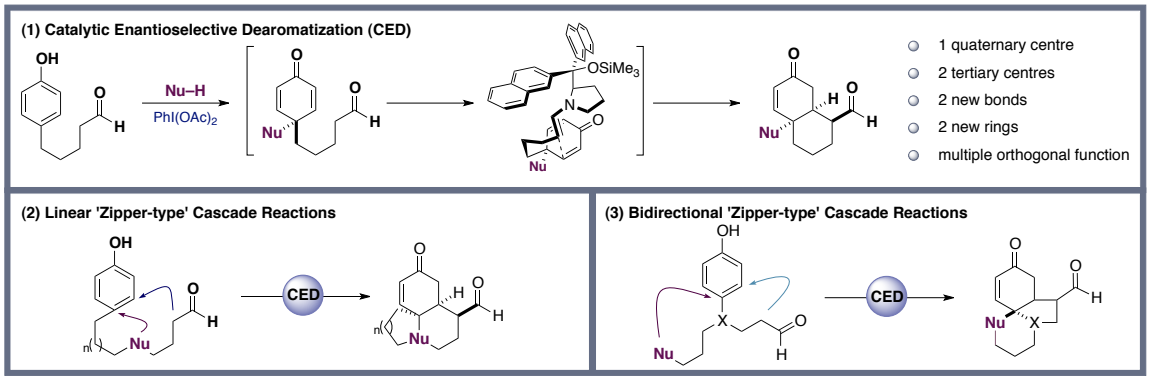
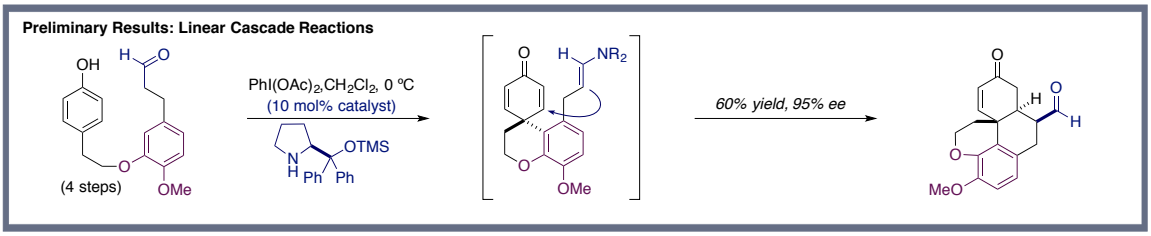
The capacity to generate enantiopure and architecturally complex molecules is pivotal to the realization of new paradigms in chemical synthesis, medicine and functionalized materials. Synthetic chemists can often generate small building block-type molecules, in excellent yield and enantiomeric excess, using asymmetric catalysis. Despite this, the development of catalytic enantioselective cascade reactions that directly form natural product or natural product-like molecules are less common; rapid access to these non-racemic complex structures would greatly facilitate many synthetic campaigns in natural product chemistry and chemical biology. The project undertaken by the researcher over the past twelve months involves the development of new catalytic strategies for chemical synthesis, wherein catalytic cascade processes are designed around transforming a common functional motif to a diversity of enantiopure natural product and natural product-like architectures quickly and efficiently.

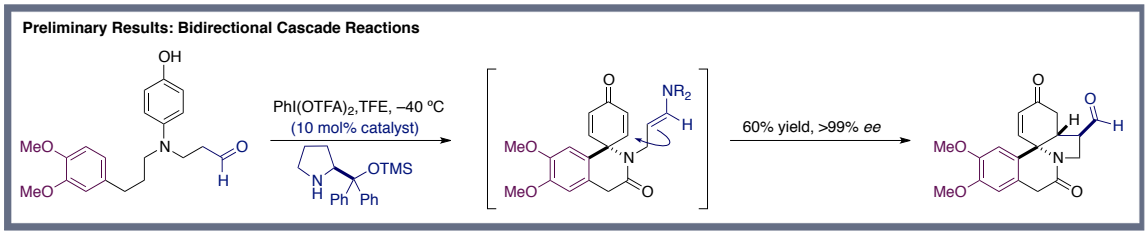
The Gaunt group has developed a catalytic enantioselective dearomatization strategy that enables the direct transformation of planar latently functionalized phenols into highly complex enantiopure molecules. In this transformation, an external nucleophile is added to the para-position of a phenol during the oxidation step, followed by an enantioselective desymmetrizing enamine intramolecular Michael addition. In considering the dearomatization step of the tandem process, it is possible to design reactions wherein an internal π-nucleophile participates in the phenol oxidation to form a structurally complex and symmetrical dienone intermediate that can be intercepted as before through an enantioselective Michael addition. The result would be the direct formation of a highly complex and chiral molecule that is 'natural product-like' from a simple linear precursor that is readily assembled. A key aspect of this process is the concomitant formation of quaternary stereocentres embedded within a complex molecular structure that contains valuable orthogonal functionality. Using such a strategy would enable synthetic chemists to generate new exciting molecules with novel scaffolds and to design extremely direct strategies to the synthesis of natural products; both tactics will enable chemist to interrogate biological problems with an armoury of structurally diverse enantiopure molecules.



