Review Article

Comprehensive Review on Current Developments of Tandem Reaction Based Organic Synthesis

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ABSTRACT

Novelty of cascade reactions has been a challenging facet of organic reactions. Tandem reaction is a powerful method for building a polycyclic skeleton. A huge variety of cascade reaction has been carried out under various reactions, such as nucleophilic /electrophilic attack, organo metallic reaction, organocatalytic cascade, pericycliccascade, transition metal catalyzed reaction, radical and cascade reactions. During a cascade reaction, just one reaction solvent, one workup procedure, and one purification step are needed, thus significantly increasing synthetic efficiency. This review work focused on various examples of cascade reactions in total synthesis with particular development of current trend application therein. The examples cited in this review work demonstrate the exact benefit of these processes in the synthesis of complex molecules and uplift their future potential effects in the field of organic chemistry.

Keywords: cascade, tandem, pericyclic, organocatalytic, green synthesis.

INTRODUCTION

The task of design and constructing a cascade reaction is a challenging facet of organic chemistry by the way one can achieve a novelty, purity and huge yield to synthetic strategies. Results obtained in cascade reactions were found to be stunning and instructive though it has been a demanding task in today chemistry field [1.]A variety of cascade reactions, carried out under multiple reaction conditions, such as pericyclic, polar, radical, and transition metal catalyzed reaction conditions, have been investigated. Cascade reaction develops a fascinating branch of organic chemistry which intends to a wide variety of research in recent years. Benefits of cascade reactions relays on atom economy time consuming, labour and resource management.[2]The banner of green chemistry leads the cascade reactions as several transformations has been done in one synthetic operation. Target based synthesis achieves the ultimate test of reaction design and applicability. To achieve specific targeted molecules can be attained by cascadesynthesis.[3]It is a modern phenomenon for the improvement of practical efficiency and enhanced synthetic planning. Nature of cascade reactions, which often involve many distinct steps, can at once make them rather hard to classify. For convenience, we have grouped the examples that follow into five sections: nucleophilic, electrophilic, radical mediated, pericyclic, and transition-metal-catalyzed processes. This classification scheme is rather arbitrary, particularly in the case of examples that feature more than one class of reaction, before tackling the chosen examples, however, some discussion regarding the terminology and organization of this review is warranted. Different authors use varying definitions as to what constitutes a cascade process. A variety of terms, including "cascade", "domino", "tandem", and "sequential", are used in the literature, often seemingly interchangeably and with liberal abandon, although efforts have been made to restore order to this area of reaction terminology. To encompass the entire above descriptors the term cascade" employed for our subjective purposes. It also adopted a rather inclusive attitude in order to capture as broad a spectrum of creative reaction design as possible[4]. For example, the strictest definition of a cascade process would discount any example in which the reaction conditions are altered during the process; we will include not only these but also sequences in which further reagents are added at various points ("one-pot" transformations).however, exclude multidirectional reactions in which two or more reactions occur on the same substrate, but essentially in isolation of one another. It is hoped that this review will serve not only to put into perspective recent accomplishments in the field but also to provide further impetus and inspiration for the implementation of new cascade strategies of broader generality and scope in the future. Many of the examples highlighted here are based on the use of biosynthetic considerations to guide synthetic strategy (biomimetic synthesis), a paradigm that has witnessed a renaissance in recent years[5.] Riding the wave of green chemistry, catalytic cascade reactions have become one of the most active research areas in organic synthesis.

In a cascade reaction, just one reaction solvent, one workup procedure, and one purification step are needed, thus significantly increasing synthetic efficiency[6].Featuring contributions from an international team of pioneers in the field, Catalytic Cascade Reactions demonstrates the versatility and application of these reactions for synthesizing valuable compounds. Recent progress relating to heterocycles would be accounted.

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- Cascade reactions catalyzed by ruthenium, iron, iridium, rhodium, and copper
- Palladium-catalyzed cascade reactions of alkenes, alkynes, and allenes
- Application of transition-metal catalyzed cascade reactions in natural product synthesis and drug discover

Gold-catalyzed cascade reactions forming a number of bonds by one operation are useful for the creation of polycyclic compounds. Many stereogenic centers would be created at the same time. Reduction of reaction steps leads to saving reagents, energy and reduction of wastes. Therefore, cascade reaction is important from the economical point view from the green chemistry[7-11].

