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The Mechanism of Inverse Electron Demand Diels-Alder Reaction and Its Applications

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Abstract. Organic synthesis depends heavily on the Diels-Alder cycloaddition reaction because it allows efficient ring system construction. The inverse-electron-demand Diels-Alder (IEDDA) reaction stands out as a variant because it creates complex molecular frameworks with high regio- and stereoselectivity through rapid assembly processes. The IEDDA reaction enables the rapid synthesis of polycyclic structures through the combination of electron-deficient dienes with electron-rich dienophiles which shortens the synthesis process compared to traditional methods. The review demonstrates the diverse applications of IEDDA reactions in total synthesis by showing its use in building natural products and pharmaceuticals as well as specialized organocatalysts. The reaction forms multiple carbon-carbon bonds during a single operation which makes it essential for constructing complex scaffolds found in alkaloids and terpenoids and other biologically significant compounds. The reaction's predictable selectivity decreases the requirement for complex protecting group manipulations which leads to improved synthetic efficiency. The IEDDA reaction enables the synthesis of sterically congested heterocycles and strained ring systems which traditional methods find difficult to access. The IEDDA reaction demonstrates its value in modern organic chemistry because it works for both intermolecular and intramolecular transformations. The IEDDA reaction remains essential for streamlining complex molecular architecture synthesis because it continues to advance as synthetic methodologies evolve thus maintaining its importance in drug discovery and materials science.

Keywords: IEDDA reaction, Polycyclic synthesis, Natural products, Heterocycles

1. Introduction

Natural products exhibit highly diverse and complex structures. Their stereochemical features, including geometric isomers (cis/trans isomerism around carbon-carbon double bonds) and optical isomers (different spatial arrangements around chiral centers) give rise to their biological specificity. This enables them to bind to specific biological receptors to elicit biological responses. However, naturally occurring molecules are present in limited quantities and cannot meet the increasing demand for medicinal applications. Therefore, total synthesis provides a renewable approach for accessing these compounds.

Most organic compounds found in nature are cyclic rather than acyclic, due to their increased thermodynamic stability. Hence, efficient cycling methods are essential for synthesizing these

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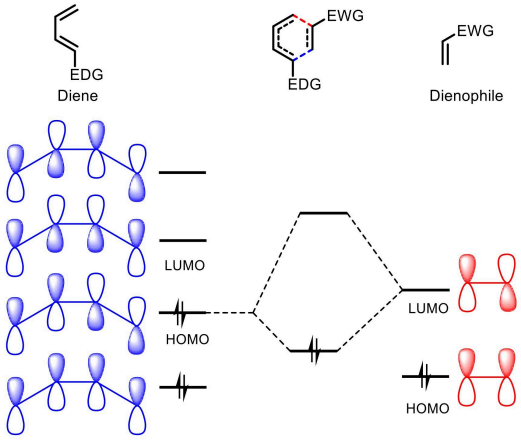
molecules. A proposed mechanism is the inverse electron-demand Diels-Alder (IEDDA) reaction, a concerted cycloaddition reaction involving an electron-deficient diene and an electron-rich dienophile. This contrasts with the normal Diels-Alder reaction, in which the conjugated diene is electron-rich, and the dienophile is electron-deficient. This reversal of electronic character expands the scope of accessible cyclic structures, particularly for heterocyclic compounds.

Cis-hydroindole scaffolds represent an important structure found in numerous natural alkaloids such as (+)-minovincine, vindolinine, and kopsinine. Their synthesis possesses significant challenges, especially in achieving high enantio- and diastereoselectivity while keeping a reasonable yield. Traditional approaches to ring construction often rely on chiral pool synthesis, stepwise functionalization, or Michael additions. In recent years, catalytic asymmetric reactions have given rise to alternative synthetic routes with higher efficiency. Among these, Zang et al. demonstrated the application of the IEDDA reaction in the synthesis of cis-hydroindole scaffolds. They make use of electron-deficient pyrones and electron-rich cyclic enamines, catalyzed by a chiral N, N′-dioxide/$Mg(OTf)_2$ complex. The product is then used as a building block for the formal total synthesis of (+)-minovincine. This approach validates the utility of IEDDAR reactions in complex natural product synthesis for constructing heterocyclic frameworks.