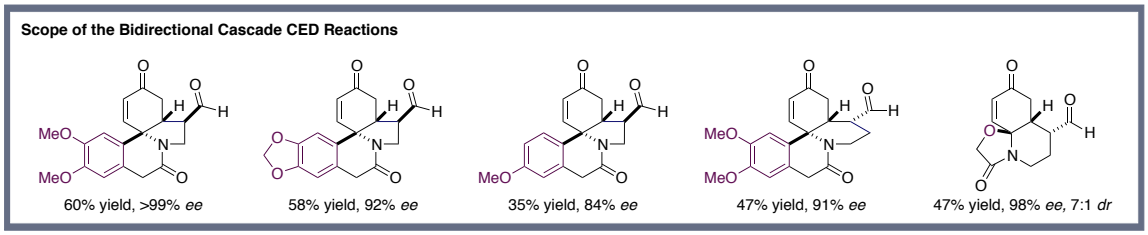
The primary goal of the first year of this project was to expand the scope of the CED reaction to include more complex substrates that resemble natural products or natural product-like scaffolds. In order to explore the cascade CED reaction on more complex systems, two initial model systems were designed where the nucleophile and aldehyde are tethered in the same molecule. This 'zipper-type' reaction involves the folding up of a molecule containing latent reactive functionality, triggered by the dearomatization and the catalyst. The intramolecular dearomatizing nucleophile could be envisioned to occur through a linear zipper reaction or a bidirection zipper process, providing accessing to two complimentary frameworks. To assess this hypothesis preliminary experiments were performed that validated this strategy and provided an excellent platform upon which to develop this research; the linear zipper reactions has been demonstrated to work in excellent yield and very high enantiomeric excess.



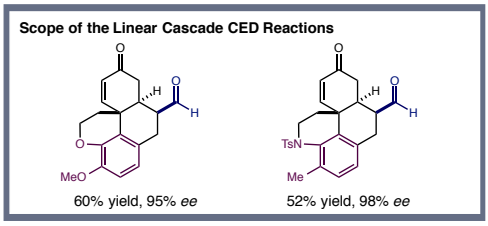
Following the preliminary success with the initial linear zipper-type substrate, a model substrate for the bidirectional zipper-type process was designed and evaluated under the reaction conditions developed for the linear cascade process. While the desired tetracyclic scaffold was observed under these conditions, this substrate required further optimization, including changes to the oxidant, solvent and temperature when compared to the linear analogue. Once optimized conditions were discovered, the cascade transformation proceeded efficiently to provide the tetracyclic product in good yield and excellent enantioselectivity as a single diastereomer.



After completing the initial bidirectional cascade substrate, focus remained on the bidirectional system and a substrate scope study was undertaken. A total of five substrates were completed, four employing intramolecular aromatic carbon-based nucleophiles, while the fifth uses a tethered hydroxyl nucleophile during the dearomatization. Each substrate required focused attention and optimization to achieve good yields and enantioselectivity. Remarkably, all of the substrates bearing carbon-based aromatic nucleophile provided the products as single diastereomers. In addition to the completed substrates shown below, there were also unsuccessful nucleophiles, including substrates bearing silyl enol ether and electron neutral aromatic nucleophiles.



Having demonstrated a range of substrates for the bidirectional zipper-type cascade reaction, our attention turned back towards the linear substrates. Linear phenol substrates were prepared that bear aromatic nucleophiles and the aldehyde handle on the same tether. As we observed with the bidirectional substrates, each new phenol requires dedicated attention and optimization to achieve the desired levels of efficiency. Two examples of linear zipper-type cascade substrates have been completed with good yields and excellent enantioselectivity, both as single diastereomers.



Alongside this project, the application of this technology to the synthesis of morphine and its analogues has been initiated with another colleague from the Gaunt group. This exciting project, along with the CED reaction development, published in high impact journals in chemistry in the near future.