Types of Cascade

i) Nucleophilic Cascades/Electrophilic Cascade

Nucleophilic reactions are tandem sequences in which key step constitute a nucleophilic attack.

Bhaskar *et al*[12] designed a cascade reaction for the enantio selective synthesis of board spectrum antibiotic -(-) Chloramphenicol. Dichloro acetone was treated as starting material with epoxy alcohol in the presence of sodium hydride forms an intramolecular opening of epoxide ring yield an intermediate boron trifluoride ethylene oxide cascade reactions which on hydrolysis afforded 71% yield of –(-)chloramphenicol whereas ordinary organic synthesis took six steps to yield chloramphenicol (Fig 1).

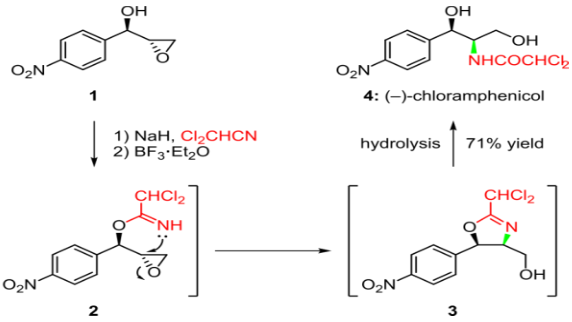

Figure 1: Nucleophilic Cascades/Electrophilic Cascade

Xinhong Yu and Wei Wang *et al*[13] synthesized a series of novel powerful synthetic technologies for the construction of complex chiral molecular structures from simpler achiral molecules in one pot synthesis with stereo control under mild conditions.(Fig 2).

Figure 2: Electrophilic Cascade

Yong Huang etal[14] designed a novel approach for of enantioselective transformations and the asymmetric catalytic addition of the elements of hydrogen flouride across a tri substituted double bonded compounds involving biochemical blueprints of cascade catalytic reactions. In this synthesis iminium and enamine activation has been combined for promoting large diversity of nucleophiles and electrophiles like furans, thiophenes, indoles, butenolides, hydride sources, tertiary amino lactone equivalents and fluorinating and chlorinating reagents respectively for the sequential addition with a wide array of α,β-unsaturated aldehydes. Thus central benefit of combining multiple asymmetric organocatalytic events into one sequence is the intrinsic requirement for enantioenrichment in the second induction cycle, as demonstrated by the enantio selectivities obtained. Hence several steps can be reduced in single steps by combining enatiomeric series of amine catalyst to obtain diastereo- and enantioselective.(Fig 3)

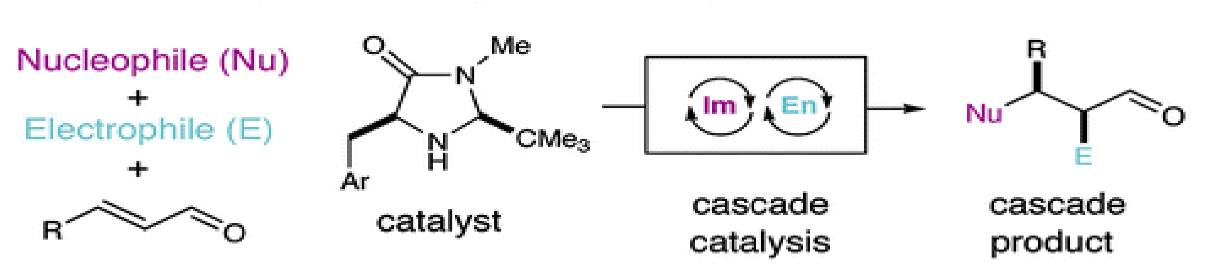

Figure 3: Cascade catalysis

BarbaraT[15]screened an enzyme initiated cascade reactions providing benefits on biomimetic strategies for natural product synthesis which has been adopted for the biosyntheses of cyclic terpenoids and polyethers

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based on the electrphilic cascade synthesis of carbenium ions and nucleophilic cascade reactions respectively involving mechanistically complementary pathways with three principles such as initiation, propagation and termination. Usage of multiple precursors has combined with various initiation steps which are kinetically favored accounts for enormous diversity in cyclic terpenoids and polyether scaffolds.

