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REVIEW ARTICLE

Oxidative phenol coupling: A key step for the biomimetic synthesis of many important natural products

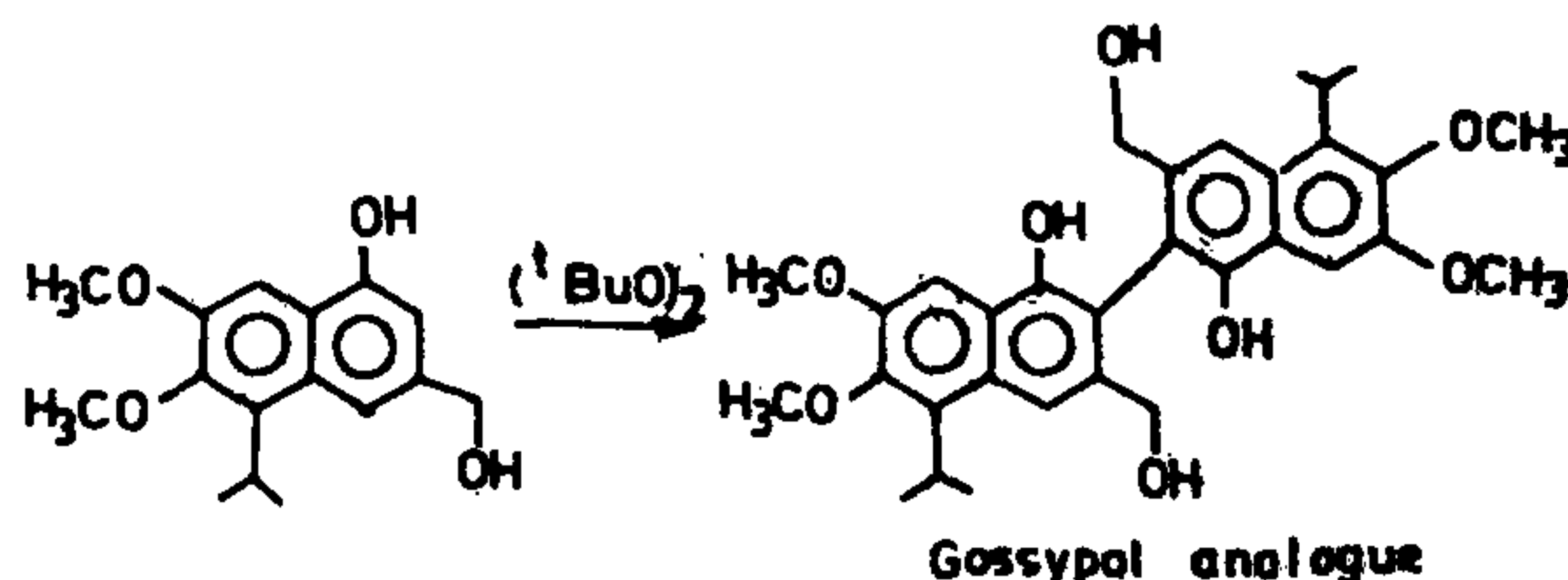
Tarasankar Pal and Anjali Pal

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

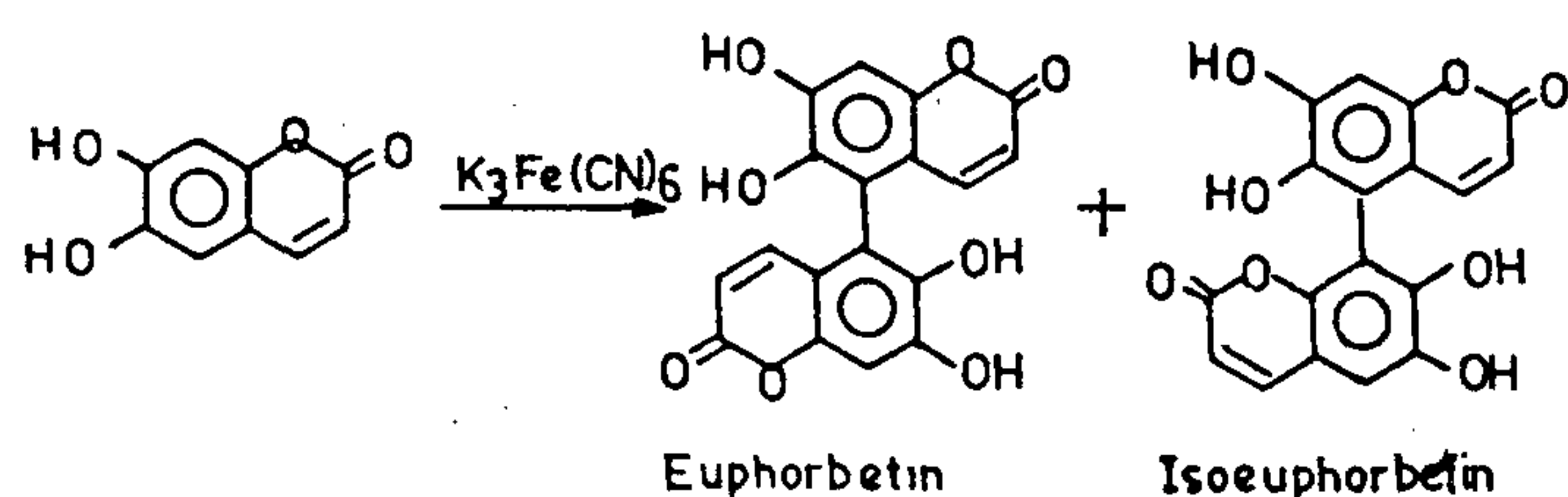
We present here the oxidative phenol coupling (OPC) reaction utilizing various reagents and leading to biomimetic synthesis of many natural polyphenolics.

OXIDATIVE phenol coupling (OPC) reaction incarnates a 'C–C' or 'C–O' bond between phenolic moieties through oxidation as delineated in all the schemes described here. OPC thus becomes a fundamental method for the synthesis of hydroxylated biaryls¹. The reaction has previously been of little significance and synthetic value because it could not be controlled to the desired step. Unwanted side products were also