In addition, this review also discusses how the IEDDA reaction addresses other synthetic challenges, with particular emphasis on frontier-orbital considerations, reaction mechanism and the in situ generation of dienes for the construction of paeoveitol.

2. Molecular orbital theory

In the normal Diels-Alder reaction, molecular orbital (MO) theory shows that the conjugated diene serves as the highest occupied molecular orbital (HOMO) donor, while the dienophile acts as the lowest unoccupied molecular orbital (LUMO) acceptor. This orbital interaction is facilitated by attaching electron-donating groups (EDGs) to the diene and electron-withdrawing groups (EWGs) to the dieneophile [1].



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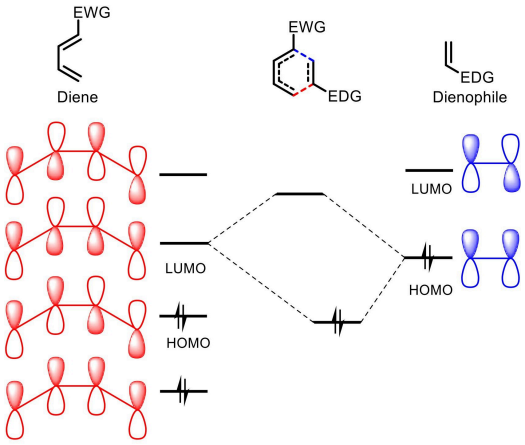


Figure 1. MO diagram of normal Diels-Alder reaction compared with IEDDA reaction [1]

As shown in figure 1, this inverse electron-demand variant exhibits the opposite electronic characteristics. EWGs such as carbonyls and nitriles are present on the diene [2], while EDGs such as amines and alkoxides are present on the dieneophile. This causes the HOMO and LUMO designations to be reversed compared to the normal Diels-Alder reaction. However, successful cycloaddition still requires good orbital overlap between the HOMO and LUMO with a small energy gap [3].

3. Synthesis of minovincine using IEDDA reaction

A major advantage of the IEDDA reaction compared to traditional ring-construction reactions such as Michael addition or aldo reactions is its reduced step count, combined with milder reaction conditions. The synthesis of cis-hydroindole scaffolds exemplifies the utility of IEDDA reaction.

Traditional synthesis of these structurally complex molecules with multiple stereocenters is challenging, as it typically requires asymmetric Michael addition reactions, which are stepwise and require multiple steps. In contrast, IEDDA reaction is a concerted reaction that can establish multiple stereocenters simultaneously.

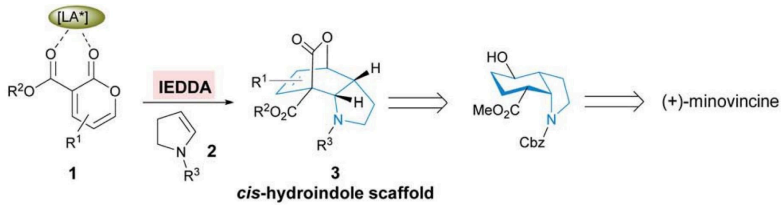


Figure 2. Synthesis route of a cis-hydroindole scaffold between 3-carbomethoxy-2-pyrone (diene) and cyclic enamines (dienophile) [1]

This reaction in figure 2 occurs between 3-carbomethoxy-2-pyrone (diene) and cyclic enamines (dienophile). The 2-pyrone is an electron-deficient diene because the electronegative oxygen atom creates electron withdrawal from the conjugated system. Cyclic enamines are electron rich dieneophiles due to nitrogen's ability to donate electron density through resonance with the carbon-carbon double bond. The reaction produces excellent yields and enantiomeric excess (ee), up to 99% and 95%, respectively, while establishing four contiguous stereocenters [4].

The chiral catalyst is crucial for enantiocontrol. The chiral N,N'-dioxide (L3-PiMe$_2$) ligand coordinates to Mg(OTf)$_2$ in a tetradentate manner, forming an octahedral complex through

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coordination of amide oxygens and two nitrogens to the Mg (II) centre [5]. The Mg(II) centre then coordinates to the carbonyl oxygen atoms of the ester group on 2-pyrone, which lowers the LUMO energy of the electron deficient 2-pyrone and reduces the HOMO-LUMO gap with the electron-rich cyclic enamine [4].

