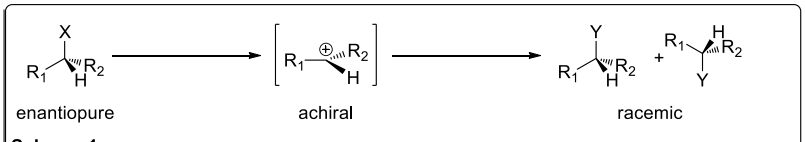
Memory of Chirality in Organic Synthesis

Every undergraduate learns that the reaction of an enantiopure sp^3 centre that is trigonalised will yield only racemic products in the absence of any external factors (chiral auxiliary, ligand, etc) (**Scheme 1**). However, it has emerged that it is possible for an enantioenriched product to be formed if an intermediate possesses what is known as *conformational chirality*, leading to *memory of chirality* (MOC). The idea that an enantioenriched product could be produced despite loss of the initial chiral centre was first proposed by Seebach *et al.* in 1981.



Scheme 1

For a reaction to have any hope of MOC, the requirements are (**Figure 1**):

1) Enantioselective formation of conformationally chiral intermediate from chiral SM.
2) Conformationally chiral intermediate must be slow to racemize.
3) Chiral intermediate must show enhanced reactivity towards product formation compared to racemisation.

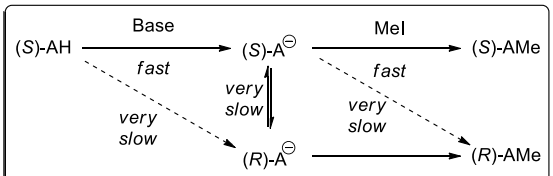
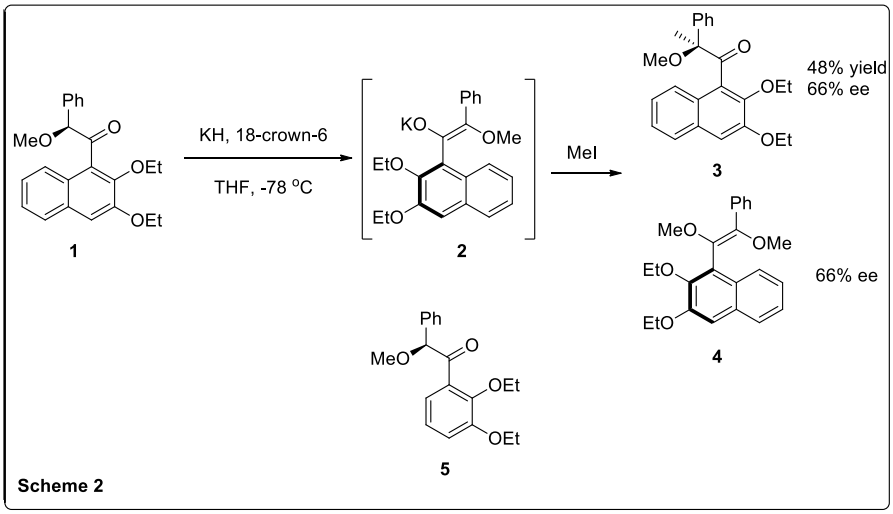


Figure 1

Enantioselective α-alkylation of carbonyl compounds

In 1991, Fuji *et al.* reported an alkylation of chiral biaryl ketone **1** with potassium hydride and methyl iodide.[1] They reported only a moderate erosion of ee in the product from 93 to 66% (**Scheme 2**). They suggest an axially chiral enolate intermediate **2**. Evidence in support of this is isolation of axially chiral enol diether **4**, with an initial ee of 66% that was found to erode over time. Furthermore, monoaryl analogue **5** resulted in complete racemisation in the product.



Scheme 2

In 1998, Fuji proposed that enolates of α-amino acids could be alkylated with MOC by one of three possible mechanisms (**Figure 2**).[2]

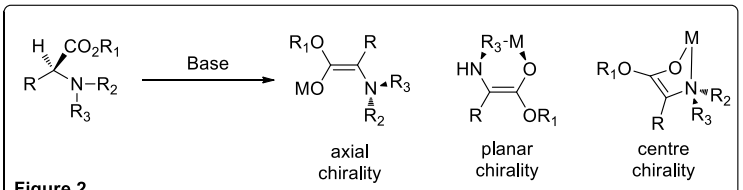
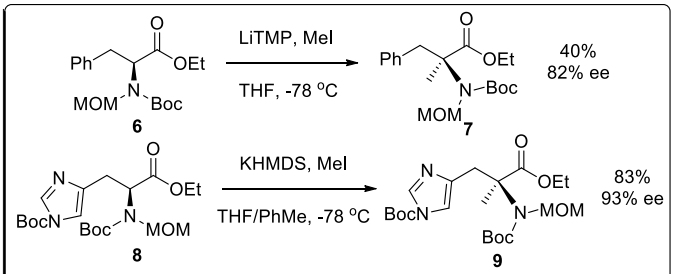