formed if the aromatic substrate had several sterically or electronically comparable positions. But, later, it gained tremendous attention with the discovery of a prodigious number of natural products such as lignans,² xanthenes³ and a wide variety of tetrahydroisoquinoline alkaloids⁴, which had been assumed^{5–7} and later confirmed to be biosynthesized involving OPC of appropriate precursors. This reaction thus gained a new dimension by

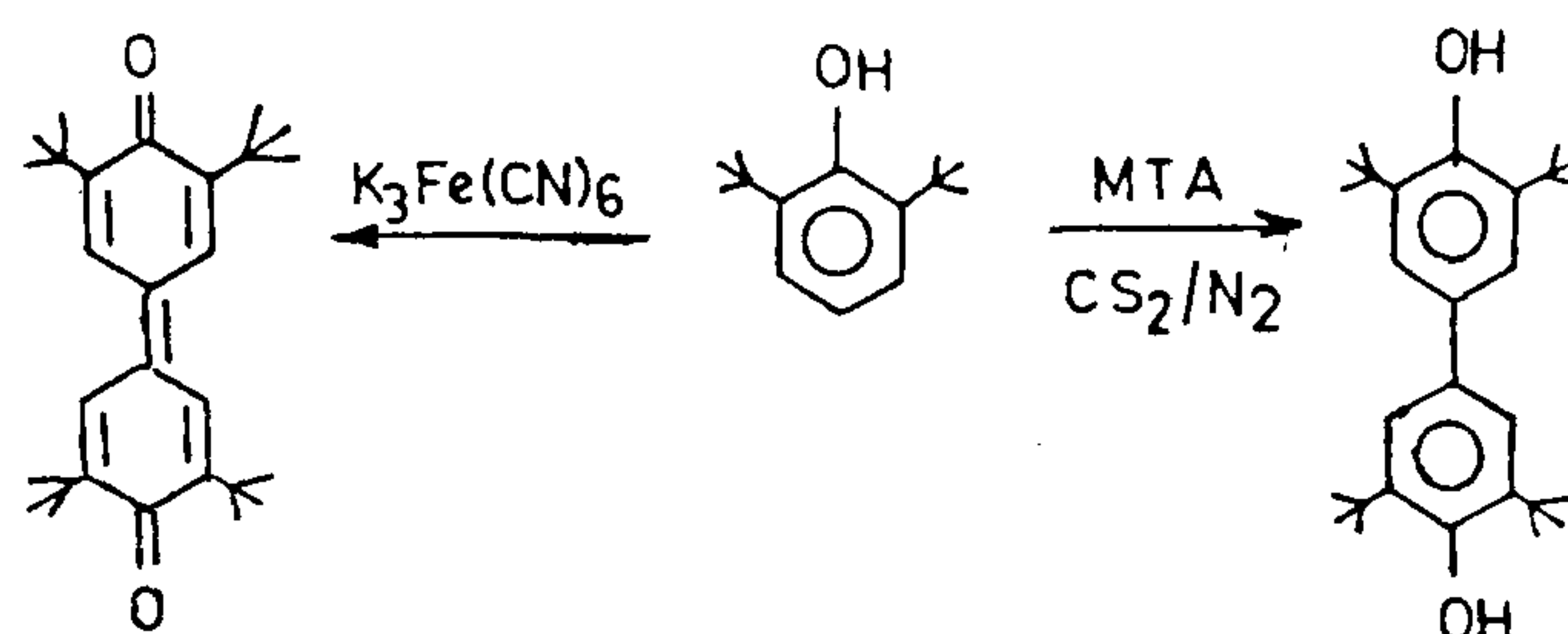
providing an excellent laboratory method for mimicking certain biosynthetic steps. This has initiated extensive studies on the reaction on a wide variety of phenolic compounds, leading to the successful biomimetic synthesis of many natural products, viz. gossypol analogue,⁸ a well-known male antifertility agent (Scheme 1); euphorbetin and isoeuphorbetin⁹, two coumarin dimers (Scheme 2); several alkaloids¹⁰; dimers



