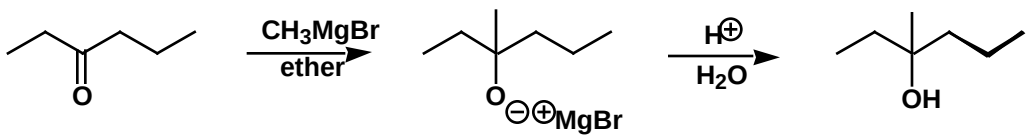
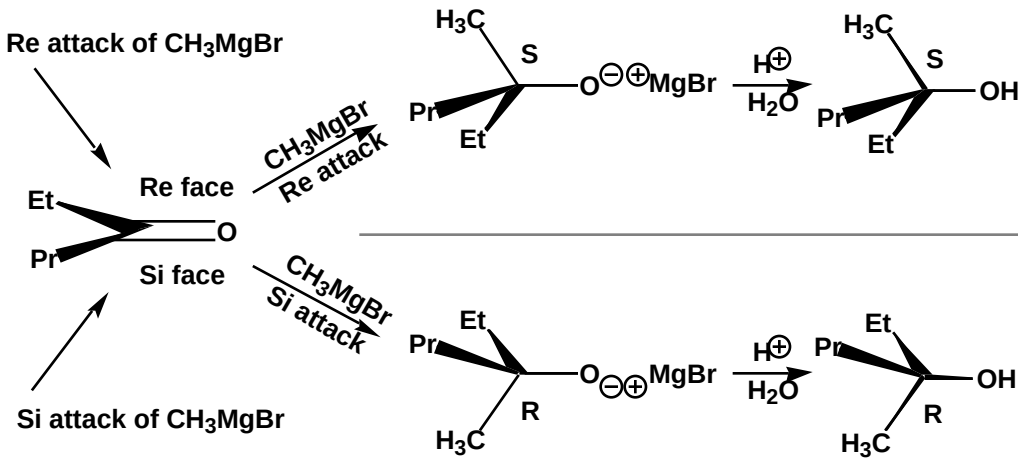
Text Related to Segment 17.07 ©2002 Claude E. Wintner

Further consideration of the synthesis of the previous segment will make apparent that both Grignard addition steps result in products containing a stereogenic center. While it is true that in the first case, 3-hexanol, the stereogenicity then is lost during the subsequent oxidation, in the final product, 3-methyl-3-hexanol, the stereogenic center remains. In the absence of a controlling chiral influence we must expect, and indeed we find, that the achiral reagent methylmagnesium bromide cannot discriminate between the enantiomorphous faces, Re and Si, of 3-hexanone, so that a racemic mixture of the enantiomers of 3-methyl-3-hexanol is the result:



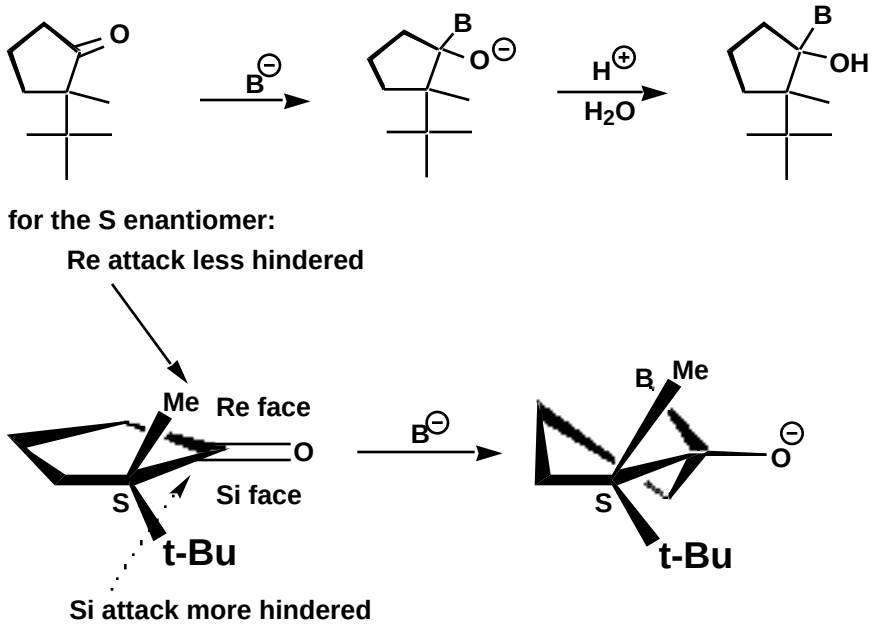


the achiral reagent methylmagnesium bromide does not discriminate between the enantiomorphous faces of 3-hexanone, producing both enantiomers of 3-methyl-3-hexanol in equal amount

