

INORGANIC "ENZYMES"? TRANSITION METAL ATOMS AS ASSEMBLY AND CONTROL CENTRES IN ORGANIC SYNTHESIS*

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EVERY synthetic organic chemist is struck by the contrast between the subtle and efficient assembly and activation conferred by enzymes and the often rather clumsy and inefficient laboratory processes. It is possible to derive methods to exercise the kind of control of individual molecules, present in biological systems, in the laboratory? Any detailed imitation is difficult, since enzymes work by using macromolecular cavities to surround, to place, and to activate appropriately the reacting entities employing primary and secondary bondings. To "engineer" such cavities is a more difficult task than to synthesise the molecules; otherwise much the same results, but by the inverse method of specific assembly around a centre instead, of inside a cavity, can be achieved by the use of transition metal atoms with appropriate ligands.

Classical organic synthesis requires the formation of new bonds, between molecules and inside molecules, and the setting up of the desired substituents and positions of unsaturation. This is achieved by the use in the skeleton (endogenous activation and control) of appropriate functional groups which can react with each other to form the new bonds. Such functional groups are similar to those required as the final substituents. In planning a synthesis the junction processes are dominant, and the necessary reactivities represented by the required functional groups leave structural remnants in the skeleton which may or may not be the substituents needed in the final product. Usually they have to be modified

for this purpose, requiring often many additional stages, each representing reverse compound interest in overall yields. Some lateral control, of stereochemistry and reactivity is exercised, based on the non-classical principles of conformational analyses, but is seldom complete and often requires the setting up of structures, such as rings, which require eventually to be broken. The advent of use of elements like B, Si, and P is notably assisting this approach, but the control still has to be exercised through the skeleton, and leaves remnants, often undesirable, within it. Chemists find this a challenge, but the subject is really not an intellectual game, but a practical set of procedures to produce rapidly and efficiently the derived products.

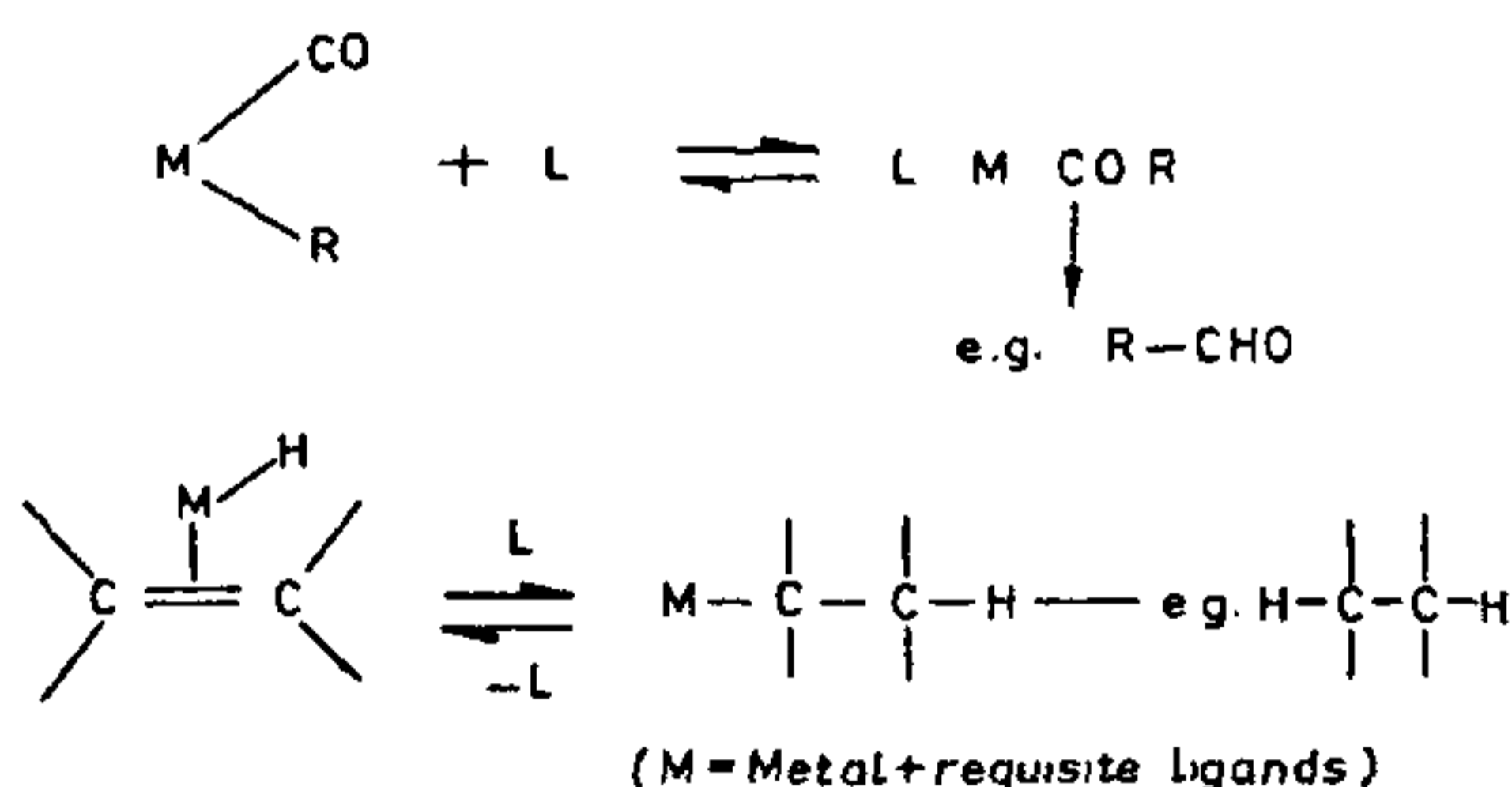
The ideal situation would be to superimpose lateral control by fixing to the side of a molecule, a group which can control reactivity and stereochemistry (including chirality); the group can readily be added and removed, and leaves structural remnants which can readily be dealt with (such as unsaturation). In short, the erection of a sort of removable scaffolding, or using a jig or template. Some surface catalytic methods in fact do this in part, but are usually at present not sufficiently predictable, controllable and specific.