Scheme 1.



Scheme 2.



Scheme 3.

of hydroxylated phenanthrenes and dihydro phenanthrenes¹¹, constituents of high altitude Himalayan orchids; polyhydroxy flavones¹²; lignans¹³; xanthenes¹⁴ and many more compounds. The importance of the reaction is also clear in the light of different medicinal and biological utility of many coupled products. Among these properties are antitumour-anticancer activity, hormonal characteristics, colouring properties, and drug activity. Often attempts to duplicate a natural product lead to the formation of another isomer¹⁵ not occurring in nature. With time, extensive diversification of the OPC reaction has grown with respect to variations in the phenolic and related substrates as well as through the availability of newer oxidizing agents and optimization of the reaction conditions. Achievement of regiospecificity and stopping the reaction at the desired stage is now possible in many cases.

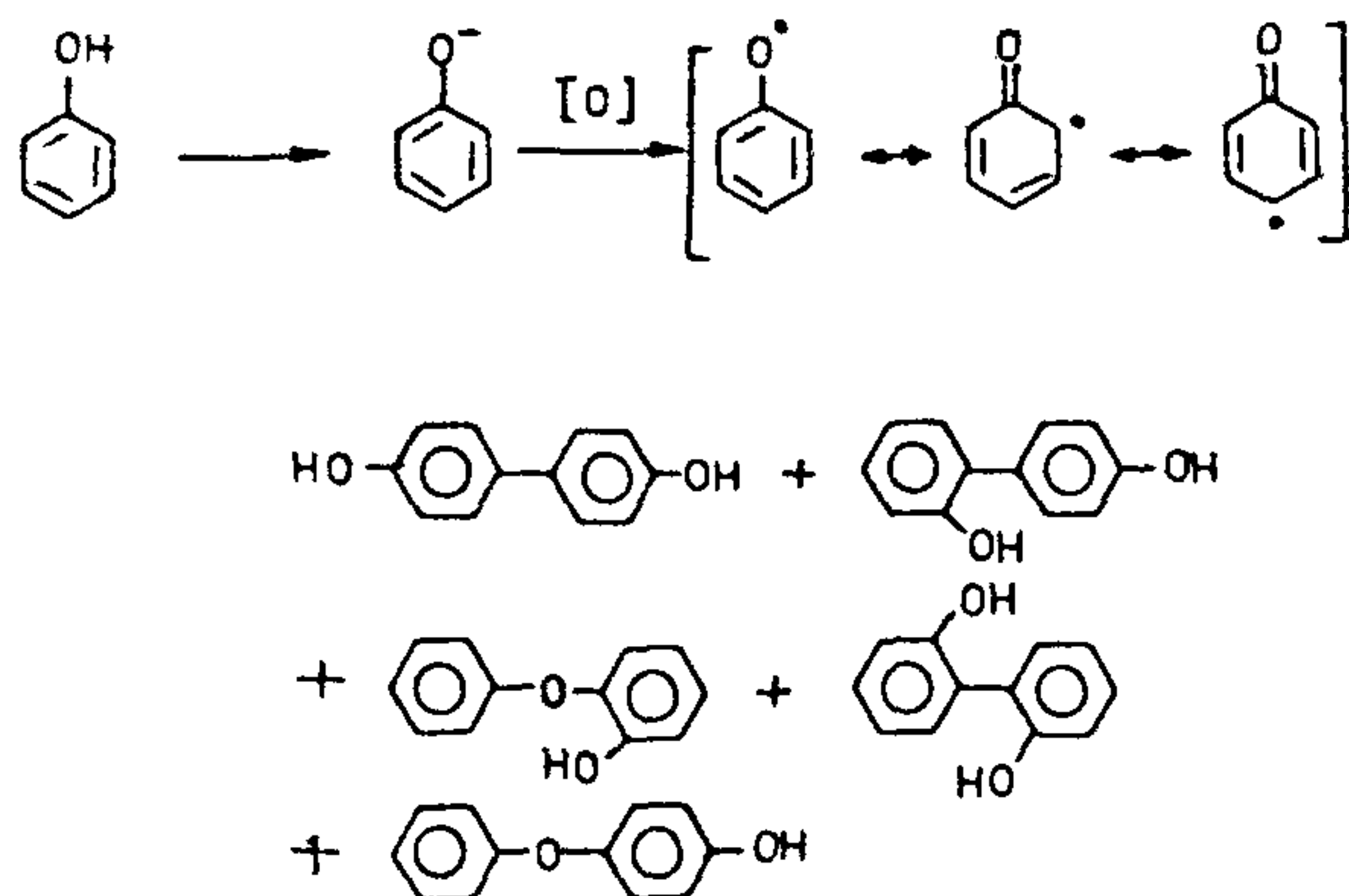
Reagents of both inorganic and organic origin such as $FeCl_3$ (ref. 16), $K_3Fe(CN)_6$ (ref. 17), $AgOH$ (ref. 18), $K_2Cr_2O_7$ (ref. 19), $KMnO_4$ and K_2MnO_4 (ref. 20), iodobenzene diacetate²¹, active MnO_2 (ref. 22), manganese tris acetylacetonate (MTA)²³, tert-butyl peroxide, isoamyl nitrite²⁴, $O_2/NaOH$ (ref. 18), RuO_2 (ref. 25) and enzymes²⁶ have been used for this purpose. Irradiation by ultrasound in the presence of an oxidizing agent²⁷ has also been an efficient method for product formation. Solid-supported reagents such as Ag_2CO_3 on celite²⁸, $FeCl_3$ bound to SiO_2 (ref. 29), phosphomolybdic acid adsorbed on silica gel¹¹ also proved to be efficient reagents for the phenol coupling