Figure 2

The first example of this alkylation of amino acids utilising MOC involved treatment of phenylalanine derivative **6** with lithium tetramethylpiperidide, and quenching with methyl iodide, resulting in only minor erosion of ee to 82% (**Scheme 3**).[3] A further study showed that histidine derived **8** could be methylated with only a tiny loss of enantiopurity, with a product ee of 93% using KHMDS as the base.[4]



Scheme 3

In order to clarify the mechanism by which chirality is transferred in the reaction, **6** was treated with KHMDS and quenched with TBSOTf in order to isolate the enolate intermediates of the reaction. Silyl enol ethers **10a** and **10b** were recovered in a 2:1 ratio in 83% yield. NMR analysis showed that the MOM methylene protons in both structures appeared as an AB quartet, suggestive of restricted rotation around the C_α-N bond. Variable temperature NMR studies suggested that the barrier to rotation was 16.8 kcal mol^{-1} at 365K, with a half-life of racemisation of 7 days at -78 °C. As such, the potassium enolate would also be expected to have a significant half-life at such low temperatures. A plot of $\ln(\frac{ee^0}{ee^t})$ against temperature affords a barrier to rotation of 16.0 kcal mol^{-1} at -78 °C, with a half-life of racemisation of 22 hours (**Figure 3**), leading the authors to suggest that the retention of chirality in the product proceeds through an axially chiral intermediate.

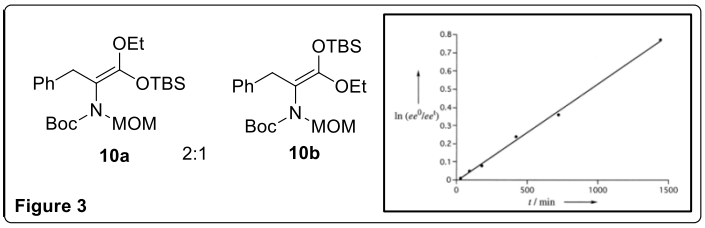
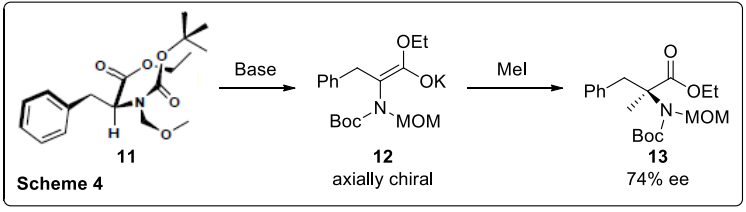


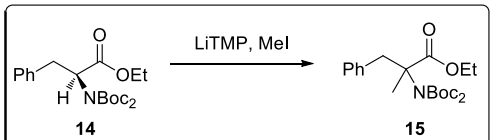
Figure 3

The authors then went on to suggest a model for the reaction, based upon molecular modelling for the most stable conformer of the starting material (**Scheme 4**).



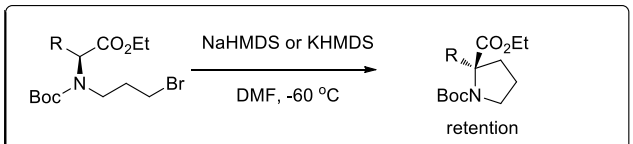
Scheme 4

Further confirmation for this hypothesis was confirmed by treating compound **14**, which could not be expected to proceed *via* an axially chiral intermediate. Indeed, it was found that α-methylation of **14** yielded only racemic product **15** (Scheme **5**).



Scheme 5

This sort of methodology has also been applied to the intramolecular alkylation of α-aminoesters, with a haloalkyl tether placed on the nitrogen. Treatment of compounds **16a-c** with Na or KHMDS resulted in formation of proline-derivatives **17a-c** with *retention* of configuration (**Scheme 6**).[5]

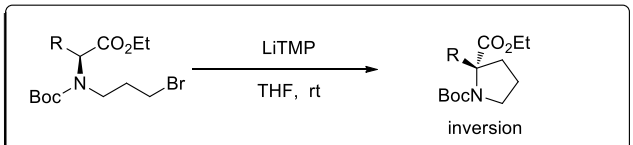


16a - R = Bn
16b - R = $MeSCH_2CH_2$
16c - R = iPr

17a - R = Bn, 98% ee
17b - R = $MeSCH_2CH_2$, 97% ee
17c - R = iPr, 94% ee

Scheme 6

However, later studies using LiTMP as the base resulted in an inversion of configuration at the α position (**Scheme 7**).[6]



