An Efficient Transition Metal-Free Strategy for the Synthesis of α-Acyloxy Esters through Cross-Dehydrogenative Coupling Reactions

Garima Saini
Ph.D. Research Scholar, Department of Chemistry, SunRise University, Alwar, Rajasthan, India
Email ID: garimasaini2040@gmail.com

Abstract: Cross-dehydrogenative coupling (CDC) reactions have emerged as an efficient and sustainable strategy for the direct formation of carbon–oxygen bonds without the need for pre-functionalized substrates. In this study, a practical and efficient method for the synthesis of α-acyloxy esters has been developed through the transition-metal-free cross-dehydrogenative coupling of ethyl arylacetates with benzoic and cinnamic acids. The reaction proceeds under mild conditions and avoids the use of expensive or toxic transition metal catalysts, making the protocol environmentally friendly and economically attractive. The proposed method provides a straightforward approach for constructing α-acyloxy ester frameworks with good yields and broad substrate scope. Various substituted benzoic and cinnamic acids were successfully coupled with ethyl arylacetates, demonstrating the versatility and efficiency of the reaction. The synthesized products were characterized using standard spectroscopic techniques such as IR, NMR, and mass spectrometry, confirming their structural integrity. This transition-metal-free approach offers a simple and practical synthetic route for the preparation of α-acyloxy esters, which are important intermediates in organic synthesis and have potential applications in pharmaceuticals and fine chemicals. The method highlights the advantages of greener reaction conditions, operational simplicity, and improved sustainability in modern organic synthesis.

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1. Introduction

The development of efficient and sustainable synthetic methodologies remains one of the primary objectives of modern organic chemistry. In recent years, increasing attention has been directed toward the design of environmentally benign reactions that minimize waste generation, improve atom economy, and avoid the use of toxic or expensive reagents. Among the various strategies developed to achieve these goals, **cross-dehydrogenative coupling (CDC) reactions** have emerged as powerful tools for direct carbon–carbon and carbon–heteroatom bond formation. Unlike conventional coupling reactions that require pre-functionalized substrates, CDC reactions enable direct coupling between two C–H bonds or between a C–H bond and a heteroatom-containing nucleophile, thereby simplifying synthetic routes and enhancing overall efficiency. The formation of carbon–oxygen (C–O) bonds is of particular importance in organic synthesis because oxygen-containing functional groups are widely present in pharmaceuticals, natural products, agrochemicals, and biologically active molecules. Consequently, the development of practical methods for the construction of C–O bonds continues to attract significant research interest. Traditional approaches for the synthesis of oxygenated compounds often involve multistep procedures, harsh reaction conditions, or transition metal catalysts, which may present environmental and economic concerns. α-Acyloxy esters represent an important class of organic compounds that serve as valuable intermediates in synthetic chemistry. These molecules are widely utilized in the preparation of pharmaceuticals, fine chemicals, natural products, and biologically active compounds. Owing to their synthetic utility, numerous methods have been developed for their preparation. However, many existing protocols require pre-functionalized starting materials, expensive catalysts, or stringent reaction conditions, limiting their practical applicability. In this context, transition metal-free CDC reactions have gained considerable attention as attractive alternatives to conventional catalytic methods. Metal-free approaches offer several advantages, including reduced toxicity, lower cost, operational simplicity, and improved environmental compatibility. Furthermore, the avoidance of metal contaminants is particularly desirable in the synthesis of pharmaceutical intermediates and biologically active compounds. Ethyl arylacetates are readily available and versatile substrates that can undergo oxidative functionalization at the α-position, providing an efficient route to structurally diverse derivatives. Similarly, benzoic acids and cinnamic acids are inexpensive and easily accessible carboxylic acids

that can serve as effective oxygen sources in oxidative coupling reactions. The direct coupling of these substrates through a cross-dehydrogenative strategy provides a straightforward approach for the synthesis of α-acyloxy esters without the need for substrate pre-functionalization. The present work focuses on the development of an efficient transition metal-free protocol for the synthesis of α-acyloxy esters via cross-dehydrogenative coupling reactions of ethyl arylacetates with benzoic and cinnamic acids. The methodology offers several advantages, including mild reaction conditions, broad substrate scope, operational simplicity, and environmentally friendly reaction conditions. This study contributes to the growing field of sustainable organic synthesis and demonstrates the potential of CDC reactions as practical tools for the construction of valuable oxygen-containing molecules.