The bulky chiral ligand blocks approach to the re-face of the diene, making the si-face more accessible. This facial selectivity results in high enantioselectivity (up to 95% ee). The enamine approaches the 2-pyrone from the less sterically hindered si-face, and a (4+2) concerted cycloaddition occurs, forming two new C-C bonds and creating a six-membered ring [4].

The reaction proceeds through an endo transition state due to favorable secondary orbital interactions between the diene and dienophile substituents. These weak interactions stabilize the endo transition state despite greater steric hindrance compared to the exo alternative [6]. The chiral catalyst dissociates from the product, yielding a bicyclic cis-hydroindole scaffold with confirmed stereochemistry (3aR,4R,7S,7aS) [4].

The cis-hydroindole scaffold can be used for the formal total synthesis of Minovincine. The first step is the hydrogenation of the carbon-carbon double bond,catalysed by Crabtree's catalyst [7]. This produces compound 4, a fully saturated tricyclic intermediate. The next step involves the hydrolysis of the lactone ring using KOH, opening the lactone ring, followed by decarboxylation to remove CO2, which replaces the carboxylate group with a hydrogen [4], and methyl esterification using $TMSCH_2N_2$ [8]. This produces compound 5, an open-chained cis-hydroindole ester. The OH group requires protection to prevent unwanted side reactions. This is achieved by reacting it with TBSCl (tert-butyldimethylsilyl chloride) [9]. The next step is to remove the Cbz (benzyloxycarbonyl) protecting group.This is accomplished by hydrogenolysis under Pd catalysis [10]. Compound 7, a secondary amine, is produced. This is followed by a reaction with 1,3 diiodopropane. The nitrogen acts as a nucleophile, attacking the carbon bonded to iodine, forming compound 8 [11]. The tricyclic system is reconstructed using LDA (lithium diisopropylamide), a non-nucleophilic superbase. It deprotonates the hydrogen to the methyl ester, creating a carbanion [12], which attacks the carbon attached to iodine in an SN2 mechanism [11]. This closes the ring and displaces iodine. Finally, the TBS protecting group is removed with HCl, revealing the alcohol [13]. It is then oxidised to a ketone using pyridine-SO3 complex.This forms a known intermediate that can be converted to minovincine in three additional steps [4].

4. Synthesis of paeoveitol 75

Another example that demonstrates the significance of IEDDA reaction in total synthesis is the synthesis of Paeoveitol. Its structure presents challenges including a tetracyclic ring system and three contiguous stereocenters. There are foursynthesis routes reported by Zhao, Chen, Xie, and Bhat and Mehta. This discussion focuses on Bhat and Mehta's synthesis route as it is the shortest and most atom-economical approach. Unlike the synthesis of minovincine, the IEDDA reaction is used in the last step. This reaction involves two key components: paeoveitol-D (electron-rich dienophile) and an ortho-quinone methide (o-QM) precursor (electron-poor diene).

The dieneophile synthesis begins with 3-methylcyclohexenone, which undergoes ruthenium-catalysed dihydroxylation, forming a cis vicinal diol. This is achieved using $RuCl_3•3H_2O$ and $NaIO_4$ in aqueous ethanenitrile [14]. The diol is then reacted with pyruvic aldehyde dimethyl acetal under $TiCl_4$ and tributylamine. This forms a hydroxybenzofuran intermediate [1]. To complete the dienophile synthesis, the methyl group is oxidised to a ketone using $Mn(OAc)_3$ and TBHP, forming paeoveitol-D [15].

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The diene synthesis begins with 2-ethylhydroquinone. This molecule has two hydroxyl groups at the 1,4 positions with a methyl group at position 2. The first step introduces an acyl group through acetylation [16]. This forms a diacetate intermediate, which serves as protection for the hydroxyl groups. Friedel-Crafts rearrangement(Fries rearrangement) follows [17], forming a hydroxyaryl ketone. The ketone is reduced to a secondary alcohol using $NaBH_4$.