An alternative method which can in principle be rationally and predictably used for lateral control, after sufficient basic investigations of the type we have been carrying out for about 17 years¹, is the employment of transition metal atoms as assembly and control centres. This may well be combined with surface catalysis techniques.

*Summary of the Robert Robinson Lecture of the Royal Society of Chemistry, U.K., delivered in Bangalore on 8 December 1981.

Why use transition metals? The basic reason is the ability of the d -orbitals to become involved in geometrically defined bonding of a number of ligands, including π -bonding with olefins with back-donation to the olefin π -orbital. The metal atoms are therefore electronically amphoteric, according to demand in reaction, unlike the main group metals which are purely cationoid, and also hold groups firmly in fixed geometrical situations.

This helps to meet in two ways, the desired synthetic requirements. One involves the ability of cis-attached groups to bond with each other ("inversion" processes) involving, for example, the formation of new C-C or C-H. The π -bonded olefins are effectively and directly functionalised in this way because of the ability of alternation with σ -bonded systems involving loss or gain of ligands through 14 or 16 electron systems (the coordinatively saturated metal normally has 18 electrons). Examples are:



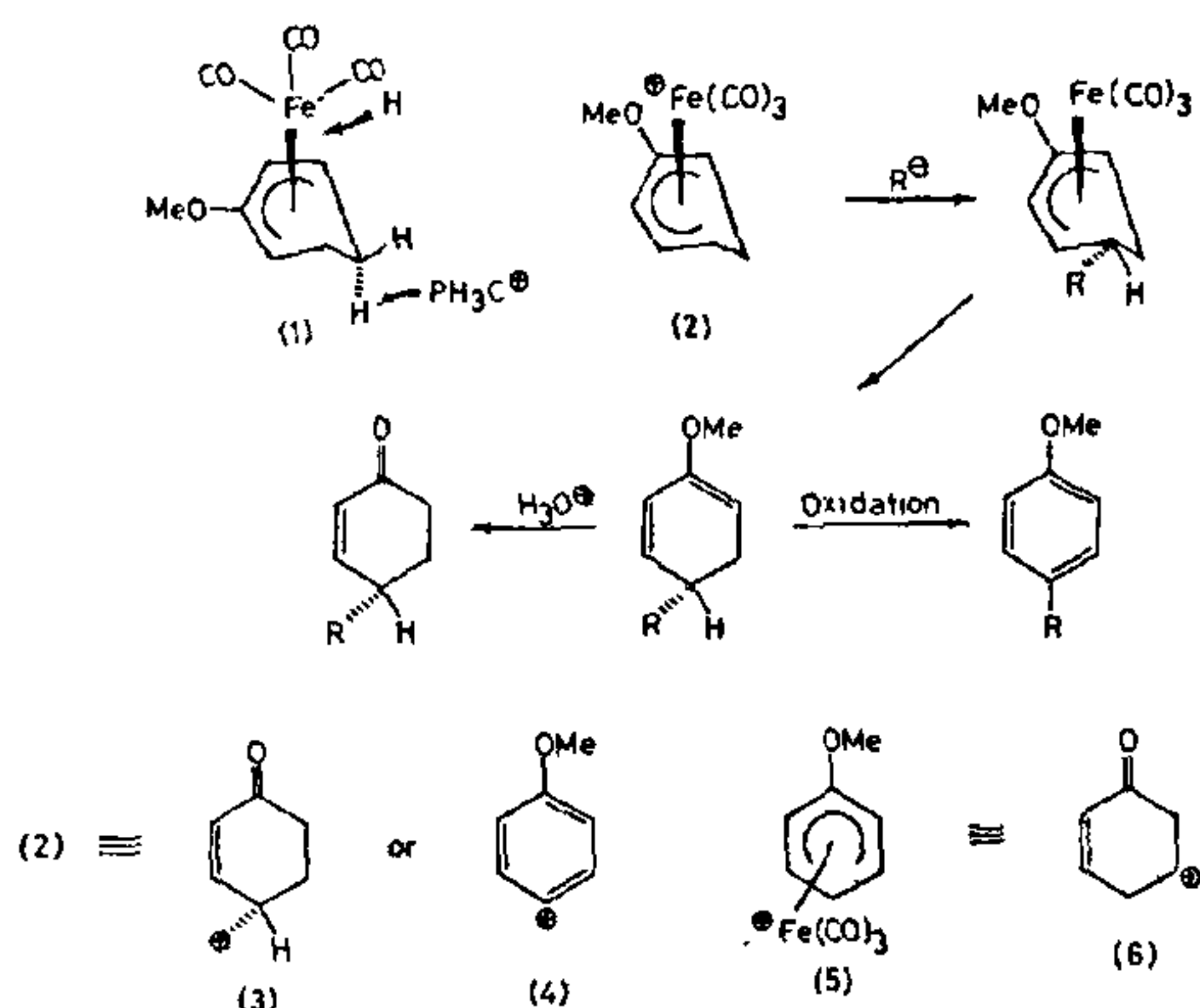
Many processes are reversible. Most known catalytic processes are of these types.

