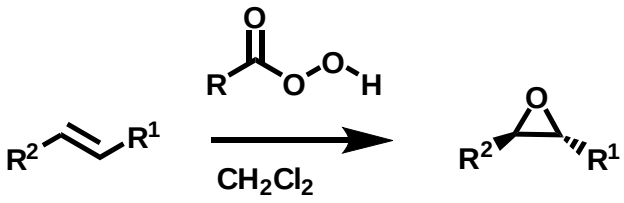
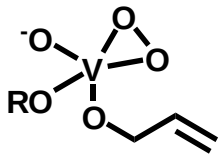
Enantioselective Catalysis

Asymmetric Epoxidation.

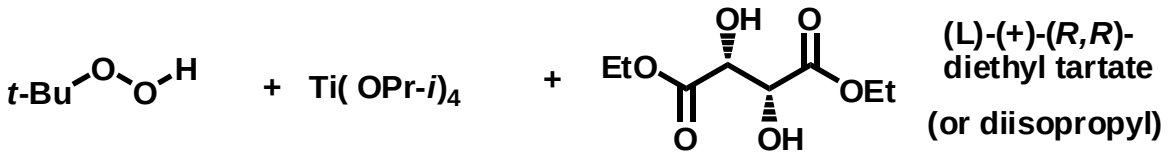
You have already seen in 59-331 that a very common method for converting alkenes to epoxides involves the reaction of the former with peracids.



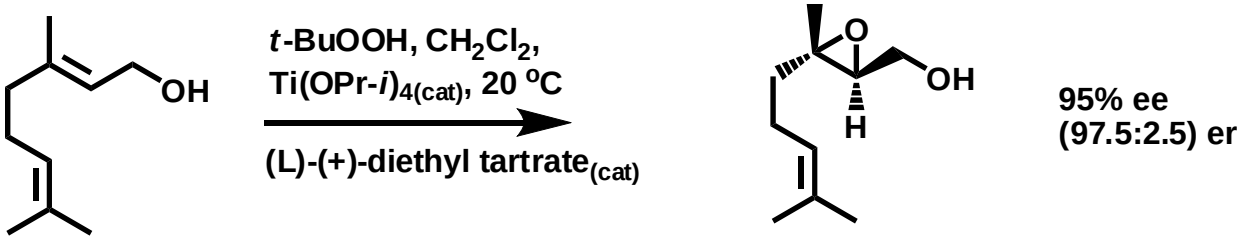
There is a well-known alternative to this, which employs metal complex catalyzed oxidation by a alkyl hydroperoxide. The original method involved a $V(O)(OR)_3$ complex and *t*-BuOOH; it is selective for allylic alcohols, because the V^V alkoxide (shown below) is likely a critical intermediate in the epoxidation. That leaves the OR's for potential sources of making a chiral catalyst, using some kind of chiral alcohol.



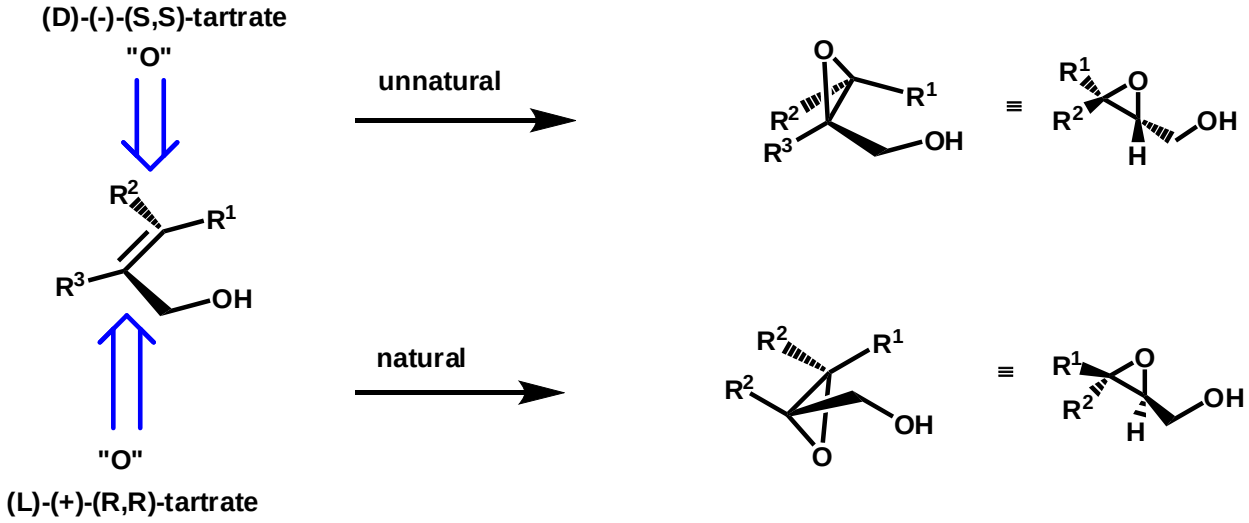
Other transition metal based compounds (i.e., Mo, Ti) are known for this process, too, and in particular the Ti^{IV} catalysts can be made to operate enantioselectively. The overwhelmingly employed set of reagents are:



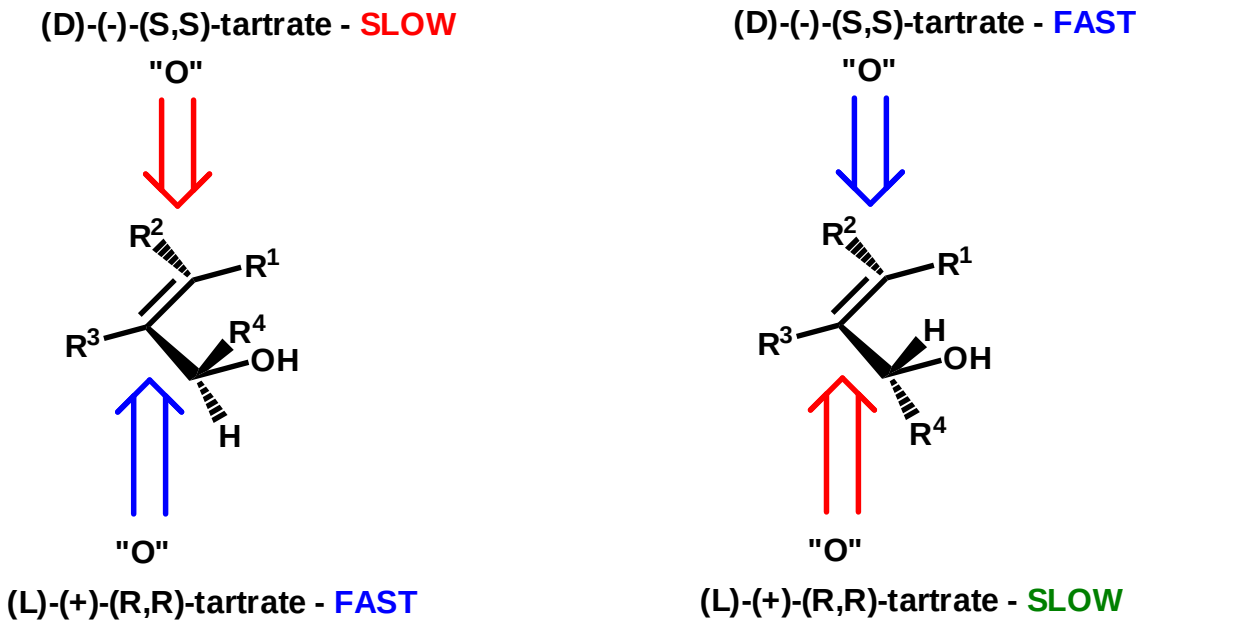
This is particularly useful in that the naturally occurring enantiomer (shown) of diethyl tartrate is pretty cheap (100 g, $65, 2012 dollars), and even the unnatural enantiomer ((S,S)-) isn't *too* bad (25 g, $122, 2012 dollars). Furthermore, 3 Å molecular sieves are added to make the reaction reliably catalytic in Ti^{IV} and tartrate. Typical loadings of the catalysts are anywhere from 5 mol% Ti^{IV} + 6 mol% tartrate to 10 mol% Ti^{IV} + 12 mol% tartrate. This process is called the Katsuki-Sharpless epoxidation (older books tend to leave out Katsuki). Here's a simple example:



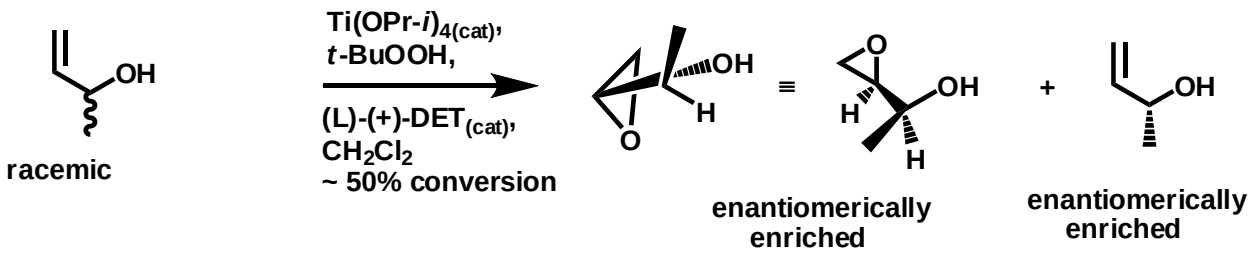
This first thing to notice is that the stereosepecific with respect to alkene geometry; *cis*- alkene substitutents on the alkene give *cis*- substituents on the epoxide and *trans*- gives *trans*-. The direction of asymmetric induction, is also stereospecific (depending upon the tartrate enantiomer), and a model is useful that is totally empirical. In it, of you lay out the allylic alcohol such that the alcohol is out from and to the right, the natural tartrate based complex attacks from the bottom face, while the unnatural tartrate based reagent attacks from the top face.



In addition, it is possible to accomplish a kinetic resolution on alcohols that have a chiral centre but are racemic (in other words, have one enantiomer react faster than the other), and as a result you can get enantiomerically enriched epoxide and unreacted allylic alcohol (recovered starting material) if the reaction is stopped at ca. 50% conversion. Here's schematic showing why….

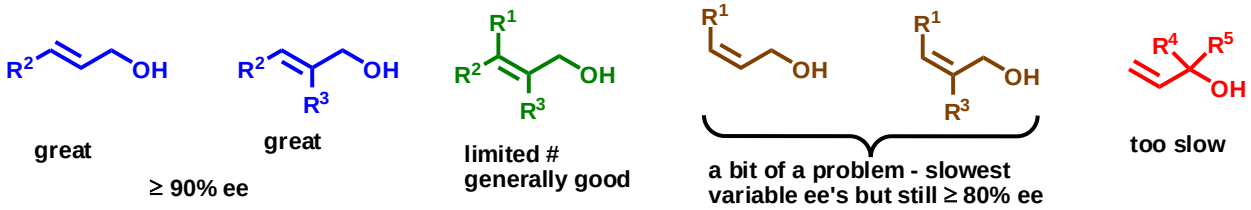


The rate difference between the two (diastereotopic) faces are large to massive (16:1 = 82% ee to 700:1) at -20 °C, often giving excellent results.

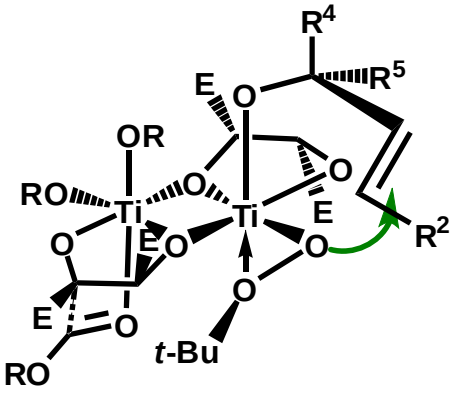


The functional group tolerance turns out to be pretty good. Of the common functional groups, only amines (-NR_2), carboxylic acids (-CO_2H), thioethers (-SR), phenols (Ar-OH), and phosphines (-PR_2) are not tolerated. For carboxylic acids and phenols, there are fairly simple protections available (esters and phenolic ethers, respectively).

Not every alkene that is an allylic alcohol undergoes epoxidation under these conditions equally well, however, as there is some steric hindrance issues when too many R groups get in the way of the alcohol function. As a general rule.