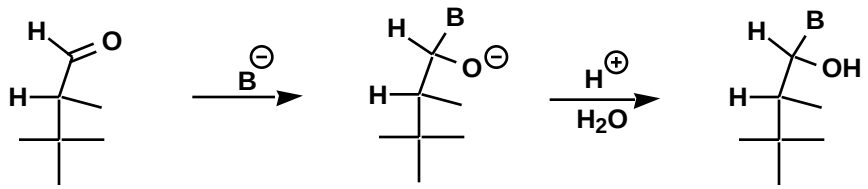
At the same time, we must recall the enzymatic result of Segment 6.07, and we must realize that in principle, given the involvement of a suitable chiral reagent, an

enantioselective synthesis of either R- or S-3-methyl-3-hexanol should be attainable. In experimental practice, in cases similar to this particular one, it has been possible to generate enantiomeric excesses of one enantiomer or the other on a case-by-case basis. However, a practical, widely applicable stereospecific (enantiospecific) general chemical method for producing a single enantiomer in uniformly high enantiomeric excess is not yet available, as of this writing. Such a method must be capable of delivering an achiral grouping mediated by (one enantiomer of) a chiral reagent, as we shall discuss below in somewhat greater detail.

It is well to bring up here a related circumstance. When two approaches of a reagent to a substrate will result in diastereoisomers, then in principle diastereoselective partitioning of the reaction products always must occur, because in principle the energies of the transition states leading to the diastereoisomeric products always must differ. In the case depicted in the following figure the carbonyl group has diastereomorphous faces, as a result of the presence of an adjacent stereogenic center having a single absolute sense of chirality. We are dealing only with the S enantiomer. Given the rather rigid cyclopentane ring, and the relative bulk of a t-butyl as opposed to a methyl group, stereoinduction of the reaction in the single (Re) sense shown can be expected. Note that this is a *diastereoselective* reaction. In the product the original S center remains, and a new center is favored in one sense of chirality over the other (we do not give a C-I-P specification, because we do not specify the attacking base).

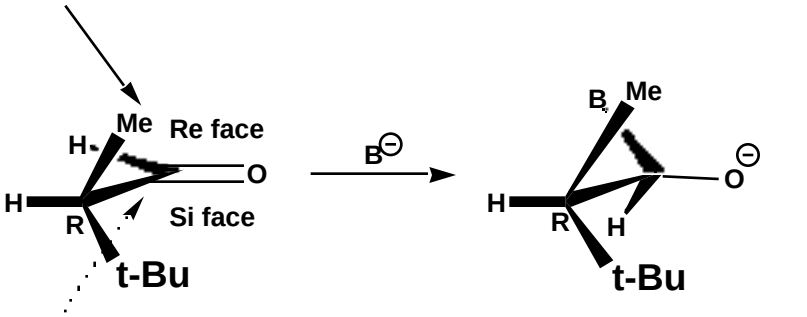


In a related second example (next figure) the matter is somewhat complicated by the fact that there is more conformational mobility, but the principle is identical. The conformation shown is the most favorable one for the reaction, and again the Re attack is favored sterically for the comparable absolute configuration of the fixed center (R in this case because the C-I-P ranking of the groups changes when H replaces C in going from the first to the second example). Clearly, in each case the result will be reversed for the enantiomeric starting material.



