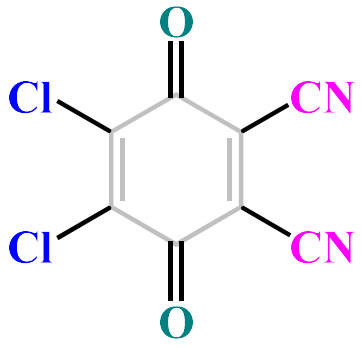
Course Name: Methods in Organic Synthesis
Paper Number: 202
Section: B
Course Instructor: Dr BK Singh
Study Material (Name of Topic/ Chapter): Oxidation / DDQ

Dichloro Dicyano Quinone (DDQ)



By Dr. BK Singh
Department of Chemistry
University of Delhi
Delhi- 110007

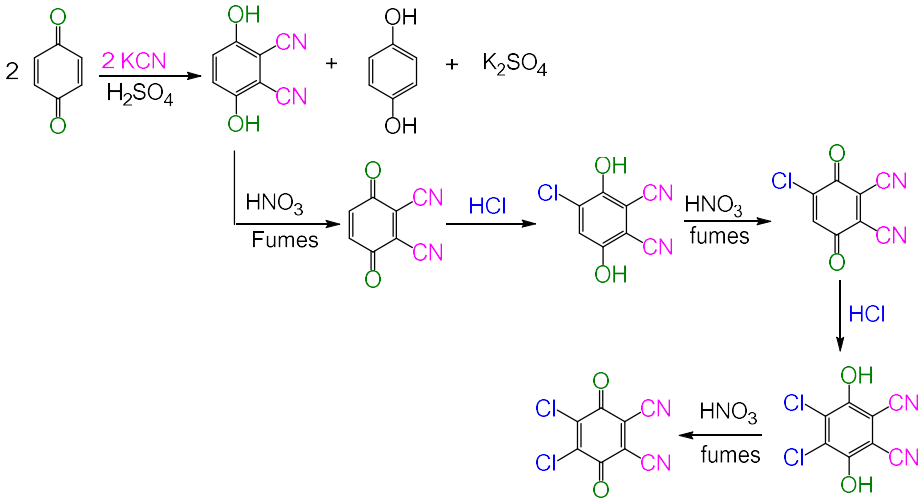
Dichloro Dicyano Quinone (DDQ)

With the considerable development of selective organic chemistry in the last decade, specific reagents have seen their potential increase dramatically. The spectrum of their applications in modern organic chemistry has been enlarged to offer new challenging synthesis opportunities.
Not an exception, DDQ has been investigated as a powerful oxidising agent by several research groups, and was proved to be useful for a wide range of reactions. The fact that DDQ is now industrially produced by the company Simafex, France, makes it a reagent of choice in terms of selectivity and availability, compared to other methods giving similar results.

Although several uses of DDQ have been mentioned in many patents from the pharmaceutical and chemical specialties industries, we will restrict this article to an overview of organic reactions where we trust DDQ has a significant contribution.

Synthesis

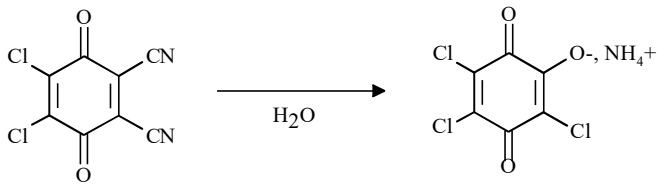
DDQ can be prepared in a six step procedure, involving cyanation and chlorination of benzoquinone (Scheme 1). as described in the litterature[1].



(Scheme 1)

Stability

It is known that DDQ reacts with water (Scheme 2) : hydrolysis of the cyanid-ion may occur after SN2-mechanism, giving a deep-red colour ammonium salt in solution.



(Scheme 2)

Dr. BK SINGH, Department of Chemistry, University of Delhi

Stability is generally increased in acidic conditions, and at low temperatures. DDQ might decompose at temperatures above 200°C, giving HCN vapors .