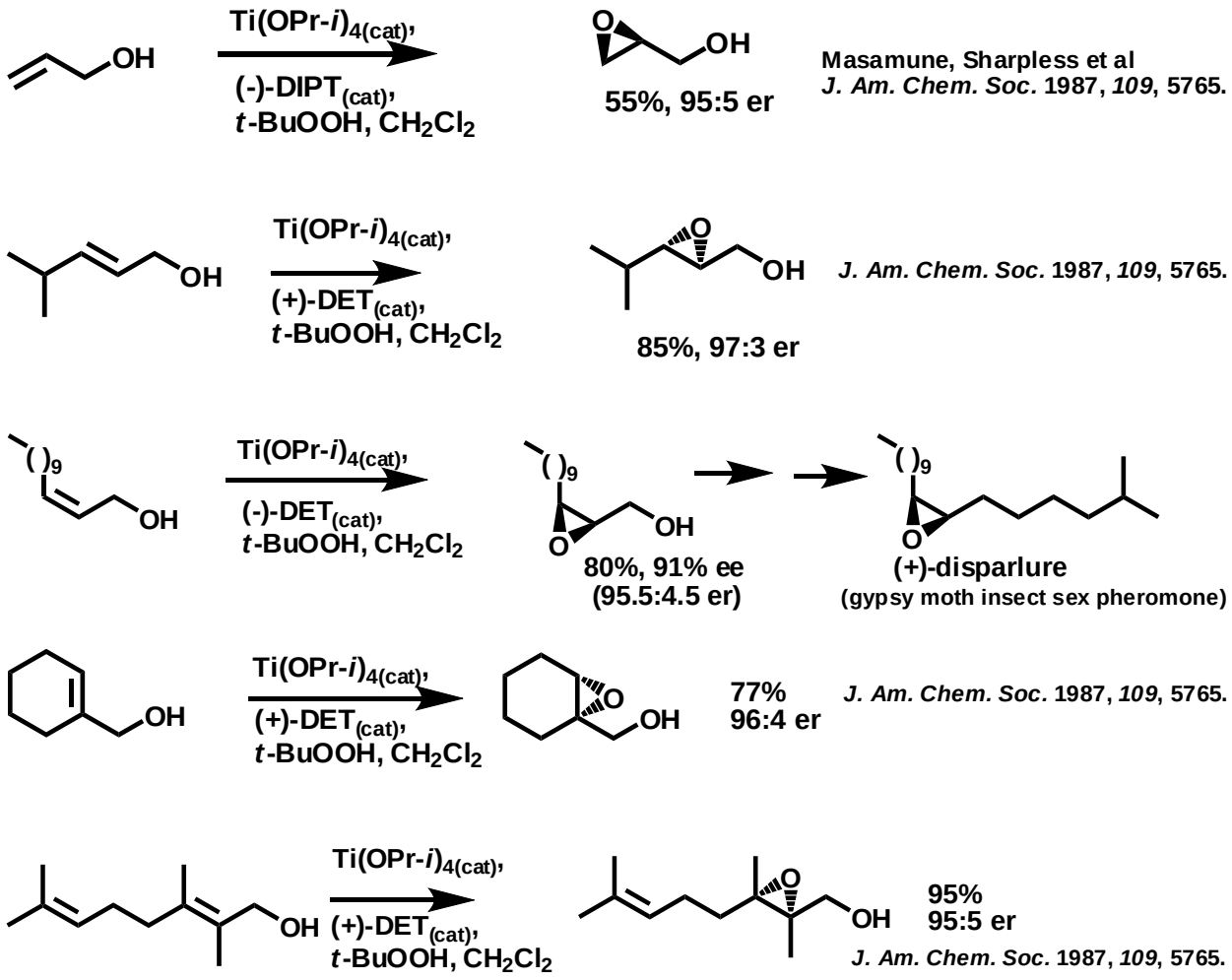


This was all developed empirically, so the mechanism is proposed rather than unequivocal, but the proposed 'loaded catalyst' is



'loaded catalyst"
Comprehensive Organic Synthesis
1991, V 7, Ch. 3.2

Selected examples: mostly taken from Gawley, Aube, *Principles of Asymmetric Synthesis*, Elsevier, 2012



Asymmetric Dihydroxylations

See Kolb, H.C.; VanNieuwenzhe, M. S; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

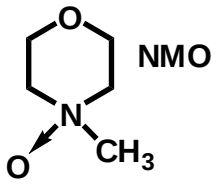
Recall that alkenes can be converted to 1,2- (*vic*-) diols by the use of OsO_4, followed by a workup that breaks up the osmate ester.

