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Review Article

Green and sustainable strategies in Pd-catalysed heterocycle synthesis

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ABSTRACT
Palladium-catalyzed reactions have become a cornerstone of modern organic synthesis, particularly in the formation of heterocyclic frameworks that are widely important in chemical and pharmaceutical research. Despite its effectiveness, the high cost of palladium has prompted continuous efforts toward its recovery and reuse to maintain economic practicality. Simultaneously, the growing demand for sustainable and environmentally responsible synthetic methods has encouraged the development of greener approaches in catalysis. In this context, palladium-catalyzed strategies designed with sustainability in mind have attracted significant attention in recent years. This review brings together a variety of such methodologies that incorporate green chemistry principles. Emphasis is placed on approaches such as the use of environmentally benign or solvent-free reaction media, recyclable palladium catalysts, tandem or one-pot processes, and the use of air or other mild oxidants. These strategies collectively aim to minimize waste, enhance atom efficiency, reduce operational costs, and improve the overall safety profile of synthetic procedures. By presenting these advancements, the review underscores the potential of sustainable palladium-catalyzed methods in heterocycle synthesis and provides insight into selecting efficient and eco-friendly protocols for both research and industrial applications. It is intended to serve as a concise and useful reference for ongoing efforts toward greener synthetic practices.

1. Introduction

Over the past few decades, palladium has become one of the most widely used catalysts in organic synthesis, particularly in the formation of heterocyclic rings [1-7]. Transition-metal catalysis, especially palladium-catalyzed reactions, has proven highly efficient for constructing complex molecular frameworks with excellent selectivity and yield.

Despite its advantages, the use of palladium presents several challenges. Palladium is an expensive and limited metal resource, making the recovery and recycling of the catalyst essential for practical and industrial applications. The economic viability of palladium-catalyzed processes therefore depends heavily on efficient catalyst reuse and waste minimization.

To address these concerns, modern synthetic chemistry increasingly focuses on sustainable and green approaches. Researchers are developing eco-friendly synthetic methodologies that reduce hazardous waste, improve atom economy, and minimize environmental impact. Green chemistry principles encourage the use of recyclable catalysts, safer solvents, and energy-efficient reaction conditions.

As a result, there is growing interest in palladium-catalyzed green synthesis, particularly for heterocycle formation. Current research aims to enhance the sustainability of these reactions while maintaining high efficiency and product quality. These advancements contribute to the development of a more environmentally responsible and economically sustainable chemical industry.

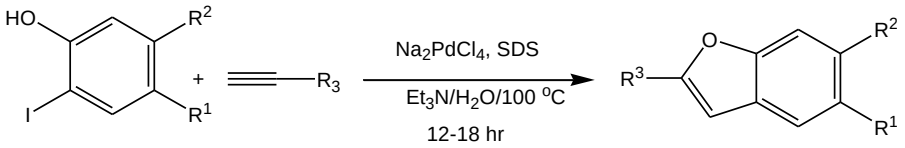
Sustainable strategies in organic synthesis increasingly emphasize the development of palladium-catalyzed green synthetic methodologies that combine high efficiency with minimal environmental impact. These approaches involve the use of solvent-free reaction conditions or greener solvents such as water, ethanol, and ionic liquids to reduce the use of hazardous chemicals. Considerable attention is also given to the recyclability and reuse of palladium catalysts, which helps lower operational costs and improves the economic viability of the process. One-pot tandem reaction strategies are widely employed to minimize reaction steps, reduce purification procedures, and decrease waste generation. In many modern protocols, air or molecular oxygen is utilized as an environmentally friendly oxidant instead of toxic oxidizing agents. These sustainable methods aim to reduce waste and unwanted by-products while enhancing atom economy and reaction efficiency. Overall, such strategies provide cost-effective, safer, and environmentally benign alternatives for modern organic synthesis.

Heterocyclic compounds play a vital role in synthetic organic chemistry and have extensive applications in the pharmaceutical industry due to their diverse chemical and

biological properties [8-34]. The reactivity and biological activity of heterocycles are strongly influenced by ring size. Five-membered heterocyclic rings are generally more reactive and often exhibit higher biological activity, making them common structural motifs in natural products and therapeutic agents. In contrast, six-membered heterocycles are comparatively more stable and are widely used as important pharmaceutical scaffolds. Larger or smaller heterocyclic rings are less common because of ring strain and instability, which usually result in lower reactivity and biological activity. A few reviews have covered sustainable methods of heterocyclic synthesis [35-36]. However, there is always the scope of different perspectives and coverage on this field.

2. Discussion

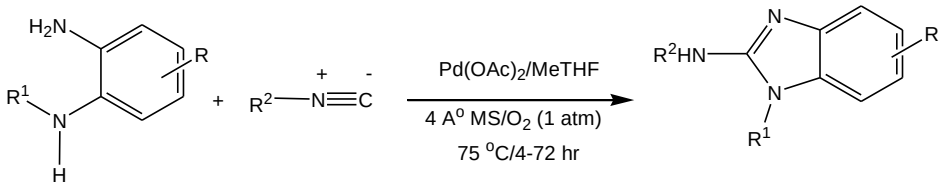
In 2010, Ranu, Saha, and co-workers reported a nano-palladium-catalyzed one-pot synthesis of functionalized benzo[b]furans through Sonogashira coupling of 2-iodophenols with aryl acetylenes, followed by a 5-endo-dig cyclization process [37]. The protocol utilized palladium nanoparticles generated in situ in water under aerobic conditions, eliminating the need for any additional ligand or additive.