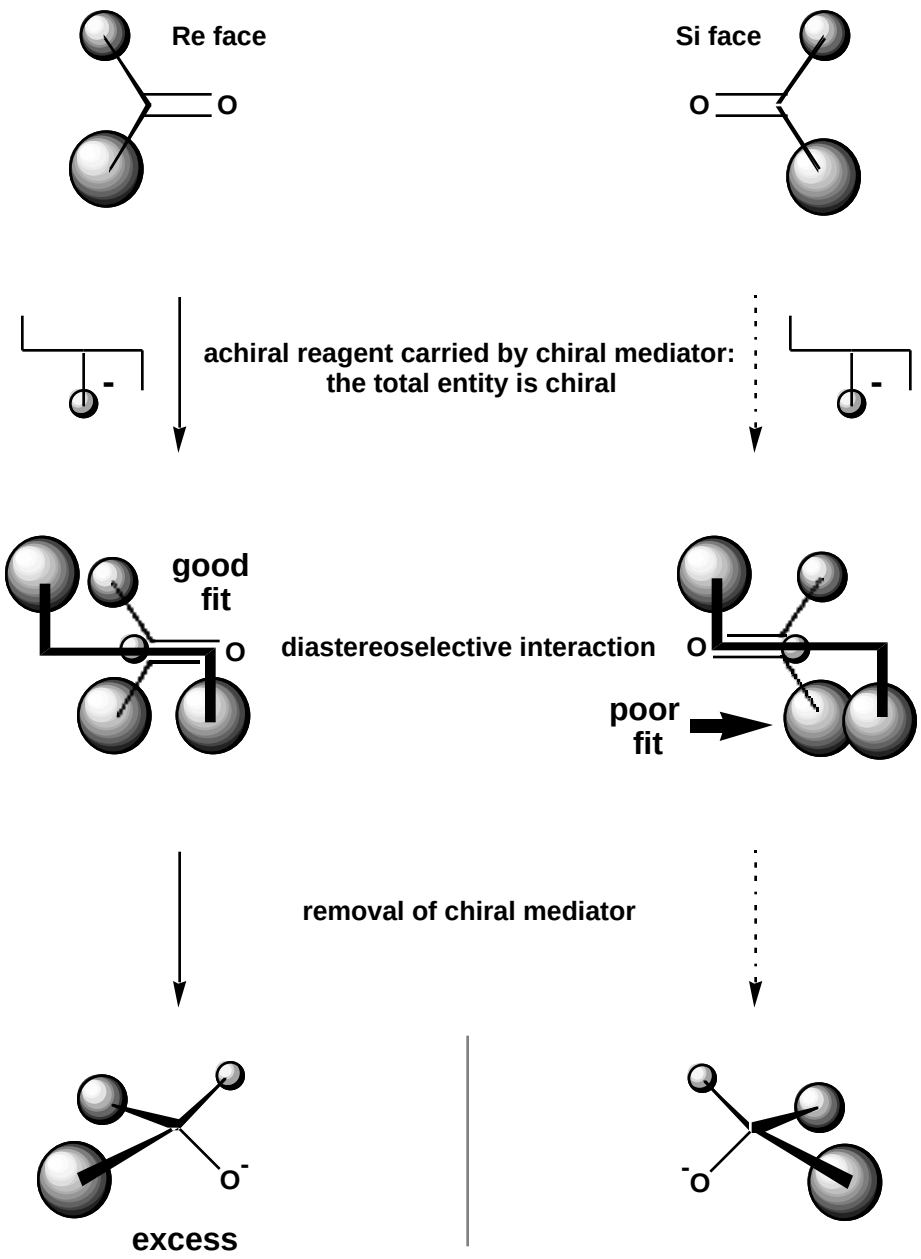
for the R enantiomer:

most favorable transition state conformation favors Re attack



Si attack more hindered

In concluding these words concerning stereoselection, it should be emphasized that in order to carry out the several *enantioselective* transformations to which we have alluded previously (see, for example, Segment 12.06), it is, in fact, always necessary to convert an enantiomorphous relationship into a diastereomorphous one, so that one may achieve an energy difference between two transition states, and hence a partitioning of the populations of the products. This is precisely what occurs when a chiral reagent is used to control the addition of an achiral grouping to the enantiomorphous faces of a substrate. A cartoon of this idea is offered in the final figure. A single enantiomer of the chiral reagent must be used. Its relationship with the enantiomorphous faces of the substrate will be diastereomorphous; energetic partitioning then can occur. Note that, in principle, an energy difference between the two transition states of "only" 4.2 kcal/mole should suffice for a one-thousand-to-one partitioning! Finally, if the mediating chiral reagent is removed at the conclusion of the reaction, an enantiomeric excess of one product remains: an enantioselective reaction has been achieved as a result of the mediation of a diastereoselective interaction:



principle of enantioselective reaction

It will be clear that in the foregoing discussion we have not concerned ourselves with what may be called the chemical technology of stereoselective reactions, now a vast domain, but rather with underlying principles. In general, while it often is not so difficult to observe small diastereoisomeric or enantiomeric excesses

in such reactions, it is nevertheless true that the achievement of high enantioselectivities is by no means a trivial undertaking, and until now has tended to require the development of specialized conditions which frequently must be varied considerably from case to case. Doubtless, very significant progress in this area will continue to be made in the near future.