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The application and evaluation of pericyclic reactions in the industrial synthesis of medicines and alkaloids

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Abstract:

The research is based on the development of the pericyclic reaction which has been discovered effectively in the production of clinical drugs. People has increasingly noticed that it can increase the purity of the final product and have paid attention to applying it in further synthesis.

The research aims to evaluate whether the pericyclic reaction can be used in large-scale production for relative medicines or alkaloids and whether it is possible to use it in medicines with other structures. Essentially, all the research is supported by secondary research, and the samples are sourced from relevant previous analyses. The researcher uses the samples and databases and compares them to illustrate the benefits and hidden drawbacks of the pericyclic reaction.

After discussion, the researcher concludes that the pericyclic reaction can be widely applied if the structure of the substance meets the reaction's requirements, enabling large-scale synthesis of appropriately structured medicines or alkaloids.

Keywords: Pericyclic reaction; Industrial drug synthesis, Alkaloids, Large-scale production.

1. Introduction

The past decades have seen the rapid development of pericyclic reactions from their initial discovery to in-depth theoretical analysis. Pericyclic reactions are a type of synergistic reaction that changes the configuration of molecules by altering the positions of the π electrons and the σ bond simultaneously (Woodward, 1965). In this way, they can transform the molecular structure into a more complex configuration in a single step. It can be used to synthesize medicines or alkaloids with stereoisomers which show obvious advantages.

The meaning of stereoisomers is that some of the natural substances will have the property where they have the same molecular formula but the structures are mirrored to each other (Pesteur, 1848). Those molecules are called stereoisomers.

Stereoisomers often show distinct properties not only in biological areas such as medicine treatment but also in optical differences. Stereoisomers can be divided into several types such as chiral isomers,

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endo-exo isomers and so on. Chiral isomers are a type of stereoisomers that are non-superimposable mirror images of each other. Despite exhibiting similar physicochemical properties among them, their specific arrangements can significantly affect their functions (Pesteur, 1848).

Reactions that preferentially produce one stereoisomer in significantly higher yield are said to have stereoselectivity (Athelstan, 1985). This property can help to define more efficient synthesis pathways. Pericyclic reactions exhibit strong stereoselectivity and can provide high yields at low cost due to the mild conditions required, such as simple heating or ultraviolet light (Michael, 1992).

Compared with the traditional methods for synthesizing similar structures, they don't need to extensively purify the product after reacting, as the configuration of the product can be selectively controlled by adjusting reaction conditions such as ultraviolet or simple heating (Michael, 1992).

Nowadays some of the medicines and alkaloids are synthesized in the laboratory by using this approach to construct some complex structures with few rings and minimal additional atoms. For example, in the case of $PGF_{2\alpha}$, traditional synthesis methods often produce both configurations of the compound, but the exo-product lacks biological activity and negatively affects the yield ratio of the desired endo-product. Dr.Li and his team (2024) suggested a new way to convert the cyclic ester into a ketone during the process. They used Claisen rearrangement, a type of pericyclic reaction, also known as [3,3]-σ migration, to achieve this transformation (Li, 2024).

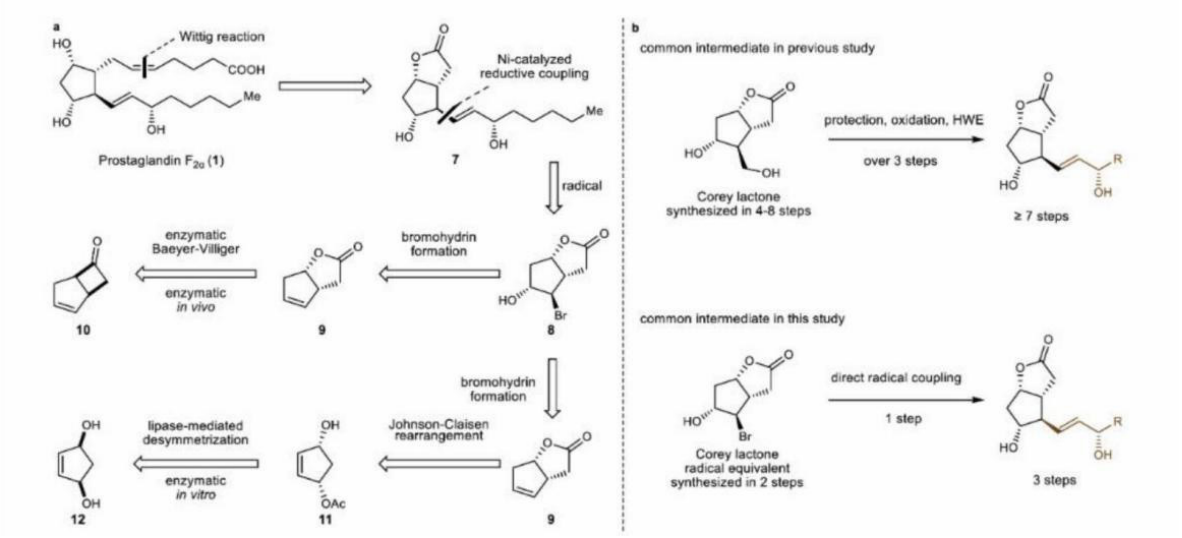

Figure 1 The reverse synthesis process and the [3,3]-σ migration (synthesis from 11 to 9)

As shown in Figure 1, during the transformation from compound 11 to 9, the Johnson-Claisen rearrangement converts the cyclic ester—an intermediate in the process—into the endo-product with the exo-product being nearly absent.

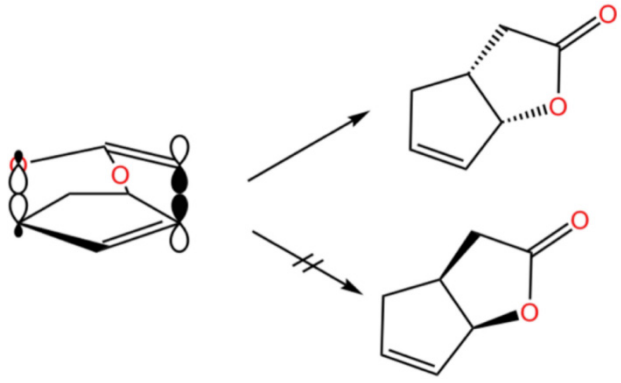

Figure 2 The type of the products (upper one is endo-product and lower one is exo-product).

In recent years, people have gradually realized that the purity of medicines can significantly affect the efficacy of the treatment, especially for chiral compounds. As mentioned earlier, purification is essential in the synthesis of tradi-

tional medicines, such as $PGF_{2\alpha}$. Although there are some efficient purification methods, such as membrane separation, these technologies are too expensive and sophisticated for industrial-scale use, as they require complex equipment operations. In this way, resource consumption needs to be factored into production costs, rendering it impractical to scale up the equipment for use in industrial production (Nemoto, 2007). This highlights the value of reactions with inherent stereoselectivity, which offer much greater potential for future development. Although pericyclic reactions offer obvious advantages and are expected to improve the efficiency of medicine synthesis in large-scale industrial production, until now, the research in this domain is still limited to laboratory settings. Whether pericyclic reactions can be effectively applied in large-scale industrial production systems and how to implement them is still unknown. This research aims to evaluate whether pericyclic reactions are suitable for large-scale industrial production and to explore why these reactions can yield high efficiency and why varying reaction conditions may alter the configuration of the product.

2. Literature review

2.1 Mechanism analysis of pericyclic reactions

Pericyclic reactions are roughly divided into three types: Electrocyclic reaction, cycloaddition reaction and σ migration reaction. These classifications are based on the mechanisms and outcomes of the reactions.