It has been known for many years that pyridine accelerates the rate of this reaction; so a reasonable approach to creating an enantioselective dihydroxylation reagent would be to make a chiral pyridine, or at least a chiral amine. Before we get to what would serve appropriately….

There are a couple of problems with this process:

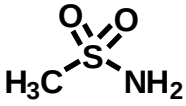
i) OsO_4 is expensive, so it would be *very* preferable to use it catalytically, and a have a cheap stoichiometric oxidant bring the Os^{VI} back to Os^{VIII}

The best choice for this oxidant is $K_3Fe(CN)_6$ with a two phase oxidation ($K_3Fe(CN)_6$ is water soluble; OsO_4 is the only oxidant in the organic phase.
The 2nd best choice is N-methylmorpholine-N-oxide (NMO), which you have seen before in other contexts as a stoichiometric oxidant.

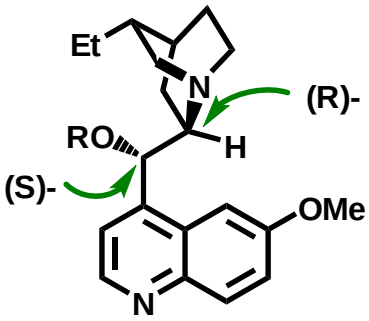


NMO

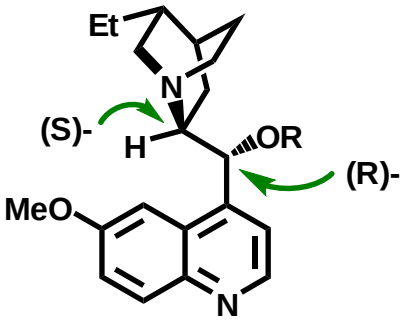
ii) The catalytic cycle has a bottleneck, which is the hydrolysis of the osmate ester product to free Os^{VI} and free diol. This break-up is accelerated by methanesulfonamide, $MeSO_2NH_2$, which increases the overall reaction rate by a factor of 50x, except for terminal alkenes.



So what chiral amines (or pyridines)? They are two or three piece combinations of one of two naturally occurring cinchona alkaloid 'ligands', link with a tether. The ligands are most commonly…



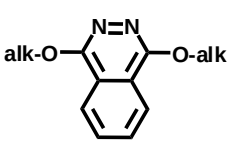
R = H dihydroquinidine (DHQD)



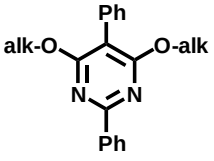
R = H dihydroquinine (DHQ)

These are not actually enantiomers of each other, but rather diastereomers, because the chirality of the C bearing the ethyl is the same in each case ((*R*)-). For the dihydroxylations, however, they function as the complementary systems to get enantiomeric products; the unofficial term **pseudoenantiomers** is commonly used. It should also be noticed that it is likely the aliphatic nitrogen atom, and not the aromatic one, that is involved in coordination to Os.

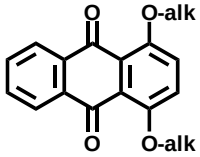
So what's that 'R' in the structure? The dihydroxylations are most commonly successful when there are two of these units in the same molecule, and they are hooked together with an ether tether, which is normally one of…



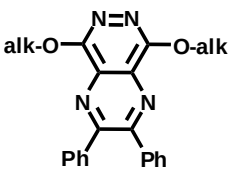
phthalazine (PHAL) historically the best