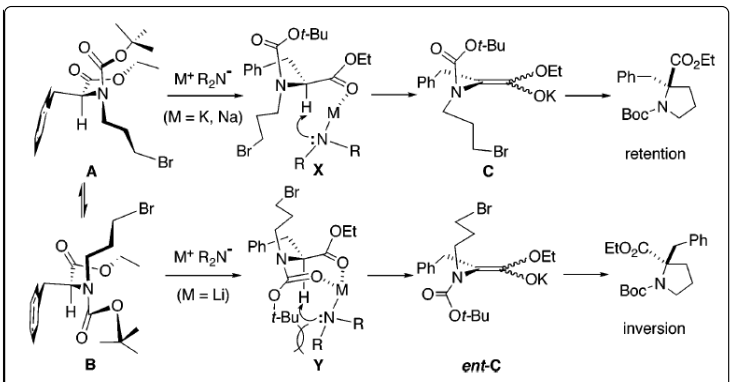
18a - R = Bn
18b - R = $MeSCH_2CH_2$
18c - R = Me

19a - R = Bn, 91% ee
19b - R = $MeSCH_2CH_2$, 81% ee
19c - R = Me, 87% ee

Scheme 7

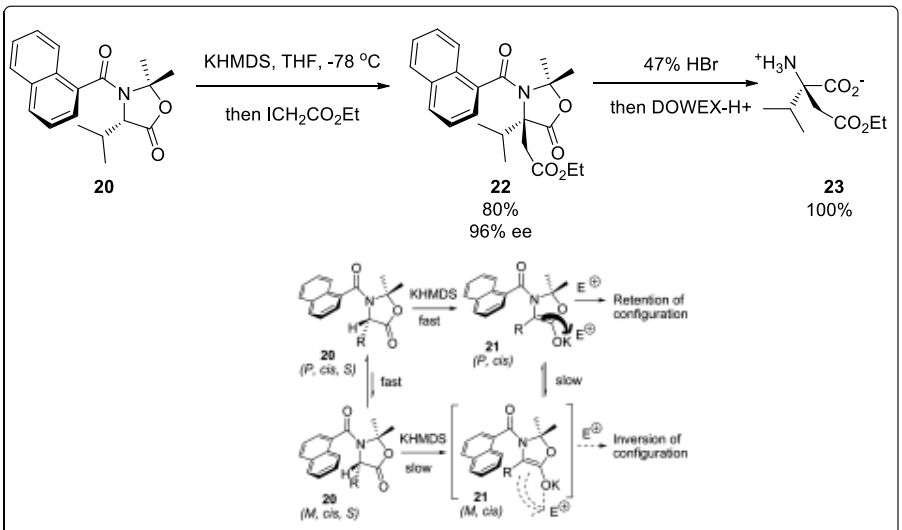
A model was proposed for this whereby the reaction with NaHMDS or KHMDS proceeds *via* deprotonation of conformer A, to give enantiomerically enriched conformer C.[7] It is suggested that deprotonation of conformer B with these bases would be unfavourable due to steric clash between the disilylazide and the Boc protecting group. However, since Li^+ is more strongly chelating than either Na^+ or K^+, it was suggested that chelation of the lithium to both the ester and carbamate carbonyl groups, stabilising transition state **Y** relative to **X**, yielding *ent*-**C** as the enantiomerically enriched enolate, and thus resulting in inversion of the product (**Scheme 8**). Solvent effects also confirm this hypothesis, with a greater degree of inversion observed with KHMDS and NaHMDS in

less strongly coordinating solvents, implying a great degree of chelation, with only 40% ee observed in toluene.



Scheme 8

More recently, Kouklovsky *et al.* have developed a chiral auxiliary based approach to quaternary α-amino acids, utilising an a centre chirality to axial chirality approach, creating a tertiary aromatic amide **20**, with hindered rotation around the Ar-C axis, thus directing the approach of an electrophile stereoselectively, in up to 96% ee (**Scheme 9**).[7]