2.1.1 Electrocyclic reaction

Substantially, the electrocyclic reaction is a reversible reaction that converts a conjugated polyene into a cyclic alkene, accompanied by a shift in the position of the double bond. Under light or heat, the π electrons at the terminal carbon atoms of the conjugated polyene cyclize to form a σ bond, resulting in a cycloalkene with one fewer π bond. In the synthesis of dihydropyridines, Aleksey and his team (2020) employed 1,6-electrocyclic reaction in the intermediate stage. In order to turn the 1-Azahextriene system compound into a DTP system, they used a pericyclic reaction to facilitate the conversion (Alekesey, 2020).

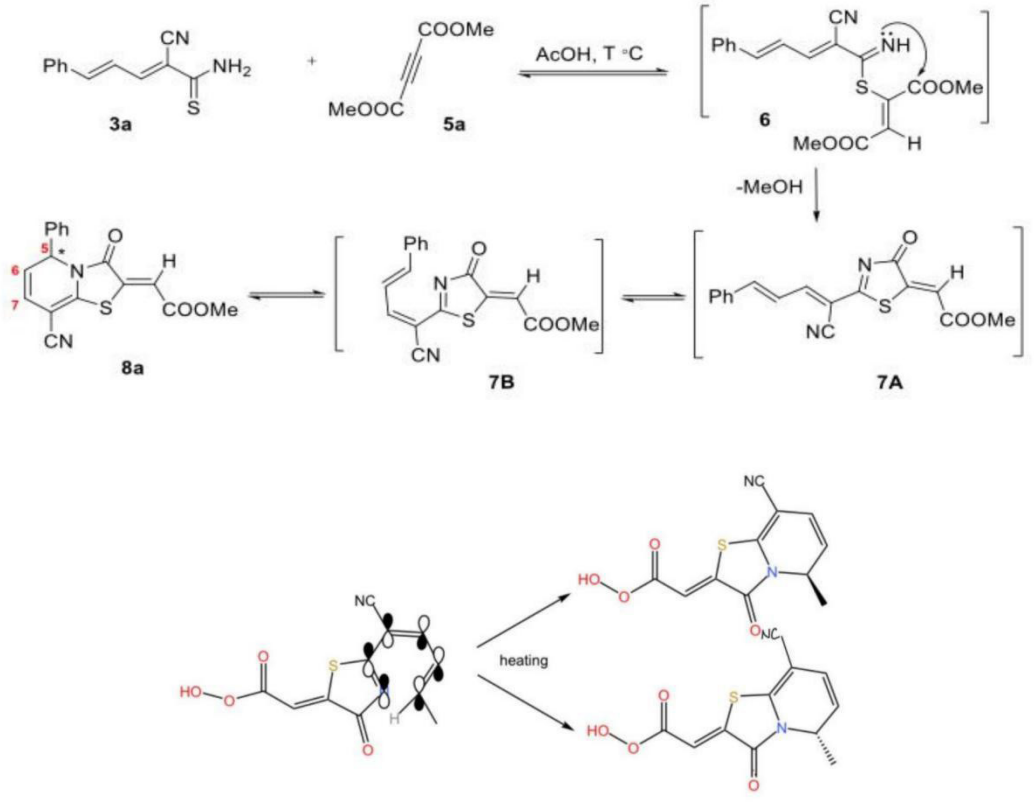

Figure 3 The samples and orbital analysis of the electrocyclic reaction.

As shown in Figure 3, compound 7 contains a six-membered ring with a conjugated system of π^6_6, and the atoms are numbered from 1 to 6, starting at the nitrogen atom and end at the carbon atom directly bonded to R1. Because the atoms in alkenes are in the same plane, after electrocyclic reaction, they can form stereoisomers. The HOMO of the molecule is symmetrical, allowing the system to undergo disrotatory ring closure under heating. As

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a result, both stereoisomeric products can form, and due to the chirality at C-6, the final product will be a mixture of stereoisomers.

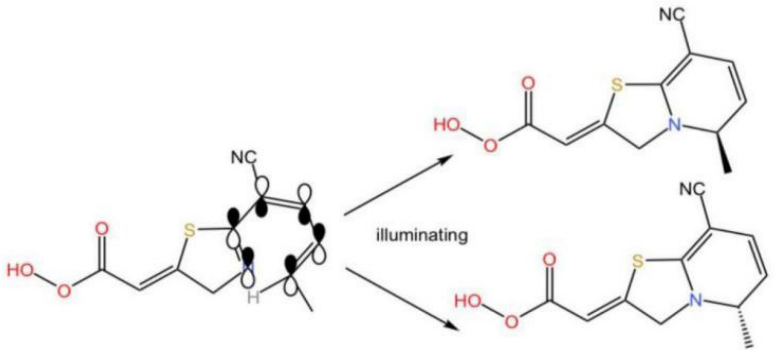

Figure 4 The effect which change the condition of the reaction

When the reaction is instead conducted under light irradiation, it proceeds via conrotatory pathway, but a mixture of products is still formed. High stereochemical purity is only possible when the resulting stereoisomers are spatially identical—that is, when only one stereoisomer is produced.

2.1.2 Cycloaddition reaction

Cycloaddition reactions are a well-known class of pericyclic reactions. While electrocyclic reactions are limited in certain applications, cycloadditions are more widely applied in some industrial production. The reactants consist of two components: a diene and a dienophile. A classic example is the reaction between ethene and buta-1,3-diene. It is a synergistic reaction which forms a cyclic transition state and finishes the reaction at the same time. According to stereochemical rules, the diene must adopt a cis-conformation for the reaction to proceed efficiently. In this case, both the HOMO and LUMO play key roles: the dienophile being electron-deficient, contributes the LUMO, while the electron-rich dine contributes the HOMO. As noted by Corti (2020), the g-C3N4/Perovskite composites used as photocatalysts for singlet oxygen generation are not a typical cycloaddition reaction, but he utilized the reaction between cyclohex-1,3-diene and oxygen. The benefit is, that oxygen has a higher electronegativity than alkenes, allowing it to exhibit stronger electron-withdrawing property when reacting using LUMO (Corti *et al.*, 2020).

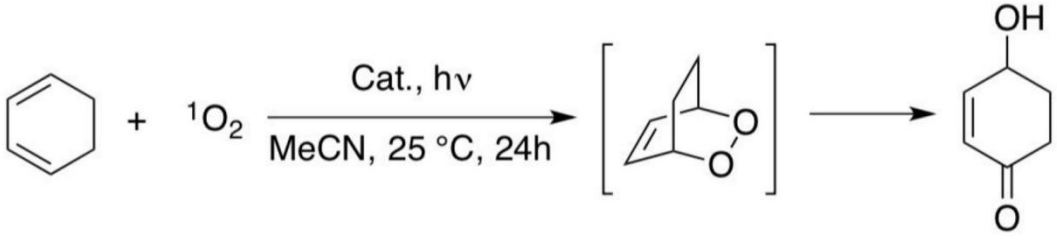

Figure 5 The samples of the cycloaddition reaction

In this case, carbon atoms 1 through 4 donate electrons from the HOMO to $^1O_2$ and they form a transition ring with four carbon atoms and two oxygen atoms and react synergistically. Unlike other pericyclic reactions, the stereoselectivity of cycloaddition arises directly from the reaction mechanism itself. Due to the synergistic mechanism, the sigma bond cannot rotate when it forms the transition state, which means that the conformation of the reactant is preserved throughout the reaction. The mechanism is illustrated below:

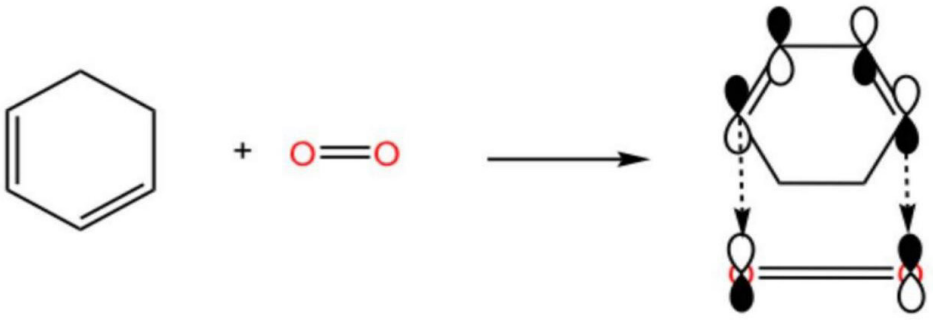

Figure 6 The orbital analysis for the cycloaddition reaction

In this process, due to the strong electronegativity of oxygen, cyclohex-1,3-diene donates electrons from its HOMO to the LUMO of O_2.