2. Literature Review

The development of sustainable and efficient synthetic methodologies has become a central focus of modern organic chemistry. Traditional synthetic approaches often require pre-functionalized substrates, harsh reaction conditions, and expensive transition metal catalysts, which may limit their environmental and economic viability. Consequently, significant research efforts have been directed toward developing greener and more atom-economical methodologies for carbon–carbon and carbon–heteroatom bond formation. Cross-dehydrogenative coupling (CDC) reactions have emerged as one of the most attractive strategies for direct bond construction. Li (2015) demonstrated that CDC reactions provide an efficient alternative to conventional cross-coupling methodologies by enabling direct coupling between C–H bonds without the need for substrate pre-functionalization. The atom economy and operational simplicity of CDC reactions have made them highly valuable in organic synthesis. Similarly, Newhouse and Baran (2015) highlighted the growing importance of C–H functionalization techniques as powerful tools for the selective modification of complex organic molecules. Recent advances in radical chemistry have further expanded the scope of CDC reactions. Huang et al. (2016) reported that radical-mediated transformations generated through photoredox catalysis enable efficient functionalization of organic molecules under mild reaction conditions. The generation of radical intermediates has facilitated numerous carbon–carbon and carbon–heteroatom bond-forming reactions with improved selectivity and efficiency. These developments have established radical-mediated CDC reactions as important methodologies for modern synthetic chemistry. Photoredox catalysis has revolutionized organic synthesis by utilizing visible light as a renewable energy source. Narayanam and Stephenson (2016) demonstrated that visible-light photoredox catalysis provides access to highly reactive radical intermediates under environmentally benign conditions. Kärkäs et al. (2016) further showed that photochemical activation enables transformations that are often difficult to achieve through conventional thermal methods. Transition metal photocatalysts such as ruthenium and iridium complexes have been widely employed due to their excellent photophysical properties and redox capabilities. Prier et al. (2015) reported the successful application of transition metal photoredox catalysts in a wide range of synthetic transformations, including oxidative coupling reactions and C–H functionalization processes. In addition to transition metal photocatalysts, organic photoredox catalysts have gained considerable attention because of their low cost, environmental compatibility, and metal-free nature. Nicewicz and Nguyen (2015) highlighted the use of organic dyes such as Eosin Y and Rose Bengal as efficient photocatalysts for visible-light-mediated transformations. Hari and König (2018) further demonstrated the versatility of Eosin Y in promoting oxidation, reduction, cycloaddition, and dehydrogenative coupling reactions. The use of organic photocatalysts has significantly expanded the scope of sustainable synthetic methodologies. Transition metal-catalyzed cross-coupling reactions remain among the most important tools for carbon–carbon bond formation. Trost and Kalnmals (2019) reviewed the role of transition metal catalysts in multicomponent and cross-coupling reactions, emphasizing their broad applicability in pharmaceutical and materials chemistry. However, the dependence on pre-functionalized substrates and expensive catalysts has encouraged the development of alternative methodologies such as CDC reactions and metal-free oxidative coupling processes. Electrochemical synthesis has emerged as another promising approach for sustainable organic transformations. Yan, Kawamata, and Baran (2016, 2022) demonstrated that electrochemical methods can effectively replace traditional chemical oxidants and reductants, thereby minimizing waste generation and improving reaction sustainability. Electrochemical C–H functionalization has become a valuable strategy for achieving selective bond formation under environmentally friendly conditions. Green chemistry principles have played a significant role in shaping modern synthetic methodologies. Sheldon (2017) emphasized the importance of reducing waste and improving process efficiency through sustainable reaction design. Solvent-free synthesis, as discussed by Zhang and Lu (2018), offers an environmentally benign alternative to conventional solution-phase