Shariar Md. Abu Sohel et al [16] pioneered a recent development by utilizing catalytic carbocyclisation of functionalized triple bonded carbon compounds with external nucleophile substrate catalysed by gold, platinum and other electrophilic metals. Substrate utilized may be of classification alkyne–alkyne, alkyne–allene, alkyne–alkene, oxo-alkynes and oxo-diynes and triynes which should tethered functionality to react with the alkyne to complete a carbocyclic ring. complex and functionalised carbocyclic products easily aligned in a tandem sequence from easily occuring alkynes and nucleophiles. Above cited synthesis meet atom economy and easily assembles besides its mechanistic benefits.(Fig 4)

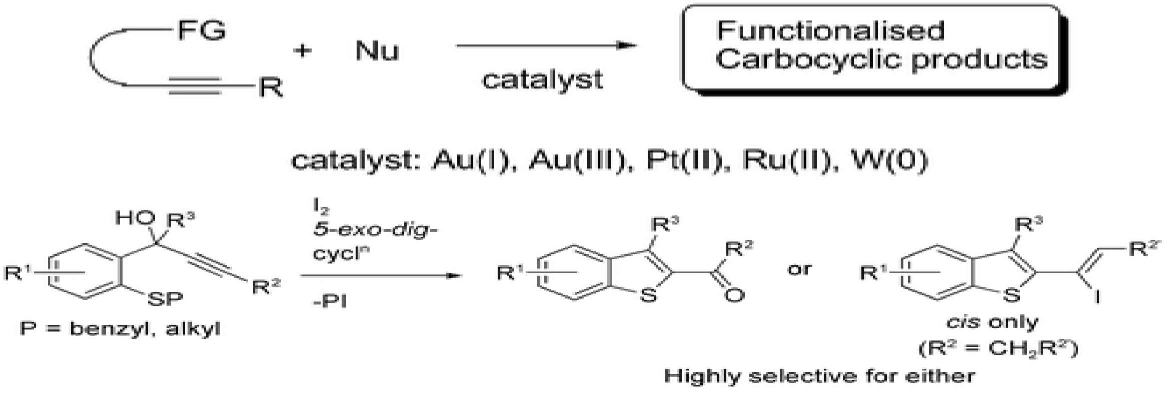

Figure 4: Enzyme cascade

Karl O. Hessian et al[17] synthesized an high selective yield of2-acyl- or 2-(1-iodoalkeny)-benzo[b]thiophene systems via tandem rearrangement and elimination or substitution processes by utilizing 2-thioxyphenyl substituent selectively undergo 5-exo-iodocyclization.Jia Wang *et al*[18] screened a series of 6,9-dihydropyrido[1,2-a] indolesvia tandem reactions of 4-(3-methyl-1H-indol-1-yl)-1,1-diphenylbut-2-yn-1-ol derivatives. Reaction was performed under very mild conditions and metal free ,solvent free 94% yield obtained in a short duration .palladium-catalyzed coupling reactions considered as potential intermediates for the synthesis of valuable compounds by allowing functional group diversification of obtained halides.

Juliano A. Roehrs *et al*[19] designed the synthesis of chalcogenophene derivatives which has found sound application in Suzuki, Sonogashira and Ullmann cross-coupling reactions as staring material promoted by di organyldichalcogenides and a halogen source cyclization reactions of diynols. Various chalcogenophenes derivatives such as -halo-selenophenes, 4-butylselenyl-selenophenes, halo-thiophenes, and 4-methylthio-thiophenes were synthesized with huge yield by utilizing same staring material. Above results revealed halogen source has significant effect o on the proportion of 4-bromo-selenophenes and 4-butylselenyl-selenophenes . The best yields of 4-iodo-selenophenes were obtained with iodine as a halogen source, while the use of NBS gave exclusively the 4-butylselenyl-selenophenes. While the 4-bromo-thiophenes were obtained when the reaction was carried out with a 1.5 molar ratio of dimethyl disulfide and halogen source. -iodo-thiophenes were attained by using dimethyl disulfide amd iodine in 0.5 difference ratio. The experiments revealed that by changing the ratio of the reagents cyclization reaction to form 4-halo-thiophene derivatives can be controlled. (Fig 5)