2.1.3 σ-migration reaction

As mentioned in the introduction, Professor Li and his team (2024) discovered a new synthesis route which uses [3,3]-sigmatropic rearrangement to form $PGF_{2\alpha}$.

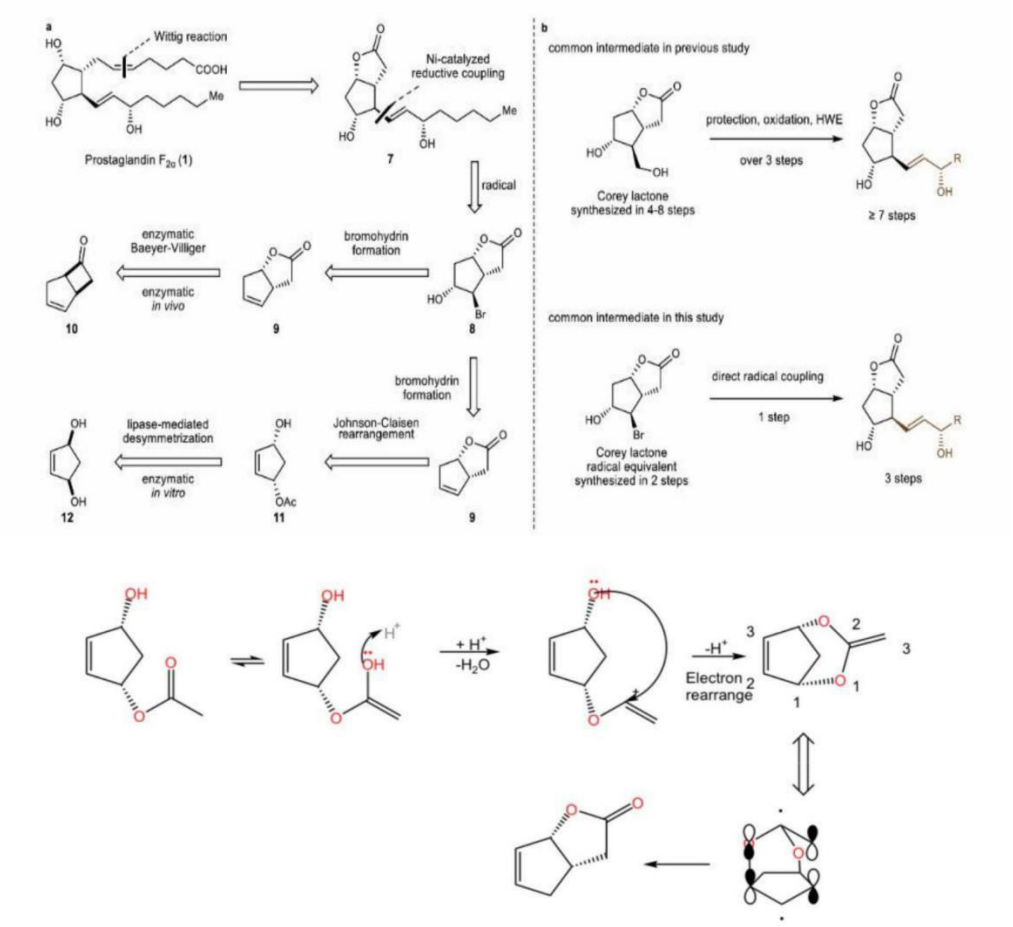

Figure 7 The possible mechanism for the sigmatropic reaction

The transformation from compound 11 to 9 requires a relatively lengthy process, starting with the formation of an ether ring. After the rearrangement from keto form to enol form, the ethanoyloxy group first neutralizes the hydrogen ion and forms a carbon cation which is then nucleophilically attacked by the lone pair from another hydroxyl group and forms a ring. Then [3,3]-sigmatropic rearrangement occurs, with face-to-face migration allowed by the symmetry of the two SOMOs, accomplishing the migration. The conformations of the product and the reactant remained unchanged, indicating that the reaction is stereospecific (Li 2024).

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3. Methodology

3.1 Research Problem and Information Collection

The primary objective of this study is to evaluate whether pericyclic reactions can be applied to large-scale industrial production. This involves analyzing drug structures, synthesis difficulty, yield, and reaction specificity. In addition, the study aims to compare the green chemistry performance of all the selected pericyclic reaction cases. Pericyclic reactions offer novel synthetic routes for many complex structures, such as five-membered rings synthesized via 1,3-dipolar cycloaddition reactions. Currently, pericyclic reactions are employed in small-scale, targeted synthesis of certain alkaloids and pharmaceuticals. The focus on large-scale industrial production is intended to determine whether pericyclic reactions can be utilized in the synthesis of a broader range of drug compounds.

The information gathered for this study includes laboratory examples of complex organic compound synthesis using pericyclic reactions, as well as experimental data demonstrating the stereoselectivity of these reactions, such as yield and rate measurements. Additionally, to understand the underlying mechanisms of stereoselectivity in pericyclic reactions, the study reviews theoretical literature, including molecular orbital theory, Hund's rule, the Pauli exclusion principle, frontier orbital theory, and energy correlation theory.

The choice of secondary research is justified for several reasons:

Stringent Reaction Conditions: Organic chemical reactions require highly controlled environments, which are difficult to replicate in a personal research setting.

Slow Reaction Rates: The reaction rates of organic compounds are relatively slow, making the time investment inefficient.

Limited Personal Capability: Individual limitations may lead to unsuccessful experiments.

Difficulty in Product Analysis: Organic compounds often exhibit similar physical and chemical properties, making it challenging to confirm reaction completion, identify the causes of by-products, or verify whether the product is the target compound.

3.2 Secondary Research Methodology

3.2.1 Search Engines, Databases, and Journals

This study utilizes the academic library as the primary search platform and Google Scholar for literature retrieval. The main journals searched are those published by the American Chemical Society (ACS). These sources were chosen for their comprehensive coverage of chemical literature and the high quality of the articles they publish.

3.2.2 Keywords Used for Literature Search

The keywords used in the literature search include:

Keywords: directly related to pericyclic reactions, such as electrocyclic reactions, cycloaddition reactions, and sigmatropic reactions.

Keywords: related to recent achievements in medicinal chemistry or biochemical organic synthesis that are relevant to pericyclic reactions, such as drugs synthesized via Cope rearrangement.

3.2.3 Evaluation and Screening of Literature

For literature screening, this study employs the CRAAP test (Currency, Relevance, Authority, Accuracy, Purpose), with the following specific criteria:

Currency: Articles published before 2020 are excluded to ensure the timeliness of the literature.

Relevance: Priority is given to articles that explicitly mention the use of pericyclic reactions, followed by those whose reaction pathways may involve pericyclic reactions.

Authority: Articles published in ACS journals are primarily selected to ensure the authority of the literature.

Accuracy: The accuracy of the articles is assessed by reading the proposed reaction mechanisms. Priority is given to examples that demonstrate the stereoselectivity or stereospecificity of pericyclic reactions.

Purpose: The purpose of each article is ensured to align with the research objectives, avoiding any deviation from the topic.