process. These special types of reagents are responsible for easier handling, separation procedures and higher efficiency. Anodic oxidations and oxidation via photochemical radical generation³⁰ are also viable methods for the OPC reaction. However, anodic oxidation may lead to solvent incorporation³¹, and with MTA, abnormal products may result³². Use of $AgNO_3$ (ref. 33) and chromyl chloride³⁴ may cause nitro and chloride group insertion. Sometimes the OPC reaction causes formation of phenyl ethers³⁵. Sometimes an attack at the benzylic position competes with the desired coupling process. Also, sometimes, OPC reaction results in quinones³⁶ or coupled quinone³⁷. A general theory has not been set up governing the formation of product; but variation of reagent and condi-

tion may lead to different products (Scheme 3) and sometimes isolated examples appear in the literature showing excellent yield. Reaction with another class of reagents including VOF_3 , $VOCl_3$, VCl_4 , thallium(III) tris trifluoroacetate (TTFA) may result in a 'non-phenolic' dehydrodimerization of electron-rich aromatic compounds³⁸.

An examination of the standard reduction potential (E^0) values for most of the reagents suggests that a reagent with lower E^0 value would behave in a milder way and cause less polymerization. This has been accomplished using Ag-gelatin complex³⁹, a weaker oxidizing agent than $AgOH$ or $AgNO_3$. Based on the E^0 values, uranyl(VI), rhodium(III), platinum(IV), and $Hg(II)$ complexes would be expected to react similarly as reagents in the OPC reaction. One such observation on the OPC reaction is the coupling of 2,7-dihydroxy naphthalene by HgO (ref. 40).

