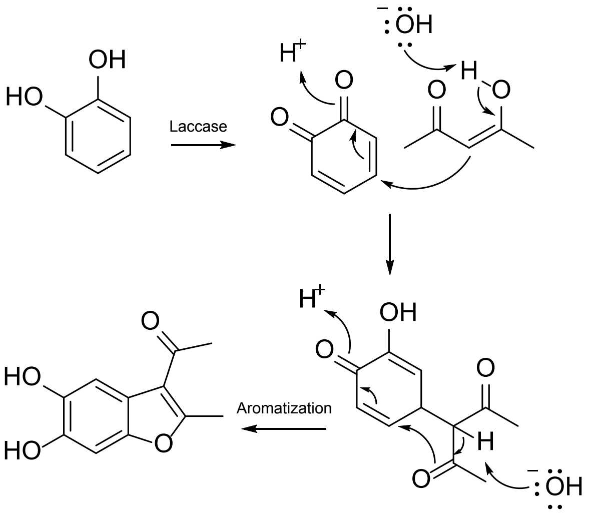
In enzyme initiated cascade reactions, there are often three transformations that can occur once the reactive intermediate is formed: fragmentations, rearrangements, and cyclizations [2]. The variety of reactions that can occur are catalyzed by various enzymes from different enzyme categories, attributing to the diversity of enzyme initiated cascade reactions.

Laccasesare a class of copper-containing enzymes that have been used extensively over the past decade to perform cascade reactions owing to their ability to create reactive intermediates via the oxidation of compounds such as catechols, hydroquinones, and various aromatic amines. A noteworthy examplethat has received much attention of late is the oxidation–Michael addition-cyclization of substituted catechols with a variety of 1,3-dicarbonyl compounds to produce substituted benzofurans (Scheme 2) [3]. Cocatalytic systems involving the use of an additional enzyme, tyrosinase [4] or a lipase [5], have also been developed for the synthesis of substituted benzofurans and the results show an increase in product yield from the cascade reaction when the action of two enzymes are combined.The laccase-catalyzed cascade reaction approach has proved to bea useful synthetic method in the synthesis of the anticancer compound vinblastine. This approach involves the oxidative–domino reaction between catharanthine and vindoline to yield the bioactive compound vinblastine after a final reducing step [6]. This result proved that it was possible to synthesize important biologically active compounds viaan enzyme initiated cascade reaction. For other laccase-catalyzed cross-coupling domino reactions, refer to a recent review written by Monti et al. [7].

The Diels-Alder reaction is one of the most important classical C-C bond forming reactions. With the aid of certain oxidoreductases, it is possible to perform this transformation via an enzymeinitiated cascade reaction. As an example, tyrosinase can be employed to hydroxylate phenol at the *ortho* position, followed by further oxidation to the *ortho*-quinone intermediate, which acts as the diene in the [4+2] cycloaddition with various dienophiles to produce the bicyclic adducts [8,9]. A similar type of transformation has also been carried out using catechols and laccases as the oxidant [10].



Scheme 1: Conversion of 2,3-oxidosqualene into lanosterol via a cyclizing cascade reaction.



Scheme 2: Laccase-catalyzed cascade reaction of catechol with acetylacetone for the synthesis of a substituted benzofuran.

***Corresponding author:** Ragauskas AJ,School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, 30332, USA, Tel: 404-894-9701; E-mail: Art.Ragauskas@ipst.gatech.edu

Received November 22, 2013; **Accepted** November 23, 2013; **Published** November 30, 2013

Citation: Cannatelli MD, Ragauskas AJ (2013) Enzyme Initiated Cascade Reactions. Organic Chem Curr Res 2: e127. doi:10.4172/2161-0401.1000e127

Citation: Cannatelli MD, Ragauskas AJ (2013) Enzyme Initiated Cascade Reactions. Organic Chem Curr Res 2: e127. doi:10.4172/2161-0401.1000e127

Besides the oxidoreductases just discussed, other classes of enzymes, such as hydrolases, have also been used to perform cascade reactions. For example, the starch hydrolyzing enzyme α-amylase has been used to react salicylaldehyde derivatives with α, β-unsaturated ketones to produce 3-substituted 2H-chromene derivatives, which are important precursors for many bioactive compounds, via an oxa-Michael/aldol condensation [10].

The field of enzyme initiated cascade reactions is continuously growing and this text has provided a brief overview introduction into these types of reactions, demonstrating their practicality in the field of organic synthesis citing just a few of the many examples.A more in depth account of enzyme initiated cascade reactions is provided by Mayer et al. [2]. Due to the dynamic and exciting nature of these types of reactions, and the facile and green nature in which they are carried out, it is easy to see why there has been an increase in popularity and no reason why this trend shouldn't continue. After all, when one thinks about the infinite amount of chemical transformations that occur in nature, the possibilities for the use of enzymes in organic synthesis seem endless.

References

1. Riva S (2013)1983–2013: the long wave of biocatalysis. Trends Biotechnol 31: 120–121.
2. Mayer SF, Kroutil W, Faber K (2001)Enzyme-initiated domino (cascade) reactions. ChemSoc Rev 30: 332–339.
3. Witayakran S, Gelbaum L, Ragauskas AJ (2007) Cascade synthesis of benzofuran derivatives via laccase oxidation–Michael addition.Tetrahedron 63: 10958–10962.
4. Leutbecher H, HajdokS, Braunberger C, Neumann M, Mika S, et al. (2009) Combined action of enzymes: the first domino reaction catalyzed by Agaricus bisporus. Green Chem 11: 676–679.
5. Witayakran S, Ragauskas A (2009) Cocatalytic Enzyme System for the Michael Addition Reaction of in-situ-Generated ortho-Quinones. Eur J Org Chem 3: 358–363.
6. Sagui F, Chirivì C, Fontana G, NicotraS, Passarella D, et al. (2009) Laccase-catalyzed coupling of catharanthine and vindoline: an efficient approach to the bisindole alkaloid anhydrovinblastine. Tetrahedron 65: 312–317.
7. MontiD, OttolinaG, Carrea G, Riva S (2011) Redox Reactions Catalyzed by Isolated Enzymes. Chem Rev 111: 4111–4140.
8. Müller GH,Waldmann H (1996) An enzyme-initiated domino hydroxylation-oxidation-carbo-diels-alder reaction cascade. Tetrahedron Lett 37: 3833–3836.
9. WitayakranS,ZettiliA,Ragauskas AJ (2007)Laccase-generated quinones in naphthoquinone synthesis via Diels–Alder reaction. Tetrahedron Lett48: 2983–2987.
10. Zhou LH, Wang N, Zhang W, Xie ZB, Yu XQ (2013) Catalytical promiscuity of α-amylase: Synthesis of 3-substituted 2H-chromene derivatives via biocatalytic domino oxa-Michael/aldol condensations. J Mol Catal B: Enzym 91: 37–43.