3.3 Cases Analysis

This study selects prostaglandin PGF-2α as a case for analysis. This case was published in 2024 by Dr.Li's research team at Shanghai Jiao Tong University, demonstrating strong timeliness. By reviewing its retrosynthetic route, it was found that the study employed pericyclic reactions as the key step for synthesizing intermediate products. Specifically, the product exhibited stereospecificity after undergoing a Cope rearrangement, yielding only the endo product without the exo product. This case meets the requirements of this study for stereoselectivity and stereospecificity, effectively supporting the potential of pericyclic reactions in large-scale synthesis.

3.4 Theoretical Basis

To gain a deeper understanding of the stereoselectivity of pericyclic reactions, this study reviews relevant theoretical literature, including the following aspects:

Molecular Orbital Theory: This theory explains the dis-

tribution and movement of electrons in molecular orbitals during pericyclic reactions, aiding in the understanding of the stereoselectivity of the reactions.
Hund's Rule: This rule describes the arrangement of electrons in degenerate orbitals, which significantly influences the stereoselectivity of pericyclic reactions.
Pauli Exclusion Principle: This principle states that two electrons in the same orbital must have opposite spins, which has a significant impact on the stereoselectivity of pericyclic reactions.
Frontier Orbital Theory: This theory accounts for the stereoselectivity of pericyclic reactions by analyzing the frontier orbitals (HOMO and LUMO) of the reactants.
Energy Correlation Theory: This theory explains the stereospecificity of pericyclic reactions by analyzing energy changes during the reaction process.

3.5 Broader Implications

The findings of this study have broader implications for the field of organic synthesis. Pericyclic reactions, with their ability to form complex structures with high stereospecificity, could revolutionize the synthesis of pharmaceuticals and other biologically active compounds. The capability to perform these reactions on a large scale could significantly reduce the cost and increase the availability of these compounds.
Moreover, the theoretical insights gained from this study may inform the design of new pericyclic reactions with enhanced efficiency and selectivity. This could lead to the development of novel synthetic routes for currently challenging compounds, further expanding the toolkit available to synthetic chemists.

4. Result and discussion

4.1 Analysis of Pericyclic Reactions Based on Experimental Data

Pericyclic reactions, characterized by their concerted mechanisms and orbital-controlled stereoselectivity, have emerged as powerful tools in synthetic chemistry. Their industrial applicability, however, remains contingent on optimizing reaction conditions to balance efficiency, cost, and environmental sustainability. The dominance of frontier molecular orbitals (HOMO and LUMO) dictates reaction pathways-conrotatory or disrotatory motions in electrocyclic reactions, or suprafacial and antarafacial interactions in cycloadditions-ensuring precise stereochemical outcomes. For example, in a conrotatory electrocyclic ring-opening, the stereochemistry of chiral centers is retained, minimizing isomer formation and simplifying purification. Despite these advantages, competing mechanisms (e.g., nucleophilic substitution versus elimination) under similar conditions can lead to mixed products, necessitating rigorous experimental validation.

4.1.1 Case Studies of Cycloaddition Reactions

Cycloadditions, particularly [4+2] Diels–Alder and 1,3-dipolar variants, illustrate both the potential and limitations of pericyclic chemistry.
The researcher references the study by Nicolaou and Chen (2012): *Rh-Catalyzed Cyclopropane-Alkyne Cycloaddition*. The substrates are silyloxy vinyl cyclopropane and alkynes, under conditions involving a Rh catalyst, dichloromethane (DCM) and room temperature. The final yield was 46%.
The modest yield suggests limitations in orbital alignment or catalyst-substrate compatibility. DCM, while inert, may poorly stabilize transition states. The Rh catalyst, though effective in activating strained cyclopropanes, might suffer from deactivation via ligand dissociation. Competing side reactions (e.g., alkyne oligomerization) could further reduce efficiency.
In comparison, the study by Burns *et al*. (2011), *Thiourea-Catalyzed Pyridinium Ylide Cycloaddition,* employed oxidized pyridinium ylide and alkyne as substrates, using a thiourea catalyst in acetonitrile at room temperature for 96 hours, yielding a final product with 95% efficiency. In this case, the dual hydrogen-bonding capability of thiourea stabilizes dipolar intermediates, enhancing regioselectivity. Acetonitrile's high polarity facilitates dipole-dipole interactions, accelerating the reaction. The extended reaction time (96 hours) compensates for the low activation energy typical of pericyclic reactions (Table 1).

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Table 1 Comparison of cycloaddition yields under Rh vs. thiourea catalysis. Burns' system (95%) outperforms Nicolaou's (46%) due to optimized orbital interactions and reduced side reactions.

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Rh-catalyzed [5+2] Cycloaddition	Intermolecular cycloaddition for Englerin A core synthesis	Rh catalyst, rt, CH_2Cl_2	Silyloxy vinyl cyclopropane derivatives + alkynes	Bicyclic core structure (89)	0.46	Nicolaou et al. (2012)
Rh-catalyzed [5+2] Cycloaddition	Intramolecular cycloaddition for Tremulenolide A synthesis	$[Rh(CO)_2Cl]_2$ catalyst, toluene, 80°C	Vinyl cyclopropane derivative (125)	Cycloheptadiene intermediate (126)	0.74	Ashfeld & Martin (2005)
Co-mediated η^5-Pentadienyl Cycloaddition	[5+2] Cycloaddition via Co complexes to form η^7-η^3-cycloheptadiene isomers	Co complex, rt, THF	Co-pentadienyl complex (167) + alkynes	η^7-η^3-Cycloheptadiene (168) or η^5-isomer (169)	60–98%	Whitecell et al. (2008)
Thiourea-Catalyzed Asymmetric Cycloaddition	Intramolecular [5+2] cycloaddition of oxidized pyridinium ylides	Thiourea catalysts (76/77), MeCN, rt, 96 h	Oxidized pyridinium ylide precursor	Seven-membered ring product	Up to 95% ee	Burns et al. (2011)
Rh-catalyzed [5+2] Cycloaddition	Regioselective intermolecular cycloaddition of vinyl cyclopropanes and alkynes	Rh catalyst (102), TFE, 90°C	Vinyl cyclopropane derivatives (119) + alkynes	Cycloheptadiene derivatives	25–95%	Shu et al. (2011, 2012)

Competing Mechanisms and Impurities

The 36-92% yield range in AZT-alkyne 1,3-dipolar cycloadditions (as reported in a medicinal chemistry study) highlights the role of substituent effects. Electron-withdrawing groups (EWGs) on alkynes polarize the dipole, increasing reactivity, while steric bulk hinders transition state formation. Microwave irradiation, as shown in recent studies, selectively excites HOMO-LUMO pairs, suppressing competing stepwise mechanisms (e.g., Michael addition) and improving yields to >90%. For cycloaddition, the Stereo control is well-maintained as Endo/exo selectivity can be predictable via the Woodward-Hoffmann rules. Also, solvent selection is not necessarily fixed in this reaction. Consider the scalability, CuAAC reactions are scalable for bioconjugation, albeit with metal contamination risks.

However, the drawbacks are obvious: catalyst costs are high, especially for noble metals (Rh, Pd), which are expensive and difficult to recover. The entire reaction time is too long, thermal activation may require hours to days. By-product formation can also affect the yield, and the competing pathways is also a factor when in (e.g., electrocyclic side reactions) complicate purification.

4.1.2 Case Studies of Sigmatropic Reactions

Sigmatropic rearrangements, such as Cope and Claisen shifts, exemplify near-perfect atom economy and stereochemical fidelity.

AZT derivative synthesis via 1,3-dipolar cycloaddition with substrates of AZT (1) and substituted alkynes under conditions of reflux in dimethoxyethane (DME) for 12-24 hours. But the yield varies widely ranging from 36% to 92%. Electron-deficient alkynes (e.g., CFa-substituted) achieve 92% yield by stabilizing the transition state. In contrast, electron-rich alkynes exhibit lower reactivity (36%), likely due to dipole mismatch.