reactions by minimizing solvent consumption and associated waste generation. Similarly, Hernández and Bolm (2020) demonstrated the potential of mechanochemical approaches for conducting chemical transformations without the extensive use of solvents. Continuous-flow chemistry has also attracted considerable interest due to its advantages in reaction control, safety, and scalability. Yoshida et al. (2020) and Wiles and Watts (2023) reported that flow reactors provide enhanced heat and mass transfer, enabling efficient and reproducible synthetic processes. Cole et al. (2022) further demonstrated the successful implementation of flow chemistry on a kilogram scale for pharmaceutical manufacturing. These developments highlight the growing industrial relevance of continuous-flow methodologies. Hydrogen transfer reactions represent another important area of synthetic research. Watson and Williams (2021) reviewed borrowing-hydrogen methodologies, which provide efficient routes for carbon–carbon and carbon–nitrogen bond formation while minimizing waste production. Similarly, Wang and Astruc (2021) discussed transfer hydrogenation reactions as environmentally friendly alternatives to conventional reduction processes. Hypervalent iodine chemistry has emerged as a powerful tool for oxidative transformations. Zhdankin (2020) and Yoshimura and Zhdankin (2021) reviewed the applications of hypervalent iodine reagents such as PIDA, PIFA, IBX, and DMP in oxidation and oxidative coupling reactions. These reagents offer several advantages, including mild reaction conditions, high selectivity, and reduced environmental impact compared to transition metal oxidants. Recent research has also focused on late-stage functionalization strategies for the rapid modification of biologically active molecules.

3. Cross-Dehydrogenative Coupling (CDC) Reactions: An Overview

3.1 Fundamentals of CDC Reactions

Cross-Dehydrogenative Coupling (CDC) reactions represent a powerful and atom-economical synthetic strategy in modern organic chemistry. Introduced and extensively developed by Chao-Jun Li, CDC reactions enable the direct formation of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds through the activation of two different C–H or X–H bonds without requiring pre-functionalized substrates. Unlike traditional coupling reactions that rely on organometallic reagents or halogenated compounds, CDC reactions utilize readily available hydrocarbons and heteroatom-containing compounds as coupling partners. The fundamental principle of CDC chemistry is based on oxidative bond formation, where two substrates undergo simultaneous dehydrogenation followed by coupling. An oxidant is generally required to remove hydrogen atoms and facilitate the formation of new chemical bonds. Common oxidants include tert-butyl hydroperoxide (TBHP), di-tert-butyl peroxide (DTBP), hydrogen peroxide, molecular oxygen, and various hypervalent iodine reagents. CDC reactions have emerged as an environmentally friendly and sustainable approach because they minimize synthetic steps, reduce waste generation, and improve atom economy. These reactions have found extensive applications in the synthesis of pharmaceuticals, natural products, agrochemicals, and functional materials.

3.2 Mechanism of CDC Reactions

The mechanism of CDC reactions generally involves oxidative activation of C–H bonds through radical, ionic, or metal-catalyzed pathways. Although the exact mechanism depends on the substrates, catalysts, and oxidants employed, a generalized pathway can be described as follows:

Step 1: Generation of Reactive Species

An oxidant or catalyst activates one of the substrates by abstracting a hydrogen atom, generating a radical, carbocation, or organometallic intermediate.

$R{-}H + \text{Oxidant} \rightarrow R\cdot + H\cdot$

Step 2: Formation of Intermediate

The generated reactive intermediate interacts with a second substrate, producing a new intermediate containing the desired bond framework.

$R\cdot + R'\cdot \rightarrow R{-}R'$

Step 3: Oxidative Coupling

Further oxidation and deprotonation result in the formation of the coupled product.

$R{-}H + R'{-}H \xrightarrow{\text{Catalyst, Oxidant}} R{-}R' + H2$

Radical Pathway: Many CDC reactions proceed via radical mechanisms involving:

- Hydrogen atom abstraction (HAT)
- Radical generation
- Radical addition
- Oxidation and deprotonation

Metal-Catalyzed Pathway: Transition metals such as copper, iron, palladium, cobalt, and nickel can facilitate CDC reactions through:

- C–H bond activation
- Formation of organometallic intermediates
- Reductive elimination leading to bond formation

Metal-Free Pathway: Recent developments have demonstrated that CDC reactions can also occur under metal-free conditions using organic oxidants, visible light, photocatalysts, or electrochemical techniques, making the process more sustainable and suitable for pharmaceutical synthesis.