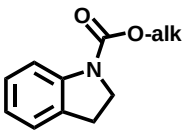
diphenylpyrimidine (PYR) sterically hindered cases



anthraquinone (AQN) 2nd best



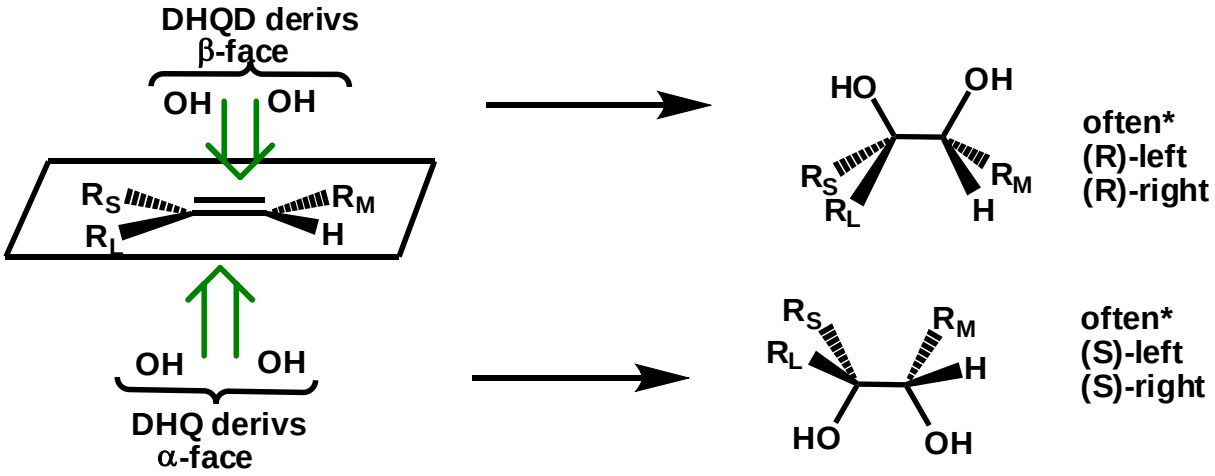
DPP similar to PHAL



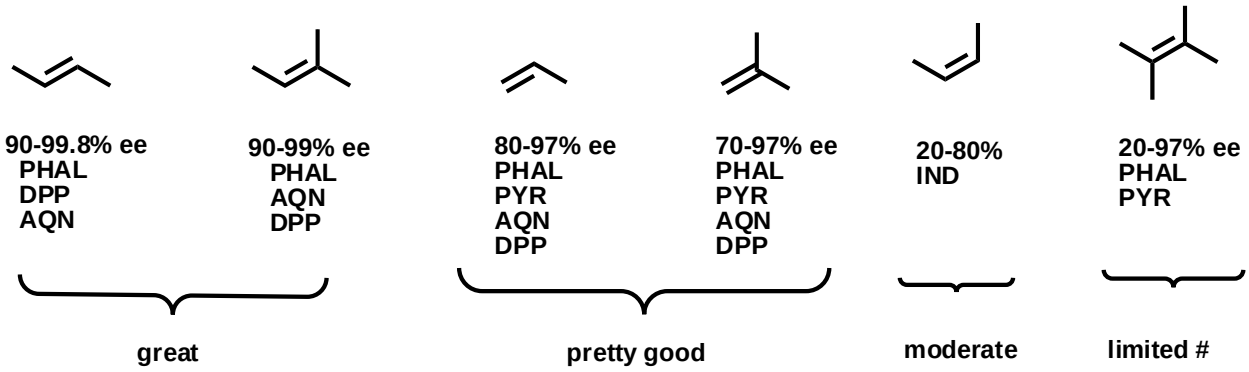
IND best for *cis*-disubst. alkenes

The way the reagent combinations are presented is shown by the following example: using the **PHAL** spacer with the **DHQD** ligand is termed **$(DHQD)_2$-PHAL**. This is sold as **AD-mix-β**. **$(DHQ)_2$-PHAL** is sold as **AD-mix-α**.

Like the epoxidation reactions, there is a mnemonic for how each of the reagents direct addition to alkenes. If one puts the alkene in a plane with the largest substituent towards the left and towards the reader. **DHQD** attacks from the top (or β- face), **DHQ** from the bottom face (or α- face), such as in:



- Not every alkene is dihydroxylated equally well. The following is a rough schematic; you'll notice that *cis*- disubstituted cases are the toughest, and really the only case where the IND spacer is used.