The other use depends on the geometrical fixation of a molecule or part of a molecule by π -bonding with lateral attachment, and then reaction of this with another molecule or a reactive part of the same molecule. An important point to note is that any unsymmetrical olefin is prochiral to complexation because the metal and its attached ligands are placed more or less vertically with regard to the plane of the olefinic system. This confers at least a partial ability to handle prochiral molecules chirally, as do enzymes.

The result of such metal attachments is that bond-forming activations, steric and chiral control are conferred, rather independently of the classical substitution of the organic system. Substitution can then be more freely chosen in the starting-materials and intermediates, to be of types leading to that derived in the product, rather than that needed to form bonds. Of course substitution is still important in deciding regiospecificity of reactions, as we shall note, and the approach has its own restrictions, but these are at least different from the classical ones.

We illustrate some aspects of control of reactions with molecules from our own work in tricarbonylcyclohexa-1,3-dieneiron derivatives, chosen because they are easily and cheaply prepared, mostly starting from the Birch reduction products of benzenes.

The uncharged complex (1) has one face of the molecule totally distinguished from the other, reactions either take place entirely on the occupied face (e.g. addition of a proton) or the opposite face (e.g. removal of hydride by trityl cation). The cation (2) reacts with a nucleophile at one or other end of the 5-carbon system linked to Fe, as directed by an unsymmetrically placed substituent, e.g. 2-OMe as here directs to the 5-position. Attack is totally stereospecific from the side opposite to the Fe, and if the cation is chiral, the new centre is fully resolved and of known absolute configuration in relation to that of the cation. Removal of $\text{Fe}(\text{CO})_3$ from the uncharged product (e.g. with Me_3NO) then leaves a fully resolved organic product. Further sequences of reactions then lead to the synthetic organic equivalents (3) and (4), the former with the relative configuration shown. The 3-OMe cation (5) is equivalent to (6), as another example. The range of nucleophiles comprises HXR (X-O, N, S, /se, P etc.), carbon nucleophiles including enolates of carbonyls, aromatic rings with activating structures (furans, indoles, phenol ethers etc.) and yields are



good.

In the full account the present author² discusses methods of preparation, reactions and many other synthetic equivalents. It is also emphasised that this is merely one example of the approach; there are many other transition metals with different properties (including cuprous derivatives which the present author was the first to employ for synthetic purposes) many other ligands, and many other types of

unsaturated system employable. The structural remnant of the approach is unsaturation, which is either useful, or readily dealt with.

Work by Vollhardt on assembly processes, Semmelhack on complexed aromatic systems, Trost on the steric consequences of Pd systems, and Pearson on the developments of the Fe chemistry are examples which can be consulted.

The point of our present discussion is to indicate the overall philosophy of the approach, and the ways of regarding it as equivalent to enzyme capabilities. Indeed, it is the author's opinion that life itself might have started with specific transition metal complexes, possibly attached to surfaces, the units being small, and statistically capable of accidental formation in resolved forms. The essential feature of self-reproducibility is however difficult to formulate in specific molecular terms.

1. Birch, A. J., *et al.*, *Tetrahedron*, 1981, 37, 289.
2. Birch, A. J., *Chem. Soc. Rev.*, 1982 (in press).