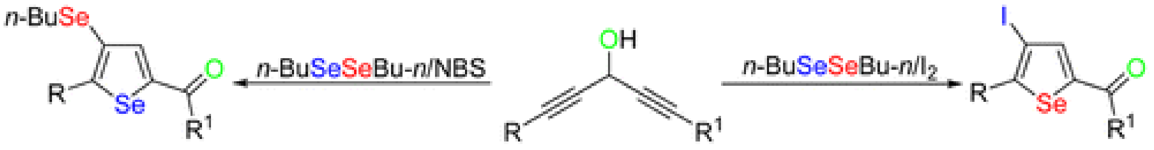

Figure 5: Iodo cascade reaction

Organocatalytic Cascades

The key nucleophilic attack is driven by organocatalysis, which is a subcategory of nucleophilic/electrophilic sequences is constituted by organocatalytic cascades

Roger A. Sheldon *et al*[20] reviewed alternative reaction media for green, sustainable organic synthesis. Liquid–liquid biphasic catalysis provides an industrially attractive method for the recovery and recycling of catalysts as an alternative to the more traditional solid heterogeneous catalysts. By utilizing nonconventional reaction media provide opportunities for facilitating and recycling of the catalyst. “The best solvent is no solvent” but if a solvent is needed then water is recommend it and

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catalysis in aqueous biphasic systems is an industrially attractive methodology which has found broad application. Similarly, supercritical carbon dioxide is an interesting reaction medium in the context of green chemistry and catalysis in various mono- and biphasic systems involving this solvent are reviewed which promote growing awareness for greener has focused attention on a atom efficient catalytic methodologies for the manufacture of fine chemicals and pharmaceuticals. . A novel and effective method for the immobilization of enzymes as cross-linked enzyme aggregates (CLEAs) is discussed and the use of a combi CLEA, containing two enzymes, for the one-pot conversion of benzaldehyde to *S*-mandelic acid is reported Alle Bruggink *et al*[21] screened the series of cascade conversions without the involvement of intermediate recovery steps by drastically reducing operation time, cost, usage of auxillary chemicals and energy. Production of waste may increase in multistep synthesis whereas it is reduced in cascade reactions. Syntheses requiring a smaller range of reaction parameters and reagents but a more intricate array of efficient catalysts might be expected. Integration with in situ product separation techniques will become mandatory, preferably by continuous processing. (Fig 6)

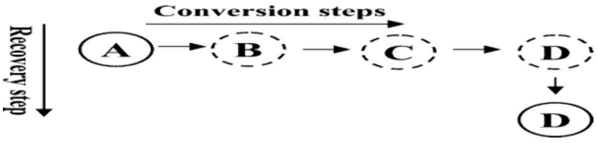

Figure 6: Cascade conversion

Christopher Grondal *et al*[22] focused the review of asymmetric organocascade reactions to the total synthesis of natural products for the developments of biologically active compounds such as pharmaceuticals and agrochemicals, has reached an extraordinary level of sophistication. The ideal synthesis devoid of step to step protocol process however it is hampered by lengthy protecting groups costly purification procedures to improve total synthesis and overcome problems cited above asymmetric protecting group free synthesis adopted.

Leanne J. Sebren**,** James J. Devery et al [23] screened a catalytic radical based dominos reaction in which combination of radical, cationic, anionic, oxidative/reductive, and transition metal mechanistic steps result in cyclizations, additions, fragmentations, ring-expansions, and rearrangements. This Perspective summarizes recent developments in the field of catalytic domino processes. Effective synthesis obtained by providing atom- and step-economical methods to complex molecules.(Fig 7)

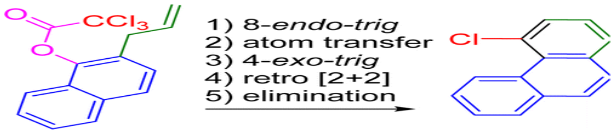

Figure 7: Radical Cascade

Dhevalapally B. Ramachary et al [24]recent developments and designs for sequential one pot combination of multicompo multi-component reactions (MCRs) catalysis cascade (MCC) reactions to focus their benefits as biomimetics in organic chemistry. One-pot sequential combination of MCRs/MCC reactions that add value to our lives can be obtained with less waste and greater economic benefits at reduced operating time and cost.