[3,3]-sigmatropic shifts in terpene synthesis while conditions are DMSO solvent, room temperature, and 2-6 days. With the yield: >99%, DMSO's high polarity stabilizes ionic intermediates, while its aprotic nature prevents undesired proton transfers. The intramolecular nature of σ-migration eliminates competing intermolecular pathways, ensuring near-quantitative yields (Table 2).

Table 2 Sigmatropic reactions achieve >99% yields due to intramolecular mechanisms, avoiding isomerization.

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
CuAAC (1,3-Dipolar Cycloaddition)	Cu-catalyzed azide-alkyne cycloaddition (AZT + alkynes)	DME reflux	AZT (1) + alkynes (various substituents)	1,4-Disubstituted triazole nucleoside analogs (2a, 2b)	36–92%	Li et al. (2010)
CuAAC	Solvent-free microwave-assisted synthesis	Microwave, solvent-free	Alkynyl pyrazolo[1,5-a]pyrimidines (11) + azides (12)	1,4-Disubstituted triazoles (13a, 13b)	93–97%	Moukha et al. (2001)

Advantages of sigmatropic reactions include:

1. Atom Economy: No byproducts are formed; all atoms are retained in the product.
2. Mild Conditions: Room-temperature compatibility reduces energy costs.
3. High Yields: Intramolecular mechanisms minimize side reactions.

Several drawbacks are noted:

1. Slow Kinetics: Days-long reactions hinder high-throughput applications.
2. Substrate Limitations: Require pre-organized π-systems for orbital overlap.
3. Solvent Dependency: Polar aprotic solvents (e.g., DMSO) are costly to purify.

4.2 Compromise in industrial perspective

Pericyclic reactions offer several advantages in industrial green chemistry. Techniques such as using microwave and photochemical methods can reduce solvent usage and energy consumption. In terms of precision, stereochemical control can also eliminate the need for costly chiral separations. Moreover, their versatility allows application in pharmaceutical synthesis (e.g., taxol side-chain synthesis) and materials science.

Regarding critical limitations, catalyst recycling remains technically challenging, especially for noble metals, which are expensive and difficult to recover. Reaction optimization is complicated by competing pathways and often requires extensive Design of Experiments (DOE). Additionally, photochemical reactors and microwave systems entail significant capital investment.

Comparative Analysis of Pericyclic Reactions in Industrial and Conventional Synthesis

Pericyclic reactions, including cycloadditions, electrocyclic rearrangements, and sigmatropic shifts, are pivotal in modern organic synthesis due to their stereochemical precision and mechanistic elegance. This analysis evaluates their industrial applicability against conventional methods (e.g., nucleophilic substitutions, Heck coupling, Knoevenagel condensations) using data from Tables 1-3, with a focus on yield, reactant complexity, and reaction conditions.

4.3 Cycloaddition Reactions vs Conventional Methods

Case Study 1: [4+2] Diels-Alder Reaction vs Heck Coupling

Table 3 The pericyclic reaction for cycloaddition process

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Chemodivergent Cascade Cyclization	Sulfonimide + salicylaldehyde cyclization (electronically controlled selectivity	Catalyst-free (e-poor) or 5 mol% DPP (neutral/e-rich), rt	Sulfonimide + 5-nitro-salicylaldehyde (R^1=5-EWG) or neutral/e-rich salicylaldehyde	Dihydrobenzofuran (e-poor) or 2H-chromene (neutral/e-rich)	81–85%	Bisag et al. (2020)
C–H Arylation	Pd/C-catalyzed C2-selective arylation of indoles	Pd/C, Polarclean/H_2O, rt	Indole + diaryliodonium salts	C2-arylated indoles	0.85	Santoro et al. (2016)
Au-Catalyzed Divergent Reaction	[4+2] Cycloaddition of furan-ynes with N-oxides	5 mol% Au catalyst (chiral anion), toluene, –10°C, 48 h	Furan-yne (1) + chiral anion oxidant	Dihydropyridone (2)	0.95	Hashmi et al.(2000)
Photocatalytic Radical Cascade	N-Arylsulfonylhydrazone γ,δ-alkenes under Ru(II) photocatalysis	Ru(II) photocatalyst, K_2CO_3, blue light, rt	γ,δ-Unsaturated N-arylsulfonylhydrazones	Tetrahydropyridazines (via dearomatization/Smiles rearrangement/carboamination)	0.81	Hu et al.(2016)
CuAAC	1,3-Dipolar cycloaddition for 1,2,3-triazole derivatives	Cu(I) catalyst, H_2O or DES, rt	3-Amino-1,2-propanediol derivatives + alkynes	1,4-Disubstituted 1,2,3-triazoles (antiviral)	0.95	Zhu et al.(2016)

Table 4 Conventional methods for cycloaddition process

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Nucleophilic Substitution	Cyclopentenone acetate + benzimidazole derivatives	Anhydrous MeCN, NaH (95%), rt, N_2, overnight	(±)-1 (4-oxocyclopent-2-en-1-yl acetate) + benzimidazole derivatives (4a–d)	2-Substituted cyclopentenones (5a–d, 6a–d)	51–67%	Mantione et al.(2016)
HDA Cycloaddition	Nitro carbonyl + cyclopentadiene [4+2] cycloaddition	TBADT (2 mol%), MeCN/H_2O (5:1), O_2, $NaHCO_3$, simulated sunlight, 1 h	Benzohydroxamic acid (5a) + cyclopentadiene (6)	HDA adduct (8a)	0.49	Quadrelli et al.(2017)
Photocatalytic Oxidation	Hydroxamic acid → nitro carbonyl intermediate	TBADT (2 mol%), MeCN/H_2O (5:1), O_2, $NaHCO_3$, simulated sunlight	Acetyl hydroxamic acid (5g) + 1,3-cyclohexadiene (7)	HDA adduct (9g)	0.63	Memeo et al.(2017)
Heck Coupling	Aryl halides + acrylates via Pd catalysis	Pd catalyst (1 mol%), 100°C, 12 h	Aryl halides (X = halogen) + acrylates	Styrene derivatives (compound 2)	0.67	Heck et al.(2008)
Reductive Amination	Amine intermediate + ketone for panobinostat precursor	Solvent/reagent undisclosed (patented)	Amine intermediate (3) + ketone derivative (5)	Panobinostat precursor (4)	0.62	Teresa basile, (2019)

The [4+2] Cycloaddition of frame-yses with N-oxides (Table 3, Row 3) is a new way to synthesize complex products. The reaction has taken place under the conditions of 5 mol% via Au catalyst in at -10 °C for 48 hours. The yield reached quite a high level of 95%. As mentioned before, the stereoselectivity resulting from orbital-controlled suprafacial or antarafacial interactions effectively suppresses the formation of isomers, with no by-products

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generated from other mechanism. Moreover, the atom economy is pretty high as only one product is obtained. However, among the reaction conditions, the primary cost-increasing factor is the use of gold as the catalyst.

Compared with the pericyclic reaction above, Heck Coupling (Table 4, Row 4) provide a useful contrast. It is conducted suing 1 mol% Pd catalyst at 100 ℃ for 12 hours, but the yield is unexpectedly limited to 67%. In this comparison, the pericyclic reaction clearly outperforms the conventional method in terms of yield (Pericyclic: 95%>Heck: 67%), however, Heck reaction requires high temperature (100℃) that avoids the need for cryogenic setups.

While Diels-Alder offers superior yields, the high cost of catalyst and the requirement for cryogenic conditions hinder its industrial adoption. Heck coupling, though lower-yielding, utilizes more affordable catalysts and simpler setups, making it preferable for bulk arylations.