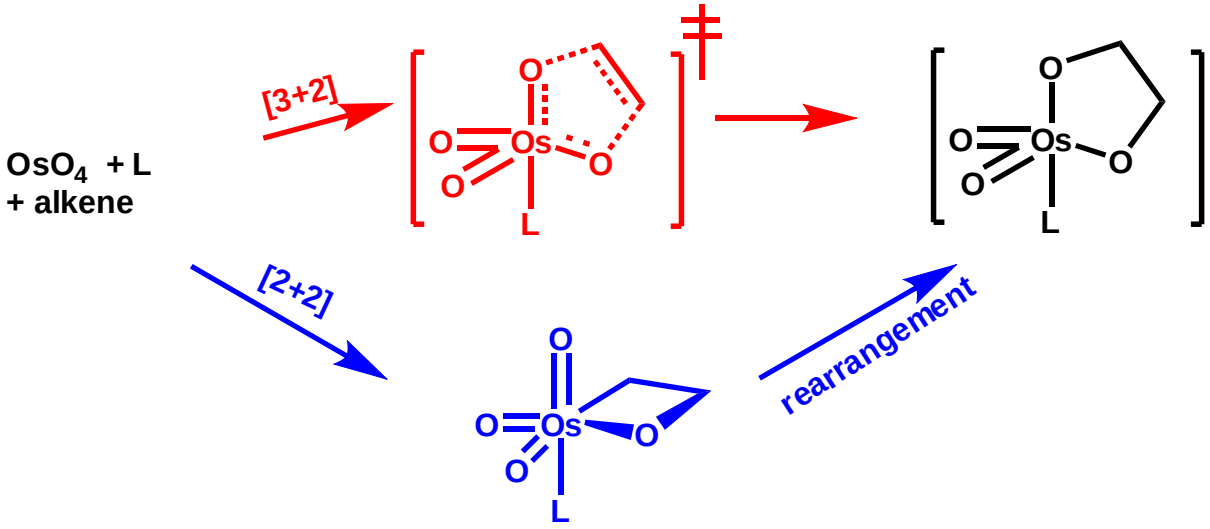
- In general, the higher end of the ranges have R_L as aromatic groups, and the lower end has R_L as aliphatic groups. The newer spacers (AQN especially) have helped out with aliphatic cases.

Typical conditions are as follows. Notice that OsO_4 is most often replaced by an osmate salt, $K_2OsO_2(OH)_4$, a non-volative,w ater soluble form of Os^{VIII}.

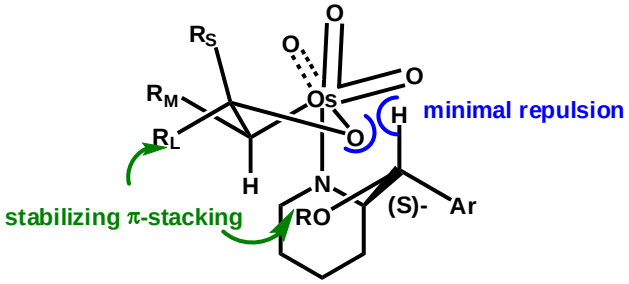
T = 0-25 °C ligand 1-5 mol% osmate $K_2OsO_2(OH)_4$ 0.2-1 mol%

Stoichiometric oxidant $K_3Fe(CN)_6$ solvent *t*-BuOH/H_2O

And the mechanism? Firstly, it was originally proposed that OsO_4 dihydroxylation of alkenes was a [3+2] cycloaddition. This view has been replaced that the initial addition is a [2+2] cycloaddition (reminiscent of a Wittig reaction), followed by a ring expansion/rearrangement.

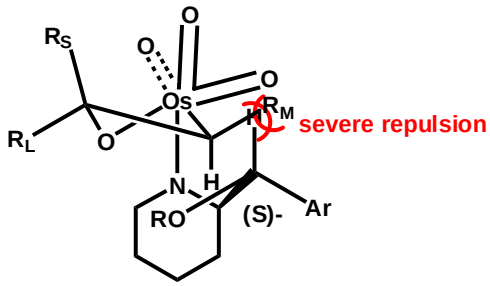


The proposed source of enantioselectivity stems from minimization of repulsive steric interactions between osmaoxetane and the benzylic carbon of cinchona alkaloid. Attractive π- stacking interactions between aryl groups on the alkene and the electron poor aromatic of the linker are the proposed source of great selectivity with aryl substituted alkenes.



good

with DHQD



bad