Toxicity

DDQ is toxic (DL50 oral/rat : 130mg/kg) by ingestion or in contact with eyes. No specific medical problem has been observed for skin contacts

To avoid any HCN fumes or other decomposition by-products, DDQ must be stocked in a cool dried area (See MSDS).

Solubility

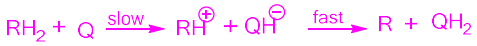
DDQ is proved to be :

- very soluble in THF and ethyl acetate.
- moderately soluble in dichloromethane, toluene, dioxane, and acetic acid.

insoluble in water (but reacts with)

Mechanism

It has been observed that the rate of the reaction with DDQ is accelerated in polar solvents, non affected by radical-producing agents, and catalyzed by proton-donor species. The mecanism is supposed to be bimolecular. In the first rate-determining step, the formation of a charge-transfer complex occurs, according to the following scheme :

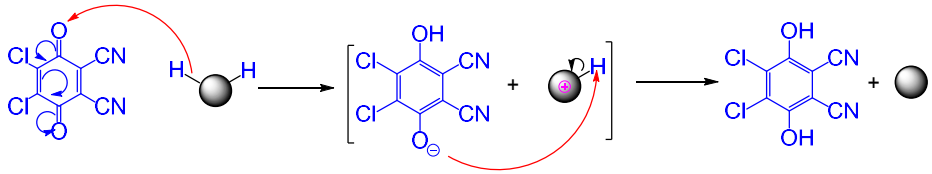


where Q : Quinone, R : reacting species, RH+ : charge-transfer complex From the charge-transfer complex,

two reactions are likely to happen :

- Elimination of a proton to give an insaturation on the molecule
- Wagner-Meerwein type rearrangement prior to the loss of proton may occur in specific cases

❑ A simplified two-step reaction mechanism containing an initial rate-determining transfer of hydride ion followed by a rapid proton transfer leading to hydroquinone formation.



For some other special reactions, a radical mechanism may be involved.

Applications

Here we review the potential applications that have been investigated by several research groups, and described in the literature, some of them having found industrial applications or been patented. They are classified by reaction type.

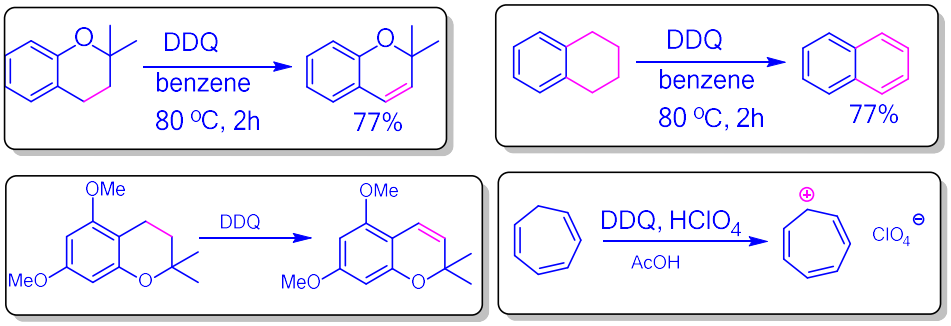
DEHYDROGENATION

Dehydrogenation with DDQ has been reported for steroid ketones, steroid pyrrazoles, heterocyclic compounds, hydroaromatic compounds, steroid lactones, alcohols and phenols.

- *Dehydrogenation of hydrocarbons*

The reaction is based on an initial rate-determining transfer of hydride ion from the hydrocarbon to DDQ,

leading to hydroquinone derivative. The feasibility of the reaction depends upon the degree of stabilization of the transition-state carbocation : it has been observed that the presence of alkenes or aromatic moieties is sufficient to initiate hydrogen transfer in presence of DDQ.
There are various examples for this reaction, such as the synthesis of chromenes starting from chromanes[2] (Scheme 3).