Radical Cascade

The key step constitutes a radical reaction. The high reactivity of free radical species renders radical-based synthetic approaches suitable for cascade reactions.

Peter J. Crick**,** Nigel S Simpkins*etal*[25] screened a radical cascade access to the pentacyclic core structure of the asperparalines (Fig 8) is described. Rdical cascade reaction comprised of 1, 6-hydrogen atom transfer followed by 6-*exo-trig* and 5-*exo-trig* cyclizations.

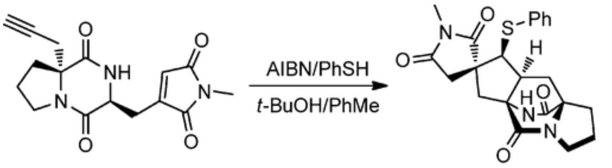

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Figure 8: Asperparaline

Pericycliccascade

Pericyclic reactions include cyclo additions, electrocyclic reactions and sigma tropic rearrangements. Pericyclic reaction contains only cascade sequences that are solely composed of pericyclic reactions or in which such a reaction arguably constitutes the key step. Schobert, *et al*[26] focused on hereterocyclic ring which has core impact of biological and therapeutic interesting compounds. Crucial drawback of heterocyclic synthesis such as the actual ring closure step tolerance of other functional groups, employs the cumulated ylide keteneylidene triphenylphosphorane Ph3P=C=C=O. patterning a novel combination of ofylidic and ketene properties in a dipolar electronic structure, it reacts with derivatives of carboxylic acids bearing additional alcoholic, imino, thiol,acid groups by a domino addition-Wittig olefination giving rise to the formation of the corresponding heterocycles with five- to seven-membered rings. Further pericyclic steps such as Diels-Alder cycloadditions, Claisen rearrangements, ene reactions, and various combinations thereof may ensue with the newly installed C=C bond. In some cases, the outcome of these processes is fully controllable by merely adjusting the external conditions. For example, allyl and cinnamyl α-hydroxycycloalkanoates could be selectively converted either to Claisen rearranged 3-allyltetronic acids or to Claisen-Conia rearranged 3-(spirocyclopropyl)-dihydrofuran-2,4-diones. The former furnished anti-HIV-active 5-spiro-3-(α-cyclopropylbenzyl)-tetronic acids upon Simmons-Smith reaction and the latter could be stereo selectively ring-opened with alcohols, amines and water to give herbicidal 3-(β-synalkoxy / amino)tetronic acids. Congenerous esters

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with di- or trialkyl substituted allyl residues undergo a formal [2, 3]-sigmatropic rearrangement also proceeding via 3-(spirocyclopropyl) dihydrofuran-2,4-diones but leading to 3- exo-alkylidene-5-spirodihydrofuran-2,4-diones which in turn rapidly

CONCLUSION

The enormous benefits associated with cascade reactions have ensured that they continue to be developed and exploited in organic synthesis. That most of the beautiful and ingenious examples described in this review of course, highlighting only successful applications from total synthesis, we neglect many cascades developed for other applications, or without a natural product target in mind. Additionally, countless examples of cascades that have gone away or failed altogether have been omitted. The synthesis of the cascade precursors themselves may also be far from trivial, and considerable experimental skill is often required to unearth suitable conditions under which the desired cascade can be affected with success. There are currently few examples of catalytic enantio selective cascade reactions, and it is likely that asymmetric catalysis of cascade processes will become increasingly prominent in years to come, with enzymatic, organocatalytic, and transition-metal-catalyzed processes at the vanguard of this movement. With the increasing pressures to fashion diverse and increasingly complex molecular architectures rapidly through efficient and economical means, cascade reactions are destined to assume an integral position in many synthetic endeavors. In order to push the state of the art of these sequences, contemporary as well as future generations of synthetic practitioners will require an increasingly precise understanding of the mechanism and kinetics of organic transformations. Gains in this fundamental knowledge, combined with a large dose of intellectual flexibility and creativity, will undoubtedly lead to even mores pectacular applications of cascade reactions in the future.

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