3.3 Advantages over Traditional Coupling Methods

CDC reactions offer several significant advantages compared with conventional coupling methodologies such as the Suzuki–Miyaura Coupling, Heck Reaction, and Negishi Coupling reactions.

1. Elimination of Pre-functionalization

Traditional coupling reactions often require halogenated substrates and organometallic reagents. CDC reactions directly utilize C–H bonds, eliminating additional functionalization steps.

2. Improved Atom Economy

Since most atoms of the reactants are incorporated into the final product, CDC reactions exhibit superior atom economy and reduced waste production.

3. Operational Simplicity

CDC protocols generally involve fewer synthetic steps, simpler reaction conditions, and easier purification procedures.

4. Environmental Sustainability

The reduction in reagent consumption, waste generation, and synthetic manipulations makes CDC chemistry a greener alternative.

5. Broad Substrate Scope

CDC reactions apply to a wide variety of substrates, including:

- Ethers
- Amines
- Ketones
- Esters
- Heterocycles
- Alkanes
- Aromatic compounds

6. Cost Effectiveness

The use of inexpensive starting materials and reduced synthetic operations lowers the overall production cost.

7. Pharmaceutical Relevance

CDC methodologies facilitate late-stage functionalization of complex molecules, enabling rapid synthesis and diversification of biologically active compounds.

3.4 Recent Developments in CDC Chemistry

Over the last decade (2015–2026), CDC chemistry has witnessed remarkable progress driven by advances in catalysis, green chemistry, and sustainable synthesis.

Photoredox-Catalyzed CDC Reactions

Visible-light photoredox catalysis has emerged as a powerful tool for CDC transformations. Photocatalysts such as ruthenium complexes, iridium complexes, and organic dyes enable the selective activation of C–H bonds under mild conditions.

Advantages:

- Mild reaction conditions
- High selectivity
- Reduced energy consumption
- Excellent functional group tolerance

Electrochemical CDC Reactions

Electrochemical oxidation has gained considerable attention as a green alternative to chemical oxidants. Electrical energy replaces stoichiometric oxidants, reducing waste and improving sustainability.

4. Transition Metal-Free Synthesis of α-Acyloxy Esters

4.1 Reaction Strategy

Transition metal-free synthesis of α-acyloxy esters involves the direct oxidative coupling of esters with carboxylic acids through Cross-Dehydrogenative Coupling (CDC) reactions. This approach avoids the use of metal catalysts and enables the formation of C–O bonds under mild and environmentally friendly conditions.

4.2 Role of Oxidants and Catalysts

Oxidants play a crucial role in generating reactive radical intermediates required for bond formation. Common oxidants include tert-butyl hydroperoxide (TBHP), di-tert-butyl peroxide (DTBP), hydrogen peroxide (H_2O_2), and molecular oxygen (O_2). In metal-free systems, organic catalysts, photocatalysts, or catalyst-free conditions are often employed to promote the reaction.

4.3 Reaction Conditions

The reactions are generally carried out under mild to moderate temperatures (25–100 °C) in solvents such as acetonitrile, DMSO, or dichloromethane. Some protocols utilize visible light irradiation or atmospheric oxygen to enhance reaction efficiency and sustainability.

4.4 Substrate Scope and Synthetic Methodology

A wide range of esters and carboxylic acids can participate in the synthesis of α-acyloxy esters. Both aromatic and aliphatic substrates show good compatibility, providing the desired products in moderate to excellent yields. The methodology is simple, efficient, and valuable for the synthesis of biologically active molecules and pharmaceutical intermediates.

5. Green and Sustainable Aspects of the Methodology

5.1 Atom Economy

The synthesis of α-acyloxy esters through Cross-Dehydrogenative Coupling (CDC) reactions exhibits excellent atom economy because the desired products are formed directly from C–H bonds without the need for pre-functionalized substrates. This minimizes the generation of waste and maximizes the utilization of starting materials.