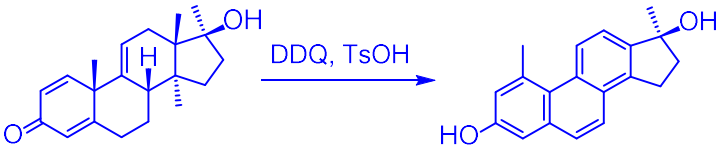


(Scheme 3)

DDQ is commonly used to add an unsaturation on terpenes and steroids.

- **Aromatization**

Aromatization of steroids may occur with a Wagner-Meerwein rearrangement[3] (Scheme 4). It allows to dehydrogenate systems containing quaternary atoms without loss of carbon.

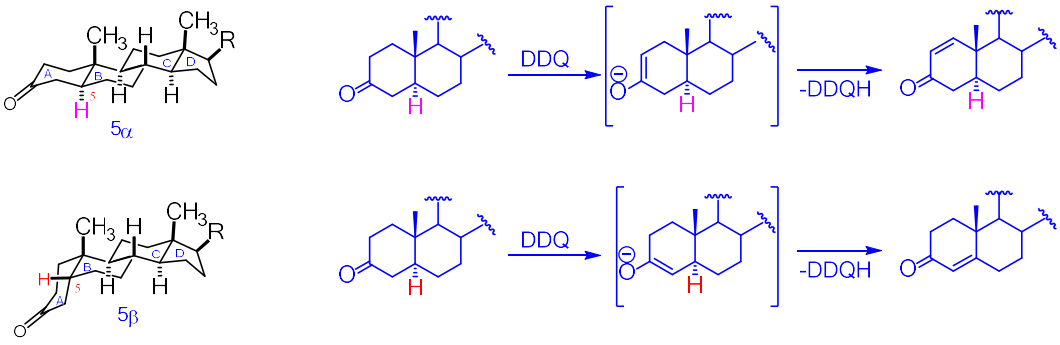


(Scheme 4)

The dehydrogenation of hydroaromatic heterocycles has been also studied : it is a powerful way to rearomatize heterocycles after they were functionalized through a nucleophilic addition.
Such reaction can be applied to the dehydrogenation of porphyrins.

- ***Dehydrogenation of carbonyl compounds and steroids***

DDQ is a versatile reagent in the synthesis of α,β-unsaturated compounds, such as 3-keto-steroïds[4]. As shown in Scheme 5, regioselective dehydrogenation of 3-keto-steroïds depends on the geometry of the molecule at the C-5 atom. The selectivity of one isomer is likely to reflect the relative steric crowding of the C-4 hydrogen atom for the two series.