The last step converts the phenol and benzylic secondary alcohol to o-QM in situ. Lewis acid ($ZnCl_2$) facilitates o-QM formation through carbocation generation and subsequent rearrangement to form the electron-deficient quinone methide [18]. When added to the mixture, it accepts the lone pair of electrons on the benzylic alcohol oxygen, making the OH a better leaving group, generating a carbocation intermediate. Then the lone pair on the phenol oxygen ortho to the carbocation shifts into the aromatic ring, forming a C=O bond. Simultaneously, the carbocation forms a π bond with the benzene ring. This breaks the aromaticity of the compound, but its high conjugative property helps stabilise the compound. The oxygen being highly electronegative makes it electron deficient and ideal for IEDDA reaction [1].

In situ generation of o-QM is important because these species are highly reactive and undergo immediate cycloaddition with paeoveitol-D. The (4+2) cycloaddition proceeds via standard IEDDA reaction mechanism to form the six-membered ring system.

5. Conclusion

The IEDDA reaction has emerged as a cornerstone of modern natural-product synthesis, especially in asymmetric synthesis. It offers a rapid concerted route to multiple bonds, stereocentres and ring systems, often under ambient conditions and efficiently. Its ability to enforce the overlapping of HOMO dienophile and LUMO diene under mild conditions makes it perfectly suitable for synthesis of structurally dense and stereochemically rich scaffolds.

Two recent case studies demonstrate its power. Particularly notable is the synthesis of paeoveitol via Bhat and Mehta's biomimetic approach and the construction of cis-hydroindole scaffolds presented by Zhang, Ren, Zhou, Liu, and Feng. The synthesis of paeoveitol explores the full potential of the IEDDA reaction in terms of molecule design and atom economy. Through in situ production of short-lived ortho-quinone methides in the presence of the generated dienophile, a complex molecule with a tetracyclic ring system can be assembled with excellent stereoselectivity. The synthesis of cis-hydroindole scaffolds highlighted their innovative methodology, especially with the use of a chiral N,N'-dioxide/$Mg(OTf)_2$ complex to produce high levels of enantio- and diastereoselectivity. Furthermore, the practicality of the product is demonstrated through the formal total synthesis of (+)-minovincine, a complex natural product.

Some may debate the practicality of the IEDDA reaction as it heavily relies on good overlapping between HOMO and LUMO; This is true. However, this can be controlled by steric effects of chiral ligands or energy matching by adjusting the side chains attached. This remains superior to traditional ring closure reactions as it is a concerted reaction under mild conditions that produces 4 stereocentres.

As synthetic methodology continues to evolve, improvements in catalyst design and enantioselective variants, IEDDA reactions are likely to expand its applications even further in medicinal chemistry, natural product synthesis, and green synthetic methodologies.

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References

[1] Rashid, S., Lone, W. I., Rashid, A., & Bhat, B. A. (2024). Inverse electron demand Diels-Alder reaction in total synthesis of bioactive natural products. Tetrahedron Chem, 9, 1-27. 10.1016/j.tchem.2024.100066

[2] R. Contreras, J. Andrés, L. R. Domingo, R. Castillo, & P. Pérez (Eds.), Tetrahedron (2005). In Effect of electron-withdrawing substituents on the electrophilicity of carbonyl carbons. Elsevier. (2nd ed., Vol. 61, pp. 417-422). 10.1016/j.tet.2004.10.085.

[3] Beutick, S. E., Vermeeren, P., & Hamlin, T. A. (2022, September). The 1, 3-Dipolar Cycloaddition. Conception to Quantum Chemical Design, 1(17), 17. 10.1002/asia.202200553

[4] Zhang, F., Ren, B.-T., Zhou, Y., Liu, Y., & Feng, X. (2022). Enantioselective construction of cis-hydroindole scaffolds via an asymmetric inverse-electron- demand Diels–Alder reaction: application to the formal total synthesis of (+)-minovincine†. Chemical Science, 13(1), 5562-5567. 10.1039/d2sc01458k

[5] Liu, X., Lin, L., & Feng, X. (2014, February 4). Chiral N, N′-dioxide ligands: synthesis, coordination chemistry and asymmetric catalysis†. Organic Chemistry Frontiers, 1(1), 298-302. 10.1039/C3QO00059A

