Late-stage C–H functionalization of complex molecules aided by single-atom editing

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Aromatic compounds are key substances with practical applications in almost every aspect of daily life, including pharmaceuticals, food additives, and polymers. Therefore, the development of new methods for the synthesis and functionalization of these compounds has been at the core of research in the field of organic chemistry since its inception. Despite significant progress over more than 100 years, this field continues to pose a challenge for scientists and offers room for improvement as full control of reactivity and selectivity—the ultimate goal of every chemical reaction—can only be achieved in limited cases. Moreover, from the perspective of sustainable development, a factor playing an increasingly significant role in modern organic synthesis approaches, many known processes for transforming aromatic compounds fall short of the ideal.

C–H functionalization addresses these concerns, providing a direct pathway to the modification of aromatic rings, making it the subject of continuous research for decades. This approach typically involves activating the unreactive carbon-hydrogen bond using catalysts based on metals (often noble metals such as palladium or ruthenium, but also more accessible metals like cobalt or iron), which can then be transformed into another bond, such as carbon-carbon. Since carbon-hydrogen bonds are commonly present, C–H functionalization can potentially be applied to virtually any organic compound. This opens up very broad possibilities while simultaneously inducing a selectivity challenge. How can one perform controlled single C–H functionalization in an organic compound containing many such bonds?

A common strategy for guiding C–H functionalization involves introducing a directing group into the modified compound. This group temporarily binds with the catalyst, thereby triggering the C–H functionalization of the neighboring C–H bond. However, in complex molecules, introducing such a group is often impossible, and synthesizing a substrate compatible with C–H functionalization requires then designing a new synthesis route. Nevertheless, recent studies demonstrate that under certain conditions, the **editing of individual atoms** is possible, resulting, for example, in the introduction of a nitrogen atom in place of a carbon atom, even in complex molecules.

This project will attempt to develop a tool that combines both of these methodologies. Editing individual atoms will enable the specific modification of a molecule, which will then be further transformed selectively through C–H functionalization. Such a solution will broaden the range of possible modifications to complex molecules, which may find particular application in medicinal chemistry. At various stages of drug activity research, it often happens that the tested compound exhibits excessive toxicity or undesirable effects. In such cases, the effects of its analogs are usually investigated, and the synthesis of these analogs often needs to start from scratch—a generally multi-step process due to the structural complexity of such compounds. The proposed solution in this project will allow modifications to complex compounds at a late stage, which is desirable due to the possibility of obtaining a series of different analogs easily, thereby increasing the chances of finding the most effective molecule. Simultaneously, the developed synthesis will minimize energy consumption and waste production compared to alternative multi-step paths for modifying organic compounds.