# 学 位 論 文 内 容 の 要 旨

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## 学 位 論 文 題 名

Development of Nef reaction for aldehyde synthesis and its application toward total synthesis of Alyterinate A
（アルデヒドを合成するための Nef 反応の開発とアリテリネート A の全合成に向けた応用）

The transformation of nitro compounds into carbonyl derivatives represents one of the most valuable reactions in organic synthesis. Among these transformations, the Nef reaction serves as a classical and versatile method for converting nitro compounds into aldehydes, ketones, or carboxylic acids. Despite its broad utility, the aldehyde-forming variant of the Nef reaction has been relatively underdeveloped, largely due to the intrinsic instability of aldehydes and their susceptibility to degradation and epimerization under conventional conditions. Moreover, traditional procedures often depend on harsh acidic or basic environments and strong oxidants, which limit substrate compatibility and functional group tolerance. Additionally, conventional methods often suffer from competitive side reactions, including the Henry (nitroaldol) reaction, and typically require strong oxidants or acidic/basic conditions, thereby limiting substrate scope and functional group compatibility. These limitations underscore the need for new methodologies that enable aldehyde synthesis under milder and more selective reaction conditions with broader synthetic applicability.

In **Chapter 1**, a general overview of the Nef reaction is presented, including its historical development and challenges in modern synthetic chemistry. Particular attention is devoted to the development of milder protocols capable of efficiently generating aldehydes while maintaining high selectivity and functional group tolerance. Prior work in our group demonstrated that singlet oxygen generated under visible-light irradiation can efficiently mediate the conversion of nitronate intermediates into aldehydes, although extended reaction times were required. Motivated by these findings, the objectives of this study are presented to develop a more efficient, selective, and sustainable aldehyde-

forming Nef protocol under visible-light conditions and to apply this methodology to the synthesis of biologically active natural products.

**Chapter 2** focuses on the development and optimization of a visible-light-mediated, singlet oxygen-driven Nef reaction. This chapter discusses the conceptual design and experimental exploration of a photochemical system that replaces harsh reagents with mild, sustainable conditions. By employing visible light and molecular oxygen, the study demonstrates that aldehydes can be synthesized efficiently under conditions that are compatible with a broad range of functional groups. The mechanistic pathway was explored through ion chromatography, confirming the role of peroxide intermediates and providing a detailed understanding of the reaction process. The results indicate a significant improvement in reaction rate, yield, and selectivity compared to classical Nef reactions, making this photochemical approach a practical and scalable method for aldehyde synthesis.

In **Chapter 3**, the synthetic potential of the developed Nef methodology is demonstrated through its application to the total synthesis of Alyterinate A, a bioactive lignan derivative. Alyterinate A, isolated from *Alyxia schlechteri* and *Willughbeia coriacea*, possesses notable antifungal activity against *Pythium insidiosum* and exhibits moderate cytotoxicity toward cancer cell lines. Due to the scarcity of this compound from natural sources, an efficient chemical synthesis is essential for further pharmacological evaluation. The synthetic approach utilizes the newly developed Nef protocol as a key step for constructing the tetrahydrofuran (THF) ring, which is a characteristic structural feature of Alyterinate A. Further the key asymmetric Michael addition, catalyzed by the Hayashi–Jørgensen catalyst was also explored to afforded excellent stereoselectivity.

Finally, **Chapter 4** provides a general summary of the thesis, highlights the key findings, reviews the overall research outcomes, and proposes possible directions for future applications.