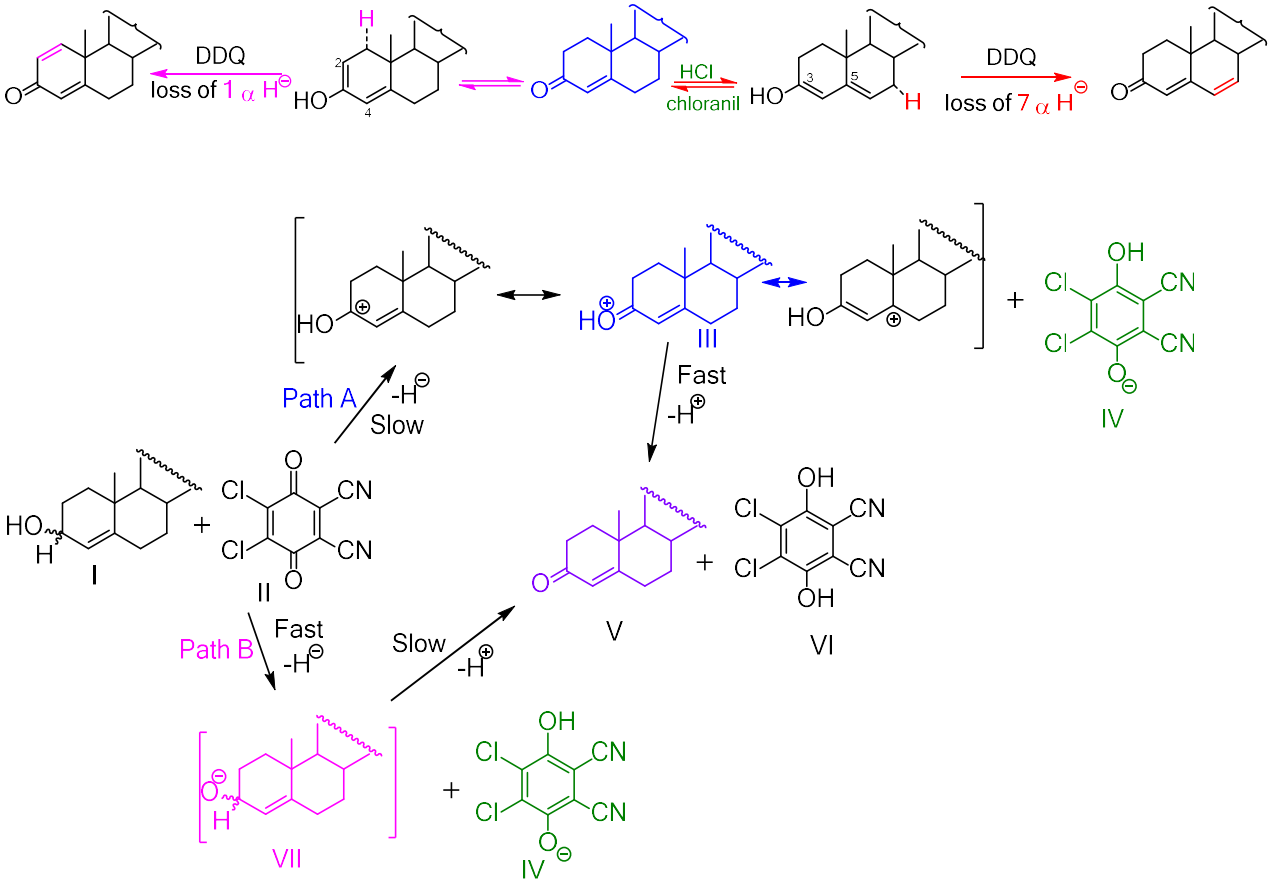
(Scheme 5)

Dehydrogenation of carbonyl compounds was used to prepare heterocyclic enones (flavones, chromones...) from the corresponding flavanones, chromanones...
Dehydrogenation of lactam-steroids has also been studied (Scheme 6), using a silylating agent (for instance, Bis(trimethylsilyl) trifluoroacetamide (BSTFA)) to improve the yield and the selectivity of the reaction.

(Scheme 6)

Extensive work[5] was done in steroid chemistry, a primary application field for dehydrogenation reactions with DDQ. It has been observed that hydride ion is removed from an allylic position on the steroid to give an additional unsaturation.

It is worth pointing out the regioselectivity of DDQ in such dehydrogenations, where for instance, its chemical analogue chloranil does not react on the same position. Using the reagents in two procedures, Δ^4-3-keto-steroïds are converted to $\Delta^{1,4}$-3-keto-steroïds or $\Delta^{4,6}$-3-keto-steroïds (Scheme 7).



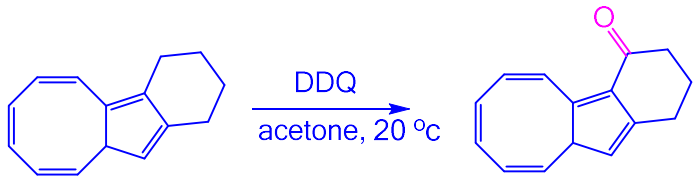
(Scheme 7)

OXIDATION

- *Alcohols*

Saturated alcohols are relatively stable to the the action of DDQ, although some hindered secondary alcohols have been oxidized with reasonable yields[6]. It has been suggested that this oxidation proceeds as a result of relief of steric strain.
On the other hand, DDQ provides a selective method of synthesis for allylic and benzylic carbonyl groups in the presence of other oxidizable groups[7].