Radical-initiated OPC to form polycyclic dimers and trimers has been observed using natural montmorillonite and smectic clays⁴¹ with favoured regio- and stereochemical control. The influence of steric, electronic and also hydrophobic character of the substrates has been documented with biocatalyst⁴² in nonaqueous solvent. Even now, newer inorganic reagents^{43,44} are being considered for successful coupling reaction. The underlying but obligatory condition is to impose milder conditions⁴⁵ to warrant better coupling instead of quinone formation. Thus macrocyclic chelates⁴⁶ and catalyst⁴⁷ have been employed. To achieve success, alteration of reaction conditions, purging of oxidizing gas have also been looked into. Stepwise coupling⁴⁸ has recently widened the horizon of OPC reaction to the greatest extent in relation to selectivity, complex-induced proximity effect, regiochemical control and percent yield conversion point of view.

Mechanistically it is believed that the first step in OPC is the generation of a phenoxy radical by the transfer of an electron to the oxidant as evidenced from the e.s.r. studies. The generated phenoxy radical then is thought to undergo a mostly homolytic coupling (Scheme 4). In extreme cases an ionic mechanism may also operate. While this mechanistic aspect has been



Scheme 4.

enlightened, more extensive work is necessary for understanding the precise mechanism of the entire reaction and there is no warranty that all phenol couplings proceed by one and the same mechanism¹.

In view of the many-fold applications of OPC reaction, one may think aloud about constructing bi- and polyaryls in a viable and efficient route. Apart from mimicking nature, this coupling process may be a passport for entering into the world of macrocycles⁴⁸. It is quite probable that this synthetic method may be accomplished by various means and is amply described in literature.

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A symposium on 'High Energy Physics in the 21st Century' was held on 11 November 1995 at the Indira Gandhi Centre for Atomic Research, Kalpakkam as a part of the 61st Annual Meeting of the Indian Academy of Sciences, 10–12 November 1995 at Madras. The four themes of the symposium were: *The Standard Model of High Energy Physics, Theoretical Scenarios for 10^3 GeV to 10^{19} GeV, Hints of New Physics from Cosmology, Astrophysics and Nonaccelerator Experiments, and New Ideas on Acceleration to Planckian Energies.* Talks bearing on these themes were given by D. P. Roy, Romesh Kaul, Ramanath Cowsik and Abhijit Sen respectively. Three of these talks along with an introductory overview (by GR) and a final summary (by RR) which were also given in the Symposium are included in the following collection.

G. Rajasekaran
R. Ramachandran

High Energy Physics in the 21st century – An overview

G. Rajasekaran

Institute of Mathematical Sciences, Madras 600 113, India

AT the beginning of the 20th century, the quest for the understanding of the atom topped the agenda of fundamental physics. This quest successively led to the unravelling of the atomic nucleus and then to the so-called 'elementary' particles – proton, neutron, pion, electron, etc. Particle Physics or High Energy Physics (HEP) made rapid strides in the latter part of this century, especially in the 60s and 70s. These developments culminated in the construction of the gauge theory of quarks and leptons. This theory which goes by the rather prosaic name of 'The Standard Model (SM) of High Energy Physics' was constructed almost in its final form by 1973 and since then it has passed with flying colours all the experimental tests performed in the next 20 years. So, at the end of the century, we now have a highly successful theory which is valid, down to a distance scale of about 10^{-16} cm (8 orders of magnitude smaller than the atomic scale). This theory can now be regarded as *the basis of all of physics except gravity*. This success story is described in the article on page 111 by D. P. Roy.

1900 A.D. —————→ 2000 A.D.
Atoms → Nuclei → Particles → Gauge theory of quarks
and leptons
—————*—————*—————→
 10^{-8} cm 10^{-16} cm

The SM is a theory for all that is known in HEP, namely the weak, electromagnetic and strong interactions of the quarks and leptons. However, this is not the end of the story. There are too many loopholes and unsolved problems within SM: Higgs and symmetry breaking, QCD and confinement, neutrinos, CP and its violation, etc. The solution of these problems may already take us beyond SM.

However, the biggest loophole in SM is the omission of gravitation, the most important force of nature. Hence, it is now recognized that *Quantum Gravity (QG) is the next frontier of HEP*, and that *the true fundamental scale of physics is the Planck energy 10^{19} GeV*, which is the scale of QG.

In quantum mechanics, there is an inverse relationship between the length scale and the energy needed to probe that scale. A few characteristic length and energy scales are given below:

Landmark	Length	Energy
Nuclear physics	10^{-13} cm	200 MeV
Standard model	2×10^{-16} cm	100 GeV
↓	↓	↓
Quantum gravity	2×10^{-33} cm	10^{19} GeV