[6] Apeloig, Y., & Matzner, E. (1995, May 1). Evidence for the Dominant Role of Secondary Orbital Interactions in Determining the Stereochemistry of the Diels-Alder Reaction: The Case of Cyclopropene. Journal of the American Chemical Society, 117(19), 5375-5376. 10.1021/ja00124a027

[7] Verendel, J., Pàmies, O., Diéguez, M., & Andersson, P. (2013, December 10). Asymmetric Hydrogenation of Olefins Using Chiral Crabtree-type Catalysts: Scope and Limitations. Chemical Reviews, 114(4), 2130-2169. 10.1021/cr400037u

[8] Kuehnel, E., Laffan, D., Lloyd-Jones, G., Del Campo, T., Shepperson, I., & Slaughter, J. (2007). Mechanism of methyl esterification of carboxylic acids by trimethylsilyldiazomethane. Angewandte Chemie International Edition, 46(37), 7075-7078. 10.1002/anie.200702131

[9] Manville, N., Alite, H., Haeffner, F., Hoveyda, A., & Snapper, M. (2013, July 28). Enantioselective Silyl Protection of Alcohols Promoted by a Combination of Chiral and Achiral Lewis Basic Catalysts. Nature Chemistry, 1(5), 768–774. 10.1038/nchem.1708

[10] Humphries, K., Möbus, K., Dunn, T., & Chen, B. (2005). Improved Catalyst for the Removal of Carbobenzyloxy Protective Groups. In Catalysis of Organic Reactions (1st ed., p. 8). CRCPress. https: //www.taylorfrancis.com/chapters/edit/10.1201/9781420028034-70/improved-catalyst-removal-carbobenzyloxy-protective-groups-kimberly-humphries-konrad-m%C3%B6bus-tracy-dunn-baoshu-chen?utm_source

[11] Hamlin, T., Swart, M., & Bickelhaupt, F. (2018, june 5). Nucleophilic Substitution (SN2): Dependence on Nucleophile, Leaving Group, Central Atom, Substituents, and Solvent. ChemPhysChem, 19(11), 1315-1330. 10.1002/cphc.201701363

[12] Sun, X., Kenkre, S., Remenar, J., Gilchrist, J., & Collum, D. (1997, may 21). Mechanism of Lithium Diisopropylamide-Mediated Ester Deprotonation: The Role of Disolvated Monomers. Journal of the American Chemical Society, 119(20), 4765-4766. 10.1021/ja970406k

[13] Lakshman, M., Tine, F., Khandaker, T., Basava, V., Agyemang, N., Benavidez, M., Gaši, M., Guerrera, L., & Zajc, B. (2016, November 17). KHF2, a mild and selective desilylating agent for phenol t-butyldimethylsilyl (TBDMS) ethers. Synlett, 28(3), 381-385. 10.1055/s-0036-1588350

[14] Shing, T., Tam, E., Tai, V., Chung, I., & Jiang, Q. (1996, January). Ruthenium-Catalyzed cis-Dihydroxylation of Alkenes: Scope and Limitations. Chemistry A European Journal, 2(1), 50-57. 10.1002/chem.19960020111

[15] Snider, B. (2009, December 26). Mechanisms of Mn(OAc)3-based oxidative free-radical additions and cyclizations. Tetrahedron, 65(52), 10738-10744. 10.1016/j.tet.2009.09.025

[16] Raja, E., DeSchepper, D., Lill, S., & Klumpp, D. (2013, july 6). Friedel-Crafts Acylation with Amides. J Org Chem., 77(13), 5788-5793. 10.1021/jo300922p

[17] Martin, R. (2009, February 12). USES OF THE FRIES REARRANGEMENT FOR THE PREPARATION OF HYDROXYARYLKETONES. A REVIEW. Organic Preparations and Procedures International, 24(4), 369-435. 10.1080/00304949209356226

[18] Caruana, L., Fochi, M., & Bernardi, L. (2015, june 25). The Emergence of Quinone Methides in Asymmetric Organocatalysis. Molecules, 20(7), 11733-11764. 10.3390/molecules200711733