Final Summary Report

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DOMDICAS — Dual Organo / Metal Desymmetrisation in Complex Alkaloid Synthesis

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Participant name
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PUBLISHABLE SUMMARY REPORT

The morphan structural motif (2-azabicyclo[3.3.1]nonane) is common to many biologically relevant alkaloid natural products. This core subunit is found within over 300 natural products, including the strychnos, daphniphyllum and madangamine families. Furthermore, it is present in many other biologically relevant molecules, such as the analgesic morphine, the cytotoxic agent aspernomine and the immunosuppressant FR901483. Unfortunately, studies into the biological profile of many of these natural products are typically hindered due to insufficient quantities being available from the natural source. In order to secure sufficient quantities and fully determine the therapeutic potential, the total synthesis of complex alkaloids containing the morphan core has been the subject of intensive investigation over the last decades.

The field of enantioselective catalysis has allowed the high efficiency in the synthesis of structurally complex and stereochemically defined molecules. In recent years, the synthetic comunity has demonstrated that the co-operative combination of aminocatalysis and transition metal catalysis is a powerful and versatile catalytic strategy for the enantioselective construction of C-C bonds, which opens the door to transformations unattainable by a single catalytic entity alone.

During the course of this project, we have developed two synthetic methodologies toward the morphan core from simple and readily available starting materials, involving simultaneously two types of catalysis. The nucleophile component is provided by enamine catalysis and the electrophile counterpart was generated by metal-activated π-systems.

Specifically, the desymmetrization of achiral alkyne-tethered cyclohexanones in a single step has been optimized to yield a family of morphan core derivatives in good yield and with excellent enantioselectivities. The dual catalyst system is formed by a chiral pyrrolidine, a silver salt and a cinchona-derived ligand. Besides the obvious benefits of a scalable reaction which can provide a large amount of a complex chiral product from a simple starting material, this unprecedented transformation has provided much useful information about the compatibility of different types of catalysis and about match/mismatch effects. Computational calculations were performed in order to rationalize the stereochemical outcome of this reaction.

As a complementary approach, the desymmetrization of achiral allene-tethered cyclohexanones was also explored, and a dual catalyst system formed by a different chiral pyrrolidine and a copper salt provided a different family of morphan core derivatives in good yield with moderate enantio- and diastereoselectivity.

In summary, we have successfully developed dual-catalyzed enantioselective methodologies for the synthesis of the morphan core. Given its reliability and scalability, this transformation is currently in use for the total synthesis of natural products containing the morphan core. Additionally, this research should be of great interest to the organic synthetic community as it advances the state of the art of dual catalysis, which will open the door to the discovery and development of novel reactivity.