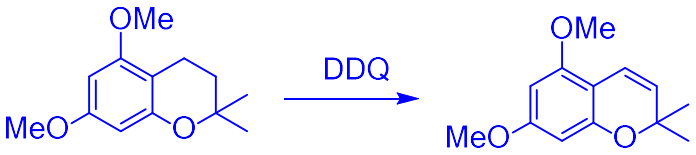
DDQ also affords the oxidation of polycyclic aromatic compounds in acetic acid (Scheme 8). The reaction proceeds via an intermediate benzylic acetate, which is hydrolyzed and then oxidized. It is disfavored by the presence of strongly electron-withdrawing substituents.



(Scheme 8)

- *Oxidative cyclization*

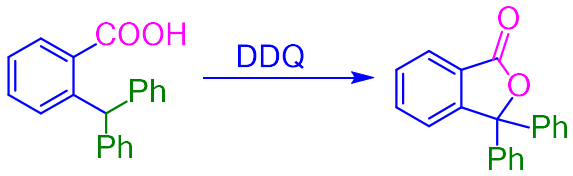
Phenolic compounds may be oxidized by DDQ : the reaction is equivalent to a cyclodehydrogenation to O-heterocycles (Scheme 9). This provides a powerful way of synthesis of various organic compounds such as coumarins, chromenes, benzofurans, spiro-derivatives[8]...



(Scheme 9)

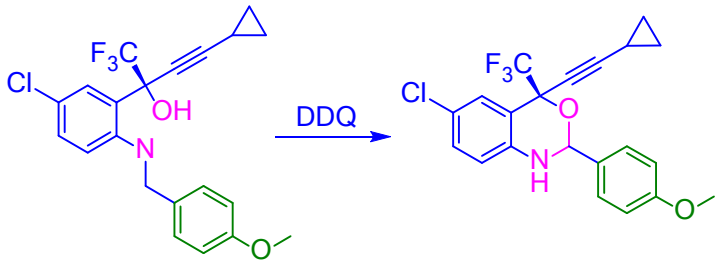
Intermolecular coupling may occur if phenols and enolizable ketones cannot undergo α,β-dehydrogenation. Thus oxidative dimerization has been observed for some starting materials such as 2,6-dimethoxy-phenol[9].

An unusual reaction has been reported by Creighton and Jackman[10], related to oxidative coupling with DDQ (Scheme 10), where the transition-state carbocation is well stabilized by substituents.



(Scheme 10)

In the synthesis of Efavirenz (SUSTIVA™: Anti-HIV) [11] by DuPont Pharm chemists, oxidative cyclization of butynol derivative is performed with DDQ in toluene to give the benzoxazine derivative (Scheme 11).

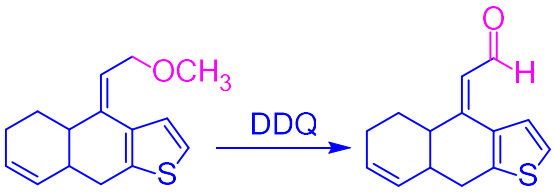


(Scheme 11)

Other similar cyclizations have been studied[12].

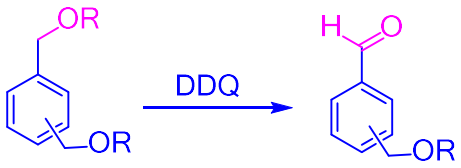
- *Allylic and benzylic ethers*

The conversion of allylic and benzylic ethers to corresponding carbonyl compounds has been studied[13]. The regioselective process can be carried out in mild conditions, affording a selective deprotection method. Oxidation of allylic or benzylic ethers is possible if no electrophilic substituent is present in the conjugated chromophore, and if no available β-hydrogen is present - otherwise a competitive dehydrogenation occurs.



(Scheme 12)

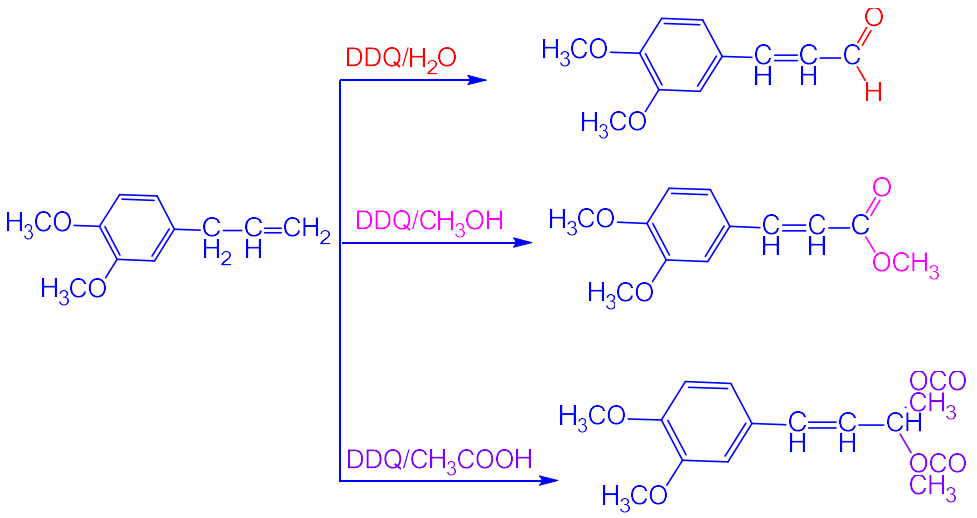
Wang[14] has proved that monooxidation of bis [benzyl-ethers] was possible using DDQ (Scheme 12). This reaction is milder and more selective than Kornblum reaction or MnO_2 oxidation that provide in a similar way the corresponding aldehyde. Regioselectivity depends on the nature of side-groups ; electronic and steric factors are also important for the outcome of this reaction.



(Scheme 13)

- *Aryl-propene double-bond*[15]

Aryl-propene double bond can be oxidized in several products, depending on the experimental conditions. Such a reaction is a powerful tool for the synthesis of cinamaldehydes or cinamic derivatives (Scheme 14).



(Scheme 14)

OXIDATIVE DEPROTECTION

DDQ has been described as a powerful and selective reagent in the deprotection reactions, in several articles and patents.
For instance, Paterson *et al.*[16] have proved that DDQ affords a facile deprotection of electron-rich silyl ethers, together with an oxidation of the resulting alcohol function. Such reaction has found a practical application in the total synthesis of the macrolide aplyronine A, where the double-bonds are retained during the oxidative cleavage of protecting groups.
More generally, this method can be applied to various allyl and silyl ethers where double-bonds have to remain untouched. A typical application could be the total synthesis of complex polyoxygenated natural products.

Mild and selective deprotection could become a strong application of DDQ, since oxidative cleavage of allylic and benzylic ethers is also made possible by analogous methods.

MISCELLANEOUS

DDQ has also been used as a mediator in carbon-carbon bond formation, or as a cyanation agent. We have found a possible application dealing with the regio- and stereoselective cyanation of aromatic steroïds in the 9α- and 12β- position by a DDQ-TMSCN complex[17].

Comparison with other reagents

- *Microbiological methods*

Such method is widely used for the preparation of modified steroïds : hydroxy groups can be regioselectively inserted ; steroïds may be aromatized, or ring D-lactones formed from progesterones ; a Δ^1-double bond can be added in Δ^4-3-ketones or $\Delta^{4,6}$-3-ketones.
The main drawback of this method is that large dilution volumes are required, and enzymes may create handling and stabilization difficulties. Moreover, equipement price is much higher than for classical reactions.

- *Selenium dioxide*

It allows to convert -$COCH_3$ into -COCHO or -$COCH_2OH$ groups, or to oxidize aromatic methyl groups into aldehyde or carboxylic acid groups, olefins into alcohols, aldehydes into carboxylic acids, steroïdal Δ^4-3-ketones into secolactones.
Globally, selenium dioxide is a powerful dehydrogenation agent, but more side reactions are likely to happen than using DDQ. Moreover, it has a propensity to enter into the molecule of the material being dehydrogenated : deselenization must then often be performed. Selenium compounds are dangerous, with a toxicity similar to arsenic compounds.