R^1= H, CO_2Et
R^2= H, Ph
R^3 = C_6H_5, 4 -ClC_6H_4, 4-FC_6H_4, 4-MeO-C_6H_4, 3-BrC_6H_4, 1-naphthyl, 4-Me-C_6H_4

Scheme 1: Nanopalladium catalysed synthesis of benzo[*b*]furans

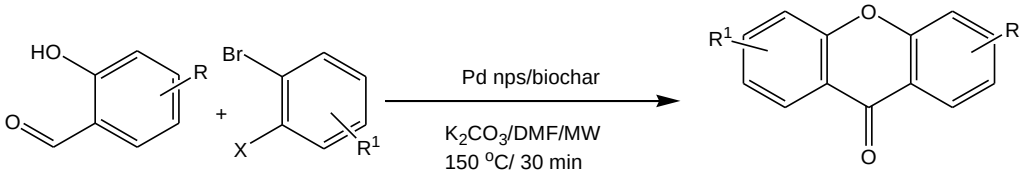
Maes, Ruud V. A. Orru, Erik Ruijter and their co-workers reported an aerobic oxidative coupling reaction between diamines and isocyanides, providing access to guanidine-derived heterocycles [38]. The transformation was carried out using palladium acetate as the catalyst under ligand- and additive-free conditions in the renewable solvent MeTHF. The use of molecular oxygen as the only oxidant further improved the green and sustainable nature of the protocol.



R= H, 4-Me, 4-Cl, 4-Br, 4-CO_2Me, 4-CN, 4-CF_3, 4-NO_2, 4-OMe, 4-F
R^1= Me, 4-methoxybenzyl
R^2 = ^{t}Bu, ^{i}Pr, -$(CH_2)_4$Me, cyclohexyl

Scheme 2: Oxidative coupling of *o*-phenylenediamines and isocyanides catalysed by palladium

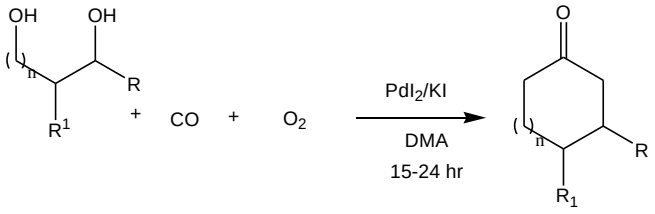
Daniel C. Gerbino and co-workers reported the development of a heterogeneous palladium catalyst consisting of palladium nanoparticles immobilized on green biochar [39]. This catalyst was successfully utilized for the synthesis of xanthones via the reaction of salicylaldehydes with dihalobenzenes. The protocol offers an eco-friendly and sustainable approach, operating under ligand-free conditions and using microwave irradiation to facilitate rapid reaction completion within a short period of time.



X= Br, Cl
R= H, 1-naphthyl,4-OH, 5-Cl, 4-NEt_2, 5-NO_2, 3-Me, 5-Br, 5-Me, 3-OMe, 4-OMe
R^1 = H, 4,5-Me_2, 5-NO_2, 4,5-$(OMe)_2$, 5-Me, 5-Br

Scheme 3: Synthesis of xanthones catalysed by Palladium nanoparticles supported on Biochar

Bruno Gabriele and co-workers successfully developed a method for the synthesis of [1,3]dioxolan-2-ones and [1,3]dioxan-2-ones via the direct oxidative carbonylation of 1,2- and 1,3-diols, respectively [40]. The reaction employed palladium iodide as the catalyst along with potassium iodide, offering an efficient approach for the preparation of cyclic carbonate derivatives.



R = H, Et, Ph, Me
R' = H, Me
n= 0,1

Scheme 4: Palladium catalysed synthesis of [1,3]dioxolan-2-ones and [1,3]dioxan-2-ones

3. Conclusions

Heterocyclic synthesis constitutes a fundamental aspect of organic chemistry, playing a crucial role in both academic research and the pharmaceutical industry. In the present era, where environmental concerns and pollution have become major global challenges, the development of sustainable and eco-friendly synthetic methodologies is of paramount importance. Consequently, there is a growing need to design greener approaches for molecular synthesis, particularly in the field of pharmaceuticals and drug development.

This review aims to highlight recent advances in sustainable palladium-catalyzed protocols for heterocyclic synthesis. We anticipate that this compilation will provide a useful reference for synthetic chemists and researchers seeking greener strategies for the preparation of heterocyclic drug molecules. Above all, we hope that this work will make a modest yet meaningful contribution toward the promotion of a more sustainable and environmentally conscious chemical future.

Authors' contributions

The author reviewed and approved the final version of the manuscript for publication.

Conflicts of interest

The author declares no conflict of interest.

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Data availability

No new data were created.

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