Recent advances in the reactions of C8-functionalization of substituted tetrahydroquinolines under ruthenium catalyst

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Abstract.
Scientists are increasingly using ruthenium catalysts to selectively add functional groups to the C8 carbon of tetrahydroquinolines that are versatile class of heterocyclic compounds with diverse applications in chemistry. This article reviews recent advances in ruthenium-catalyzed C8-functionalization reactions of tetrahydroquinolines. We explore different approaches to activate the C8 carbon of tetrahydroquinolines in a controlled way. These approaches include directed ortho-metalation, reactions that use coordination with a metal catalyst, and C-H activation methods. This review showcases the versatility of C8 functionalization, enabling the introduction of a wide range of functional groups including carbon chains (C-C bonds), heteroatoms (C-heteroatom bonds), and even the formation of new rings (cyclization reactions). In this article discusses Ru-catalyzed hydroxylation and acyloxylation reactions of tetrahydroquinolines. Beyond the functionalization itself, the article explores how these C8-modified THQs can be valuable tools for synthesizing complex natural products and potential new drugs. We then deep into the remaining challenges and promising future directions in this area of ruthenium-mediated C8-functionalization, which is experiencing rapid progress.

Keywords:
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C-H activation
Introduction.

Tetrahydroquinolines (THQs) are a fascinating class of molecules with remarkable applications in medicinal chemistry [1]. Precise functionalization of the C8 position on THQs has become increasingly crucial for drug discovery [2]. C8-functionalization of tetrahydroquinolines plays a vital role in synthesizing complex molecules with therapeutic potential [3]. However, achieving selective modification at this specific position has been challenging.

Due to their unique ring structure, tetrahydroquinolines are a valuable class of heterocyclic compounds with a wide range of applications in drug discovery [4]. (Scheme 1)

![Scheme 1](image)

Examples of natural products containing a quinoline core (I - topotecan; II - irinotecan).

Directed C-H bond activation has emerged as a streamlined and effective strategy compared to traditional methods for producing a range of functionalized tetrahydroquinolines [5].
Motivated by the development of sustainable organic synthesis methods [6], this work examines Ru (II)-catalyzed reactions for introducing acyloxy and hydroxymethyl functionalities at the C-8 position of tetrahydroquinolines. These reactions pave the way for the synthesis of a variety of C8-substituted quinolines. It's important to highlight that these Ru (II)-catalyzed reactions proceed under moderate conditions [7], a significant advantage. This, coupled with the recent progress in C-H bond activation catalysis, positions these reactions as highly convenient methods for introducing pharmacologically active groups onto quinoline molecules.

Scientists have made significant strides in C-H functionalization of quinolines at the C-8 position [8]. This is reflected in the successful introduction of a diverse range of functional groups, including aryl, alkenyl, alkyl, acyl, amido, and alkynyl groups.

**Ru (II)-catalyzed C8-acyloxylation of substituted tetrahydroquinolines with carboxylic acids.**

In recent years, researchers carried out reactions of direct acyloxylation of indolines using carboxylic acids due to their easy availability and versatility [9]. Encouragingly, this reaction can also be applied to substituted tetrahydroquinolines, similar to indolines. This reaction often proceeds under moderate temperatures and with readily available starting materials, leading to improved practicality and efficiency. One of the key benefits of direct C-H acylation with RCOOH is its exceptional atom economy. The reaction was optimized using a specific catalyst system: [Ru (p-cymene) Cl₂]₂ combined with AgSbF₆. Additionally, Ag₂CO₃ was employed to facilitate the oxidation process. This reaction has gained popularity due to several advantages, making it a powerful tool in organic synthesis.

The resulting C8-acylated tetrahydroquinolines serve as valuable building blocks for further synthetic transformations. They can be utilized in the synthesis of complex natural products and pharmaceuticals.

The exact mechanism of this reaction may vary depending on the specific catalyst system employed. However, a general pathway often involves: 1. **Ru (II) activation**: the Ru(II) catalyst reacts with a carboxylic acid to form an activated
complex; 2. **THQ coordination:** the THQ substrate coordinates with the Ru (II) complex, positioning the C-8 carbon for the subsequent transformation; 3. **C-H activation:** the Ru (II) catalyst facilitates the cleavage of the C-H bond at the C-8 position of the THQ; 4. **C-C bond formation:** the Ru complex undergoes a transformation, leading to the formation of a carbon-carbon bond between the C-8 carbon and the carbonyl carbon of the activated carboxylic acid; 5. **catalyst regeneration:** the Ru (II) catalyst is regenerated, allowing for another catalytic cycle.

After identifying the best reaction conditions, the researchers investigated the effect of substrate volume using various substituted carboxylic acids. 1,2,3,4-tetrahydroquinoline 1a served as a model compound for this exploration.

![Scheme 2](image_url)

**Scheme 2**  
Ruthenium-catalyzed acyloxylation of 1,2,3,4- tetrahydroquinoline by carboxylic acids

The Ru (II)-catalyzed C8-acylation of tetrahydroquinolines with carboxylic acids is not just efficient and versatile, but also tolerant of a wide range of functional groups. This powerful reaction has the potential to revolutionize the development of new therapeutic drugs and functional materials in the years to come.

**The reaction of C-8 hydroxymethylation of tetrahydroquinolines with formaldehyde under Ru(II)-catalyst.**

Ruthenium-catalyzed C8-hydroxymethylation with formaldehyde provides a highly selective and efficient strategy for equipping tetrahydroquinolines with a valuable
hydroxymethyl group, opening doors for diverse THQ derivatives. Tetrahydroquinolines, a class of intriguing heterocyclic compounds with a specific ring structure containing nitrogen, play a significant role in medicinal chemistry due to their varied applications. The C8 position on THQs offers a strategic site for introducing functional groups that can significantly influence their biological properties.

Traditional methods for C8 functionalization often suffer from limitations like harsh reaction conditions, low regioselectivity, or incompatibility with certain functional groups. Compared to traditional methods, ruthenium catalysis offers a way to overcome these issues by providing efficiency, high regioselectivity, functional group tolerance.

Various C-8-hydroxymethylated tetrahydroquinolines have been prepared by a one-step regioselective addition of C8-H bonds of tetrahydroquinolines to formaldehyde using Ru (II) catalyzed C-H activation under mild reaction conditions [10].

\[
\text{R \text{H} \text{N} \text{N} \text{N}} \quad + \quad (\text{HCHO})_n \quad \xrightarrow{\text{catalyst, additives}} \quad \text{R-H \text{N} \text{N} \text{N} \text{N}} \quad \text{solvent, 60°C, 12 h}
\]

**Scheme 3**

C-8 hydroxymethylation of tetrahydroquinolines

**Conclusion.**

In conclusion, recent advancements in ruthenium-catalyzed C8-functionalization of substituted tetrahydroquinolines have opened exciting avenues for the development of novel and complex molecules. This approach offers a powerful and versatile strategy for tailoring these valuable heterocyclic compounds.

Ruthenium catalysts offer several advantages for C-H
activation of tetrahydroquinolines compared to other methods: high regioselectivity, mild reaction conditions, functional group tolerance, efficiency and rapidity, atom economy, versatility. Ruthenium catalysts can be employed in a variety of C-H functionalization reactions beyond just acyloxylation or hydroxymethylation. This opens doors for introducing a broad range of functionalities at the C8 position of tetrahydroquinolines.

References:


