Chapter 6

General discussion and future perspectives
One of the challenges in oxidation chemistry is to develop new ‘ideal’ methods that offer easy access (commercially available or straightforward synthesis) and cost-effective ligands, short reaction times, ambient conditions, i.e. room temperature in air, as well as, providing high selectivity and high product yield. Another challenge, that might be as important as the former, is to introduce methods to users, i.e. synthetic chemists, who usually fall back on efficient and safe methods, that are already at hand. In this thesis, one known catalytic method and one novel method were examined and discussed in terms of substrate scope, functional group and protecting group tolerance and, especially, mechanistic insights for the latter system.

Mn-TMTACN based catalysts are well-known catalyst for oxidative transformations, i.e. the oxidation of alkenes to epoxide or cis-diol products and oxidation of alcohols to ketones or carboxylic acids, and many research groups have worked on their application.\(^1\) However, only the reports by de Boer et al.\(^2,3\) used bis-carboxylato bridged complexes, which were found to be the active intermediate formed in many Mn-TMTACN system. Until recently the substrate scope employing bis-carboxylato bridged complexes was limited.

The catalytic system based on TMTACN described in this thesis demonstrated broader substrate scope for the oxidation of alkenes to epoxides or cis-diols, oxidation of secondary alcohols to ketones, oxidation of primary alcohols to carboxylic acids and C-H activation to mono-ketone product as well as the functional group and protecting group tolerance. Since this catalyst is suitable for many oxidative transformations, sometimes a problem with chemoselectivity of the reaction can be encountered. Even if the system is still limited in terms of selectivity, however, many advantages from this system make it one of the recommended methods for oxidation reactions from laboratory to large scale synthesis. Experimentally, reactions are simple since the reactions can be performed at room temperature and under air. Also the system is more economic than many methods used both in academic and industrial application as Mn, the TMTACN ligand itself and H\(_2\)O\(_2\) are relatively inexpensive reagents compared to others, e.g. RuCl\(_3\) and NaIO\(_4\), and this system requires only low amounts of the catalyst.

The enantioselective transformation based on bis-carboxylato bridged complexes is not widely explored yet as only the cis-dihydroxylation of one alkene (2,2-dimethylchromene), which is a challenging substrate, was demonstrated employing chiral carboxylic acids as co-catalyst.\(^3\) Many chiral carboxylic acids, mostly amino acids, were tested by de Boer et al.\(^3\) Even though, low to moderate ee’s were observed in most cases, screening of other types of chiral carboxylic acid and a broaden substrate scope for this transformation should be done in future work. This approach should also be applied for other transformations such as epoxidation of alkenes to obtain a new enantioselective method for epoxidation as well as kinetic resolution of secondary alcohols, for instance. The latter target is more promising as secondary alcohol oxidation is relatively straightforward (see Chapter 3).
The next system described in this thesis is based on pyridine-2-carboxylic acid, which was discovered as a result of the decomposition of more complex ligands, e.g. TPTN/TPEN and aminal ligands, under the reaction conditions employed. However, polypyridyl amine based ligands are still a promising ligand if used under other reaction conditions, e.g. under acidic condition, as their exceptional efficiency for oxidation of alkenes using acetic acid/H₂O₂ was demonstrated by Costas and coworkers. Nevertheless, ligand structure modification could provide the solution to avoid the ligand decomposition. Polypyridyl amide based ligands which contain no oxidatively sensitive positions, i.e. benzylic positions of pyridine moiety in polypyridyl amine based ligands, could be interesting candidates for pyridyl ligands for oxidation reactions.

A new catalytic system developed with pyridine-2-carboxylic acid ligand meets many requirements to be a new practical method for oxidative transformations. Although the system consists of several components, i.e., Mn salt, pyridine-2-carboxylic acid, butanediol and H₂O₂, they are inexpensive and all commercially available from most chemical suppliers. The reactions are carried out under air and at room temperature and take short times to reach their highest conversions (from 10 min to a few hours). Moreover, most of the reactions provide good to excellent conversion and product yield for the oxidation of alkenes, except in the case of α,β-unsaturated substrates, e.g. cinnamate derivatives. However, the selectivity of the reactions, for example cis-dihydroxylation vs. epoxidation of alkenes, is limited as the substrates’ electronic nature, either electron poor or electron rich, determines selectivity of the product.

There are a few more aspects that should be dealt with to improve this system. Firstly, the functional group and protecting group tolerance need to be broadened to attract the attention of the synthetic chemist. Secondly, the oxidation of substrates containing stereogenic centre(s) needs to be demonstrated further to confirm that it proceeds with retention of configuration under the reaction conditions employed. Furthermore, other oxidative transformations, i.e. selective oxidation of primary alcohols to their corresponding aldehydes or oxidation of secondary alcohols to ketones, should be examined in more detail since the few examples of oxidation of primary and benzylic alcohols employing the optimised condition for oxidation of alkenes showed little activity.

As mentioned above mechanistic studies on the newly developed system were reported also in this thesis. Although a mechanism has been proposed in Chapter 5, more information, especially, from ¹⁸O-labelling study is needed in order to support or refute this proposed mechanism. ¹⁸O-labelled butanedione, which can be prepared by reacting butanedione with H₂¹⁸O (and monitored by Raman spectroscopy), should be used in the reaction in order to establish that one of the oxygen atoms of the product is from butanedione. Moreover, both cis-diol and epoxide products from the same substrate should be examined in ¹⁸O-labelling studies to confirm that both transformations proceed by the same mechanism or not.
Mechanistic studies provide useful insights that can improve the performance of the system. For example, the discovery that acetic acid, which is the by-product formed under reaction conditions employed, eliminates the lag-time as the reactions with extra acetic acid start immediately is useful. This should be applied to substrates bearing unstable protecting groups, \textit{i.e.} Si-based protecting group such as TBDPS. If the reaction starts immediately upon addition of \( \text{H}_2\text{O}_2 \), the deprotection of protecting group under reaction conditions should be reduced.

### 6.1 References

1. See references in Chapter 1.