4.4 1,3-Dipolar Cycloaddition vs conventional methods

Case Study 2: 1,3-Dipolar Cycloaddition vs Nucleophilic Substitution

Table 3 The pericyclic method for industrial production

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Chemodivergent Cascade Cyclization	Sulfonimide + salicylaldehyde cyclization (electronically controlled selectivity	Catalyst-free (e-poor) or 5 mol% DPP (neutral/e-rich), rt	Sulfonimide + 5-nitro-salicylaldehyde (R^1=5-EWG) or neutral/e-rich salicylaldehyde	Dihydrobenzofuran (e-poor) or 2H-chromene (neutral/e-rich)	81–85%	Bisag et al. (2020)
C–H Arylation	Pd/C-catalyzed C2-selective arylation of indoles	Pd/C, Polarclean/H_2O, rt	Indole + diaryliodonium salts	C2-arylated indoles	0.85	Santoro et al. (2016)
Au-Catalyzed Divergent Reaction	[4+2] Cycloaddition of furan-ynes with N-oxides	5 mol% Au catalyst (chiral anion), toluene, –10°C, 48 h	Furan-yne (1) + chiral anion oxidant	Dihydropyridone (2)	0.95	Hashmi et al.(2000)
Photocatalytic Radical Cascade	N-Arylsulfonylhydrazone γ,δ-alkenes under Ru(II) photocatalysis	Ru(II) photocatalyst, K_2CO_3, blue light, rt	γ,δ-Unsaturated N-arylsulfonylhydrazones	Tetrahydropyridazines (via dearomatization/Smiles rearrangement/carboamination)	0.81	Hu et al.(2016)
CuAAC	1,3-Dipolar cycloaddition for 1,2,3-triazole derivatives	Cu(I) catalyst, H_2O or DES, rt	3-Amino-1,2-propanediol derivatives + alkynes	1,4-Disubstituted 1,2,3-triazoles (antiviral)	0.95	Zhu et al.(2016)

Table 4 The conventional methods for 1,3-dipole cycloaddition process

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Nucleophilic Substitution	Cyclopentenone acetate + benzimidazole derivatives	Anhydrous MeCN, NaH (95%), rt, N_2, overnight	(±)-1 (4-oxocyclopent-2-en-1-yl acetate) + benzimidazole derivatives (4a–d)	2-Substituted cyclopentenones (5a–d, 6a–d)	51–67%	Mantione et al.(2016)
HDA Cycloaddition	Nitro carbonyl + cyclopentadiene [4+2] cycloaddition	TBADT (2 mol%), MeCN/H_2O (5:1), O_2, $NaHCO_3$, simulated sunlight, 1 h	Benzohydroxamic acid (5a) + cyclopentadiene (6)	HDA adduct (8a)	0.49	Quadrelli et al.(2017)
Photocatalytic Oxidation	Hydroxamic acid → nitro carbonyl intermediate	TBADT (2 mol%), MeCN/H_2O (5:1), O_2, $NaHCO_3$, simulated sunlight	Acetyl hydroxamic acid (5g) + 1,3-cyclohexadiene (7)	HDA adduct (9g)	0.63	Memeo et al.(2017)
Heck Coupling	Aryl halides + acrylates via Pd catalysis	Pd catalyst (1 mol%), 100°C, 12 h	Aryl halides (X = halogen) + acrylates	Styrene derivatives (compound 2)	0.67	Heck et al.(2008)
Reductive Amination	Amine intermediate + ketone for panobinostat precursor	Solvent/reagent undisclosed (patented)	Amine intermediate (3) + ketone derivative (5)	Panobinostat precursor (4)	0.62	Teresa basile, (2019)

The CuAAC reaction for synthesizing 1,2,3-triazoles (Table 3, Row 5) is also a new way for compound construction, which used Cu(I) as a catalyst in water or deep eutectic solvents (DES) at room temperature. The research reports a yield of 95%. Owing to is consistency with click chemistry principles—namely rapidity, quantitative conversion, and biorthogonality—the reaction offers significant advantages. Notably, pericyclic reaction exhibits minimal solvent requirements, with only water or DES needed in this case. However, some drawbacks remain. Residual copper necessitates post-reaction purification, especially for pharmaceutical application where metal contamination is a concern.

As a conventional counterpart, nucleophilic substitution reactions were selected for comparison (Table 4, Row 1), as both approaches can influence product stereochemistry. The condition they use was NaH (95%) with anhydrous MeCN which reacting for the whole night, but with the yield of only 51% to 67%. The substitution reaction employed NaH (95%) in anhydrous MeCN, proceeding overnight, but yielded only 51%-67%. In terms of the yield, CuAAC (95%) > Substitution (51–67%). Moreover, pericyclic reaction satisfies green chemistry criteria mor effectively by utilizing environmentally friendly solvents

such as water, in contrast to the dry organic solvents (acetonitrile) required for nucleophilic substitution.

CuAAC's high yield and green solvents align with sustainable manufacturing, but metal contamination risks necessitate additional purification steps. Nucleophilic substitutions, though lower-yielding, are entrenched in API synthesis due to operational familiarity.

4.5 Sigmatropic Reactions vs Condensation Methods

Case Study 3: [3,3]-Sigmatropic Shift vs. Knoevenagel Condensation

Table 5 Pericyclic reaction in sigmatropic rearrangment

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
RAHB-Driven Diaza-Cope Rearrangement	Resonance-assisted hydrogen bond (RAHB) for chiral diamine synthesis	DMSO-d6, rt, 2–6 days	Initial diimine (e.g., 1a) + aldehyde (e.g., benzaldehyde)	Rearranged diimine (e.g., 1b)	>99%	C. Cope et al. (1940)
Electronic Effect in Diaza-Cope	Substituent electronic effects on equilibrium constants (X=H, Y=Cl) via Hammett	DMSO-d6, rt, 2–6 days	Substituted diimine (e.g., 12a: X=H, Y=Cl)	Rearranged diimine (12b)	K_{eq} = 3.0	E. Goldschmitt et al. (1976)
Oxoanion-Accelerated Diaza-Cope	Phenolic oxoanion drastically accelerates reaction to completion	DMSO, rt, with t-BuOK	Hydroxy-substituted diimine (4a)	Rearranged diimine (4b)	>99%	Soon Mog so et al. (2012)
Steric Effect in Diaza-Cope	meta-Substituents (e.g., mesityl) enhance driving force	DMSO-d6, rt	Mesityl-containing diimine (2a)	Rearranged diimine (2b)	>99%	hyunwoo Kim et al. (2008)
Diastereoselective Diaza-Cope	Chiral aldehydes (e.g., myrtenal) react with rac-hpen for diastereoselectivity	EtOH, rt	rac-hpen + (R)-myrtenal (to form 28a and 29a)	Rearranged product (29b dominant)	>20:1 selectivity	D.S. Choi et al. (2008)

Table 6 The conventional methods for sigmatropic rearrangement process

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Knoevenagel Condensation	Aldehyde + cyanoethanethioamide → penta-2,4-dienethioamide	TEA (0.1 eq), EtOH, 60°C, 0.5 h	Cinnamaldehyde (1a) + cyanoethanethioamide (2)	3a (2-Cyano-5-phenylpenta-2,4-dienethioamide)	0.95	Ho et al. (1995); Frolov et al. (2013); Nesterov et al. (2000)
Domino Cyclization	Thioamide + DMAD → dihydrothiazolo[3,2-a]pyridine	AcOH, 60°C, 10 h	3a (penta-2,4-dienethioamide) + DMAD (5a)	8a (2,3-Dihydro-5H-thiazolo[3,2-a]pyridine)	0.87	Bleskaya et al.(2014); Deryabina et al. (2005); Berseneva et al. (2001)
Condensation-Electrocyclization	Thioamide + methyl propiolate → pyrido[2,1-b][1,3]thiazine	AcOH, 60°C, time N/A	3a (penta-2,4-dienethioamide) + methyl propiolate	12a (4-Oxo-4H,6H-pyrido[2,1-b][1,3]thiazine)	0.62	Berseneva et al. (2001)
Thiazolidinone Condensation	Thiazolidinone + aldehyde → substituted dihydrothiazolo[3,2-a]pyridine	NaOAc, AcOH, 118°C, 15 h	Thiazolidinone (9a) + aldehyde (1a)	8k (6-Methyl-2,3-dihydro-5H-thiazolo[3,2-a]pyridine)	0.59	Tatar et al. (2010)
Thioamide Cyclization	α-Methylcinnamaldehyde + cyanoethanethioamide → thiopyran	TEA (0.1 eq), EtOH, 60°C, 0.5 h	α-Methylcinnamaldehyde (1e) + cyanoethanethioamide (2)	4e (2H-Thiopyran-5-carbonitrile)	0.73	Nedolya et al. (1998); Brandsma et al. (1969); Wiehe et al. (1985)