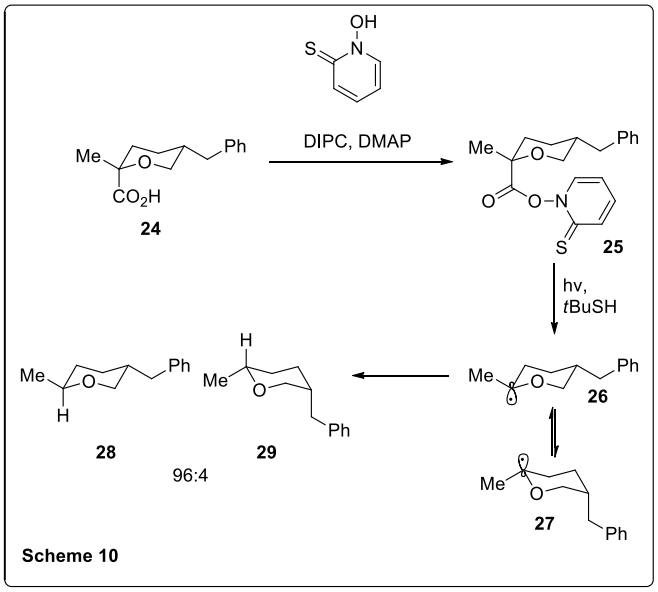


Scheme 9

The model proposed for the enantioselectivity of this reaction involved swift rotation between *P* and *M* conformers of compound **20**, only one of which was swiftly deprotonated, due to steric hindrance of the *M* conformer, leading to the *P* enolate and resulting in retention of configuration.

Memory of chirality in radical chemistry

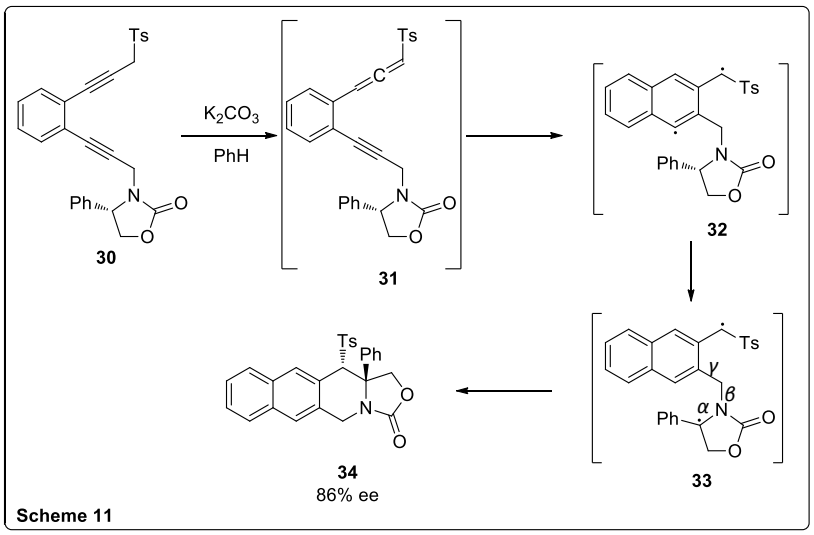
Radical decarboxylation of α-pyrancarboxylic acid **24** under Barton's conditions, leads to the formation of an axial anomeric radical, which, due to a reasonably high barrier to inversion, is able to abstract hydrogen from *tert*-butylthiol, resulting in formation of the axial product **28** in a 96:4 ratio (**Scheme 10**).[8]



Scheme 10

Similarly, treatment of the corresponding α-cyanopyran with LiDBB in THF yielded the same products in 95:5 ratio, again due to the presumably slow inversion of radical **26** due to ring flipping.[9] It was estimated that the free energy of activation for the ring flip was in the region of 5-10 kcal/mol, suggesting a considerable barrier to inversion, and hence the retention of configuration in the product. Use of a less efficient hydrogen donor such as tributyltin hydride resulted in complete scrambling of stereochemistry at the anomeric centre.

In 2010, Bertrand *et al.* reported memory of chirality in the cascade reaction of enantiopure enediyne **30** *via* isomerisation to allene **31**, Saito-Myers cyclisation to biradical **32**, 1,5-hydrogen shift to form a second biradical **33**, and finally ring closure to piperidine **34** through radical coupling in 86% ee (**Scheme 11**).[10]



Scheme 11

It is proposed that the enantioselection in the product is as a result of restricted rotation around the σ-bonds of biradical **33**. Racemisation could occur by rotation around bond α or *β,* so it is necessary that the rotation around these bonds is impeded and slow compared to rotation around *γ*. In the above case, rotation around *α* is limited by the cyclic structure, and the bulk on nitrogen slows

rotation around *β* sufficiently to enable high conservation of ee in the product, with retention of stereochemistry.

Conclusion

Whilst this method of synthesising enantioenriched products is still relatively new, compared to other areas of asymmetric synthesis, there is clearly a variety of different reactions that are amenable to this sort of process. As such, it is likely that the applicability of MOC should increase dramatically as more varied reactions are investigated with this process, but given the number of syntheses which require stereoselective alkylation of enolates, it is evident that there is already a large area where this type of methodology could be applied.

References

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9) *J. Am. Chem. Soc.,* **2000**, 9386
10) *J. Am. Chem. Soc.,* **2010**, 14742