- *Manganese dioxide*

This mild oxidising agent can be used to oxidize aromatic secondary alcohols into ketones, tertiary amines containing carbonyl groups, allylic methylene groups, or allylic alcohols into unsaturated ketones. The main difficulty is in the workup procedure, since several side reactions are possible due to the possible lack of selectivity of manganese dioxide.

- *Other substituted quinones*

The oxidation power of substituted quinones depends on the nature of substituents : their reduction potential is enhanced by electron-withdrawing groups. DDQ is known as one of the most effective reagent in this family.
We have also reviewed above that DDQ and its competitor Chloranil have in steroïd chemistry different regioselective properties. Thus dehydrogenation would not occur at the same position in the molecule. Moreover, Chloranil is less reactive and may undergo Diels-Alder cyclization.

Conclusion

In view of the previous results that have been reported by several research groups, we might conclude about high selectivity of DDQ in all kinds of organic reactions involving hydride-abstraction giving a partially stabilized transition-state carbocation. DDQ has found a wide number of applications in the steroïd chemistry field, and in the synthesis of complex natural products, where its unique regioselective properties gave excellent results for the preparation of key intermediates.
Although the main reactions seem to be dehydrogenation and oxidation (incl. oxidative coupling reactions), several articles and patents describe DDQ as a powerful and highly selective deprotection agent, that has already practical applications.

We hope new trends in organic chemistry will continue to increase this tendancy, where high selectivity is required to perform competitive synthesis of complex products. We trust that DDQ potential has not been explored yet, in particular when we briefly mention its properties to mediate carbon-carbon bond, or to perform cyanation regio- and stereoselectively.

References

1. *Fieser and Fieser: Reagents for Organic Synthesis* (Wiley), **Vol**. **1**, p.215
2. Ahluwalia, V.K. ; Jolly, R.S. *Synlett*, **1982**, 74
3. Brown, W. ; Turner, A.B. *J.Org.Chem*., **1971**, 2566
4. Buckle, D.R. ; Pinto, I.L. *Contemp. Org. Synth.*, **1991**, 7, 119
5. Walker, D. ; Hiebert, J.D. *Chem.Rev*., **1966**, 153-195
6. Iwamura, J. ; Hirao, N. *Tet.Lett*., **1973**, 2447
7. Burstein, S.H. ; Ringold, H.J. *J.Am.Chem.Soc*., **1964**, 86, 4952
8. Prashant, A. ; Kurpadanam, G.L.D. ; Srimanarayama, G. *BCJ*, **1992**, 65, 1191 / Jain, A.C. ; Khazanchi, R. ; Kumar, A. *BCJ*, **1979**, 52, 1203 / Imafuku, K. ; Fujita, R. *Chem.Express*, **1991**, 6, 323 / Lewis, J.R. ; Paul, J.C. ; *J.Chem.Soc*., **1981**, 770
9. Becker, H.D. *J.Org.Chem*., **1965**, 30, 982-989
10. Creighton, A.M. ; Jackman, L.M. *J.Chem.Soc*., **1960**, 3138
11. Drugs of the Future **1999**, 24 (2), 201-205
12. Brown, R.F. ; Jackman, L.M. *J.Chem.Soc*., **1960**, 3144
13. Lee-Ruff, E. ; Ablenas, F.J. *Can.J.Chem*., **1989**, 67, 699
14. Wang, W. ; Li, T. ; Attardo, G. *J.Org.Chem*., **1997**, 62, 6598-6602
15. Iliefski, T. ; Li, S. ; Lundquist, K. *Tet.Lett*., **1998**, 39, 2413-2416
16. Paterson, I. ; Cowden, C.J. ; Rahn, V.S. ; Woodrow, M.D. *Synlett*, **1998**, 915 17. *Synlett*, **1992**, 10, 821-822

Dr. BK SINGH, Department of Chemistry, University of Delhi