Another example is the use of sigmatropic rearrangements in terpene synthesis (Table 5, Row 1). With the condition—DMSO solvent at room temperature for about 2 to 6 days—a remarkable yield of over 99% is achieved, which is considered extremely high in organic chemistry. The advantages are obvious, the prior benefit is the high yield. Additionally, the mild conditions—room temperature and the absence of a catalyst—are also significant advantages. And the yield is nearly quantitative with no byproducts. However, the slow kinetics (2–6 days) delay production timelines, making it unsuitable for industrial-scale applications.

As a conventional comparison, the Knoevenagel condensation (Table 6, Row 1) was selected. In this reaction, a small amount of triethylamine (TEA) was used as a catalyst, with alcohol as the solvent, undergo 60°C for 0.5 hours. This method also achieved a high yield of 95%.

In terms of the yield, both reactions are comparable: sigmatropic rearrangement (>99%) and Knoevenagel condensation (95%) demonstrate high efficiency in organic synthesis. However, when considering reaction time, the Knoevenagel condensation (0.5h) is significantly faster than the Sigmatropic rearrangement (2-6 days). From an industrial perspective, sigmatropic reactions excel in atom economy but are impractical for high-throughput synthesis due to prolonged reaction times. Knoevenagel condensations, despite moderate yields, are favored for rapid scaffold construction.

4.6 Electrocyclic Reactions vs. Photocatalytic Methods

Case Study 4: Electrocyclic Ring-Opening vs Photocatalytic Oxidation

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Table 3 The pericyclic reaction for electrocyclic reaction

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Chemodivergent Cascade Cyclization	Sulfonimide + salicylaldehyde cyclization (electronically controlled selectivity	Catalyst-free (e-poor) or 5 mol% DPP (neutral/e-rich), rt	Sulfonimide + 5-nitro-salicylaldehyde (R′=5-EWG) or neutral/e-rich salicylaldehyde	Dihydrobenzofuran (e-poor) or 2H-chromene (neutral/e-rich)	81–85%	Bisag et al. (2020)
C–H Arylation	Pd/C-catalyzed C2-selective arylation of indoles	Pd/C, Polarclean/H_2O, rt	Indole + diaryliodonium salts	C2-arylated indoles	0.85	Santoro et al. (2016)
Au-Catalyzed Divergent Reaction	[4+2] Cycloaddition of furan-ynes with N-oxides	5 mol% Au catalyst (chiral anion), toluene, –10°C, 48 h	Furan-yne (1) + chiral anion oxidant	Dihydropyridone (2)	0.95	Hashmi et al.(2000)
Photocatalytic Radical Cascade	N-Arylsulfonylhydrazone γ,δ-alkenes under Ru(II) photocatalysis	Ru(II) photocatalyst, K_2CO_3, blue light, rt	γ,δ-Unsaturated N-arylsulfonylhydrazones	Tetrahydropyridazines (via dearomatization/Smiles rearrangement/carboamination)	0.81	Hu et al.(2016)
CuAAC	1,3-Dipolar cycloaddition for 1,2,3-triazole derivatives	Cu(I) catalyst, H_2O or DES, rt	3-Amino-1,2-propanediol derivatives + alkynes	1,4-Disubstituted 1,2,3-triazoles (antiviral)	0.95	Zhu et al.(2016)

Table 4 The conventional methods for electrocyclic process

Reaction Type	Reaction Details	Reaction Conditions	Reactants	Products	Yield	References (Year)
Nucleophilic Substitution	Cyclopentenone acetate + benzimidazole derivatives	Anhydrous MeCN, NaH (95%), rt, N_2, overnight	(±)-1 (4-oxocyclopent-2-en-1-yl acetate) + benzimidazole derivatives (4a–d)	2-Substituted cyclopentenones (5a–d, 6a–d)	51–67%	Mantione et al.(2016)
HDA Cycloaddition	Nitro carbonyl + cyclopentadiene [4+2] cycloaddition	TBADT (2 mol%), MeCN/H_2O (5:1), O_2, $NaHCO_3$, simulated sunlight, 1 h	Benzohydroxamic acid (5a) + cyclopentadiene (6)	HDA adduct (8a)	0.49	Quadrelli et al.(2017)
Photocatalytic Oxidation	Hydroxamic acid → nitro carbonyl intermediate	TBADT (2 mol%), MeCN/H_2O (5:1), O_2, $NaHCO_3$, simulated sunlight	Acetyl hydroxamic acid (5g) + 1,3-cyclohexadiene (7)	HDA adduct (9g)	0.63	Memeo et al.(2017)
Heck Coupling	Aryl halides + acrylates via Pd catalysis	Pd catalyst (1 mol%), 100°C, 12 h	Aryl halides (X = halogen) + acrylates	Styrene derivatives (compound 2)	0.67	Heck et al.(2008)
Reductive Amination	Amine intermediate + ketone for panobinostat precursor	Solvent/reagent undisclosed (patented)	Amine intermediate (3) + ketone derivative (5)	Panobinostat precursor (4)	0.62	Teresa basile, (2019)

The chosen pericyclic reaction is the electrocyclic opening of dihydrobenzofurans (Table 3, Row 1), which proceeds either under catalyst-free conditions or with DPP as an additive (neutral or electron-rich). The reaction requires only mild conditions, typically around 25°C, is needed yet achieves a yield of 81%–85%. A key advantage is that no catalyst is necessary, which reduces costs. Additionally, stereochemical outcomes can be controlled via conrotatory or disrotatory pathways. However, a clear drawback is that to accommodate substrate specificity, electron-rich systems require the addition of DPP.

For comparison, potocatalytic oxidation was selected as a conventional example (Table 4, Row 3). It proceeds under conditions including TBADT (2 mol%) in MeCN/H_2 O under simulated sunlight, achieving a yield of 63%.

In comparison, the yield of pericyclic reaction (81-85%) surpasses that of the traditional photocatalytic method (63%). Moreover, electrocyclic reactions do not require light sources, simplifying the process setup. From an industrial perspective, electrocyclic reactions offer higher yields and eliminate the need for photochemical equipment. However, their substrate specificity limits versatility. In contrast, photocatalytic methods, though lower-yielding, are more adaptable to diverse substrates.

5. Evaluation

During this process, the research aims to address the question of whether industrial production can adapt the pericyclic reaction on a large scale, considering both the volume of output and the potential for this method to be widely utilized in the synthesis of medicines or alkaloids. To address this, the issue has been analyzed from multiple perspectives, including green chemistry, chemical properties and the reaction conditions, ultimately leading to a comprehensive conclusion.

As secondary research, the researcher has selected several examples related to both industrial applications and academic studies of pericyclic reactions. By comparing these cases, the analysis demonstrates the advantages of pericyclic reactions in both theoretical contexts and practical implementations. These examples are appropriate and relevant for supporting the research objectives.

