ORGANIC CHEMISTRY

Synthesis with a strong hand

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NINETEEN ninety one has opened with a rash of reports[1–4] of new procedures for catalytic asymmetric synthesis. Together they show that organic chemistry is moving closer to one of its principal goals — the ability to make new carbon–carbon bonds with complete control of three-dimensional structure under very mild conditions.

Saturated carbon atoms, which constitute the backbone of most organic compounds, are connected to their neighbours through a tetrahedral arrangement of bonds. If the four bonds are to different groups, that carbon atom provides an asymmetric centre and can exist in two mirror-image forms, termed enantiomers. In most syntheses it is crucial to produce the correct enantiomer, because the wrong one will have quite different biological properties; furthermore, a molecule with more than one asymmetric centre will exist as different stereoisomers which have different physical properties. Thus controlled asymmetric synthesis is central to the aim of creating three-dimensional structures.

Tetrahedral centres are most frequently synthesized from trigonal precursors, as the example in Fig. 1 demonstrates. The problem is to discriminate between attack at the upper and lower faces of the carbonyl group, as drawn. In the natural world, this is effected by the asymmetric environment of an enzyme active site which binds the complete molecule in such a way as to ensure that the reagent can only approach from one face. The chemist cannot (yet) design reagents which can bind so selectively and comprehensively to their reactants and so uses the more limited device of specific binding of the reagent at the reaction centre.

To make a further comparison with the natural world, enzymes act in a highly catalytic manner, one molecule of enzyme turning over thousands of molecules of reactant. Traditional chemical reagents generally react on a one-to-one basis, but efficient catalytic asymmetric syntheses, as powerful as enzymes, are being discovered on an almost weekly basis.

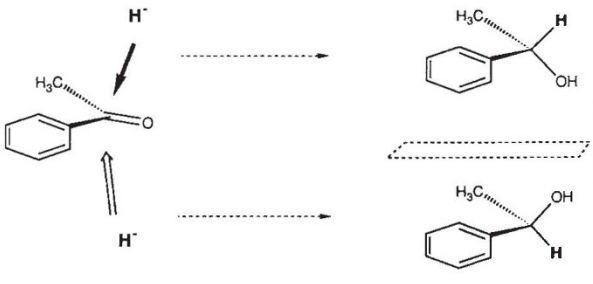

FIG. 1 Making a new asymmetric centre by addition to a double bond.

One of the highlights among the recent reports comes from Schmidt and Seebach[1], who have found an interesting new catalyst for the transfer of an ethyl group from diethyl zinc to aldehydes. This is a well-established

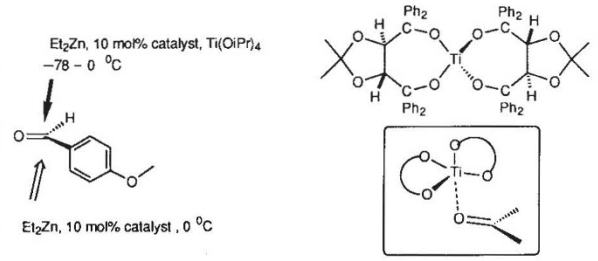

FIG. 2 Titanium complexes for control of the chirality of diethylzinc addition to carbonyl compounds.

asymmetric synthesis, which has been known since the mid-1980s and was broadly discussed in an earlier *Nature* article[5]. The new contribution demonstrates that the novel titanium complex shown in Fig. 2 is an effective catalyst for the reaction. The acidic titanium centre is necessary since it binds to the carbonyl oxygen of the aldehyde and enhances its reactivity. The rigid molecular framework of the titanium complex, with its strongly twisted conformation, acts as a chiral assembly wherein one face of the carbonyl group is accessible to the alkylzinc reagent, and the other is inaccessible. Under the conditions quoted, 91 per cent of one enantiomer and 9 per cent of its mirror-image isomer are produced in a reaction which is catalytic in titanium, representing a satisfactory, but not spectacular, asymmetric synthesis. At rather higher concentrations of catalyst, the selectivity is better.

Apart from further studies which should permit a detailed molecular description of the geometry of the reacting complex, that would be the end of the matter. But further experimentation provides startling complications. When a stoichiometric amount of a simple titanium complex, $Ti(OiPr)_4$, is added at very low temperature with the catalyst and aldehyde, and allowed to warm up slowly to room temperature, then 99 per cent of one enantiomer is produced, but it is the opposite enantiomer to the one seen in the earlier experiment — so both hands of product can be prepared using a single hand of catalyst. Obviously the second titanium complex is associating with the aldehyde, the chiral catalyst or both in some as yet unspecified way. This enticing but infuriating observation demonstrates the central feature of much current work — it is possible to make startling discoveries but our depth of understanding of them is insufficient to provide real predictive power.

Another set of results is more encouraging to those who need less complicated successes. The attractiveness of particular catalysts is enhanced if they are both efficient and readily available, and on this basis the semicorrins of Fig. 3 are very hard to beat. They are easily prepared from chiral amino-alcohols (ex amino acids), and since the first applications to asymmetric synthesis by Pfaltz and colleagues[2] they have rapidly gained in popularity. Two Harvard groups have now made fresh advances. From Evans's laboratory[3] has come the best current method for catalytic asymmetric synthesis of cyclopropanes, a process central to the preparation of environmentally friendly chrysanthemic acid-based insecticides. And Corey and coworkers[4] have demonstrated that iron–semicorrin complexes are good catalysts for the asymmetric Diels–Alder reaction, the most useful synthetic method for construction of polycyclic compounds. Making the reaction both asymmetric and catalytic is a considerable challenge, and

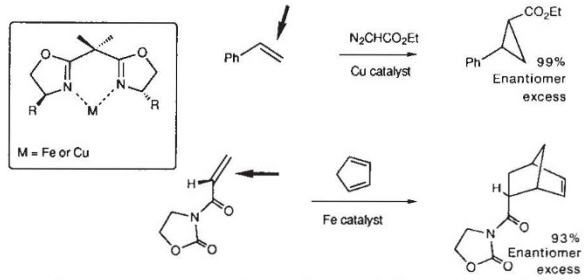

FIG. 3 Semicorrin complexes for catalytic asymmetric synthesis which enable face-specific addition to double bonds.

this paper demonstrates one of the better recent examples of how to achieve it.

In both of these catalytic reactions the excess of the desired enantiomer is high — over 99 per cent for some cyclopropanations and 93 per cent for the Diels–Alder reaction. These values are far removed from what was the norm a few years ago. The classic texts on asymmetric synthesis[6,7] tell us that enantiomeric excesses of 20–40 per cent in stoichiometric reactions were commonly acceptable, whereas we now have the prospect of complete optical purity (100 per cent enantiomeric excess), obtained through efficient catalytic reactions, within sight. □

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