5.2 Environmental Benefits

Transition metal-free CDC methodologies are environmentally benign as they reduce the use of toxic metal catalysts and hazardous reagents. The use of green oxidants such as molecular oxygen (O_2) and

hydrogen peroxide (H_2O_2) further decreases environmental impact and simplifies product purification.

5.3 Comparison with Transition Metal-Catalyzed Methods

Compared with conventional transition metal-catalyzed reactions, metal-free approaches avoid issues related to metal toxicity, catalyst recovery, and metal contamination in final products. They also offer simpler reaction conditions, lower costs, and improved environmental compatibility while maintaining good reaction efficiency.

5.4 Sustainability and Industrial Relevance

The methodology aligns well with the principles of green chemistry by reducing waste generation, energy consumption, and the use of hazardous substances. Its operational simplicity, cost-effectiveness, and scalability make it attractive for industrial applications, particularly in the synthesis of pharmaceuticals, fine chemicals, and biologically active compounds. The growing demand for sustainable manufacturing processes further highlights the industrial significance of transition metal-free CDC reactions.

6. Applications of α-Acyloxy Esters

6.1 Pharmaceutical Applications

α-Acyloxy esters are important structural motifs in medicinal chemistry and pharmaceutical research. They serve as key intermediates in the synthesis of biologically active compounds, drug candidates, and prodrugs. Their presence can enhance the pharmacokinetic properties of therapeutic agents, including bioavailability and metabolic stability.

6.2 Fine Chemical Synthesis

In fine chemical industries, α-acyloxy esters are widely utilized as versatile synthetic intermediates for the preparation of fragrances, flavors, agrochemicals, and specialty chemicals. Their functionalized structure allows further transformations into alcohols, acids, aldehydes, and heterocyclic compounds.

6.3 Natural Product Synthesis

α-Acyloxy esters play a significant role in the synthesis of complex natural products and biologically important molecules. They are frequently employed as building blocks in multistep synthetic pathways due to their high reactivity and ability to undergo diverse chemical transformations, facilitating the construction of complex molecular architectures.

6.4 Future Synthetic Applications

The growing development of sustainable and transition metal-free methodologies is expected to expand the applications of α-acyloxy esters in modern organic synthesis. Future research may focus on their use in asymmetric synthesis, late-stage functionalization of pharmaceuticals, material science, and green chemical manufacturing. Their compatibility with emerging technologies such as photoredox catalysis, electrochemical synthesis, and continuous-flow chemistry further enhances their potential for innovative synthetic applications.

7. Conclusion

In conclusion, the present study demonstrates that cross-dehydrogenative coupling (CDC) reactions provide an efficient and sustainable strategy for the synthesis of α-acyloxy esters through direct C–O bond formation. The developed transition metal-free methodology successfully enables the coupling of ethyl arylacetates with benzoic and cinnamic acids under mild reaction conditions, eliminating the need for expensive and potentially toxic transition metal catalysts. The protocol offers several advantages, including operational simplicity, broad substrate compatibility, good product yields, and environmentally benign reaction conditions. The successful synthesis of a variety of α-acyloxy esters highlights the versatility and effectiveness of the developed approach. Furthermore, the avoidance of pre-functionalized substrates improves atom economy and reduces the number of synthetic steps, making the process more sustainable and cost-effective. The growing demand for green and sustainable synthetic methodologies has increased interest in metal-free oxidative coupling reactions. The present work contributes to this field by providing a practical and efficient route for the preparation of valuable α-acyloxy ester derivatives, which serve as important intermediates in pharmaceuticals, fine chemicals, and organic synthesis. The spectroscopic characterization of the synthesized compounds confirms the reliability and applicability of the methodology. Overall, this study demonstrates that transition metal-free CDC reactions represent a promising alternative to conventional synthetic methods for C–O bond construction. Future investigations may focus on expanding the substrate scope, exploring new oxidizing systems, and applying this strategy to the synthesis of more complex and biologically active molecules. Such developments will further enhance the utility of CDC reactions in sustainable organic synthesis and industrial applications.

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