Before selecting the articles, the researcher applied the CRAAP principle to exclude outdated sources and retain only the most relevant and credible studies. A reading log was also created to record information from these sources, with only synthesis process that directly mentioned pericyclic reactions or research on pericyclic reactions being included. Based on this, the conclusions drawn are reliable.

However, due to the limited number of references of the research, some drawbacks of pericyclic reactions may not have been identified or discussed. The researcher only compared the differences between conventional synthesis and pericyclic reaction synthesis, as the impact of each method may be different, it is difficult to definitively

conclude the benefits and negative impacts. Moreover, the research did not address the condition under which industrial production could maintain pericyclic reactions. The distinction between conditions that are easy to reach or not is discussed based on laboratory setups or common sense. Although this study evaluates the potential of pericyclic reactions in large-scale industrial production through secondary research and theoretical analysis, there are still some limitations:

Limited Data Sources: Due to personal limitations, this study primarily relies on published literature data, lacking support from first-hand experimental data.

Timeliness Issues: Although this study prioritizes recent literature, some articles may still not reflect the latest research progress.

Variability in Experimental Conditions: Differences in experimental conditions across laboratories may affect the comparability of the data.

The researcher did not investigate the cost associated with creating each set of conditions, which may result in unclear conclusions.

The evaluation in green chemistry: There is no definite standard for contrasting each catalyst used in different systems, which means that the hazard for each reagent or catalyst are not clear and cannot be quantitatively analyzed.

During the entire process of the analysis, the researcher has only analyzed three typical types of pericyclic reactions, but exclude the reactions taking place on benzene rings and similar molecules. However, benzene rings are common in the majority of the medicines. Due to the lack of relevant data, the researcher can only provide a preliminary analysis and cannot conclude whether the pericyclic reaction can be applied on a large scale to a broader range of synthetic targets. In order to fully assess their industrial potential, more data from factories and industrial production cost analyses are needed.

6. Conclusion

The aim of the research is to evaluate the feasibility of applying pericyclic reactions to the large-scale production of a wider variety of medicines and alkaloids. Throughout the research, the researcher found that pericyclic reactions exhibit stereoselectivity, which improves yield and reduce the production of undesired stereoisomers. This may make the medicine testing more accurate.

According to the research mentioned before, for some chiral medicines, only one type of stereoisomer may be therapeutically effective. Therefore, ensuring the purity of chiral compounds is an important factor in industrial production. When the pericyclic reaction is compared with other methods, it offers high yield, with requirement of milder conditions and reduces the use of harmful reagents. The use of catalysts is much simpler than traditional approaches, involving basic metal elements instead of crystals with complex structures and components.

Although the reaction condition can be strict, pericyclic reactions provide novel synthesis pathways for constructing complex molecular structures.

In the future, validating the feasibility of pericyclic reactions for large-scale synthesis through experimental studies—particularly for different types of drug molecules—may be the most important direction for future investigation. Additionally, optimizing reaction conditions of pericyclic reactions to improve yield and selectivity, and refining existing theoretical models by incorporating the latest research findings to better explain the stereoselectivity, could significantly advance this field.

References

Alvarez, R. and Angel (2021). Correction: Natural polyenic macrolactams and polycyclic derivatives generated by transannular pericyclic reactions: optimized biogenesis challenging chemical synthesis. *Natural Product Reports*, 38(6), pp.1221-1225. doi:https://doi.org/ 10.1039/d1np90001c.

Alvarez, R. and de Lera, A.R. (2021). Natural polyenic macrolactams and polycyclic derivatives generated by transannular pericyclic reactions: optimized biogenesis challenging chemical synthesis. *Natural Product Reports*, 38(6), pp.1136-1220. doi:https://doi.org/10.1039/d0np00050g.

Corti, M., Chiara, R., Romani, L., Mannucci, B., Malavasi, L. and Quadrelli, P. (2020) 'g-C_3N_4/Perovskite Composites as Photocatalysts for Singlet Oxygen Generation', in Foschi, F. and Pirovano, V. (eds.) 1st Virtual Symposium on Pericyclic Reactions and Synthesis of Carbo- and Heterocyclic Systems, pp. 1–34.

Diels, O. and Alder, K. (1928). Synthesen in der hydroaromatischen Reihe. *Justus Liebig's Annalen der Chemie*, 460(1), pp.98-122. doi:https://doi.org/10.1002/jlac.19284600106.

Faita, G., Leusciatti, M. and Paolo, O. (2022). Synthesis and biological activity ofpotential antiviral compounds through 1,3-dipolar cycloadditions; Part 1: general aspects and reactions of azides. *ARKIVOC*, 2022(8), pp.19-78. doi:https://doi.org/10.24820/ark.5550190.p011.794.

Foschi, F. and Pirovano, V. (2015). *st Virtual Symposium on Pericyclic Reactions and Synthesis of Carbo-and Heterocyclic Systems*. [online] Available at: https://cirp.unime.it/wp-content/uploads/sites/41/2015/05/book-of-abstract_compresse d-1.pdf.

Gagarin, A.A., Suntsova, P.O., Minin, A.S., Pozdina, V.A., Slepukhin, P.A., Benassi, E. and Belskaya, N.P. (2020). Two Approaches for the Synthesis of Fused Dihydropyridines via a

ISSN 2959-409X

1,6-Electrocyclic Reaction: Fluorescent Properties and Prospects for Application. *The Journal of Organic Chemistry*, 85(21), pp.13837-13852. doi:https://doi.org/10.1021/acs.joc.0c01934.

Hoffmann, R. and Woodward, R.B. (1965). Orbital Symmetries and endo-exo Relationships in Concerted Cycloaddition Reactions. *Journal of the American Chemical Society*, 87(19), pp.4388–4389. doi:https://doi.org/ 10.1021/ja00947a033.

Kai and Stryker, J.M. (2013). ChemInform Abstract: [5+2] Cycloaddition Reactions in Organic and Natural Product Synthesis. *Chemical Reviews* 113(3), pp. 2244-2266. doi:https://doi.org/10.1002/chin.201319242.

Michael and Jie, C. (1992). Mechanisms ofpericyclic reactions: the role ofquantitative theory in the study of reaction mechanisms. *Accounts of Chemical Research*, 25(11), pp.537-543. doi:https://doi.org/ 10.1021/ar00023a008.

Nemoto, H. (2007). Synthetic Organic Chemistry Based on Small Ring Compounds. *Chemical and Pharmaceutical Bulletin*, 55(7), pp. 961-974. doi:https://doi.org/ 10.1002/chin.200748230.

Pasteur, L. (1848). Sur les relations qui peuvent exister entre la forme crystalline, la composition chimique et le sens de la polarization rotatoire. *Annales Chimie Phys.*, [online] 24, pp.442-459. Available at: https://cir.nii.ac.jp/crid/1571417124719940608 [Accessed 9 Mar. 2025].

Quadrelli, P., Mella, M. and Faita, G. (2023). Synthesis and Biological Activity of Potential Antiviral Compounds Through 1,3-Dipolar Cycloadditions; Part 2: Nitrones, Nitrile Oxides and Imines, and Other 1,3-Dipoles. *Arkivoc*, 2022(8), pp.257-294. doi:https://doi.org/10.24820/ark.5550190.p011.896.

So, S.M., Mui, L., Kim, H. and Chin, J. (2012). Understanding the Interplay of Weak Forces in [3,3]-Sigmatropic Rearrangement for Stereospecific Synthesis of Diamines. *Accounts of Chemical Research*, 45(8), pp.1345-1355. doi:https://doi.org/10.1021/ar2002842.

Yin, Y., Wang, J. and Li, J. (2024). A concise and scalable chemoenzymatic synthesis of prostaglandins. *Nature Communications* [online] 15(1), p.2523. doi:https://doi.org/10.1038/s41467-024-46960-y.