Review Paper

Synthetic and Mechanistic Approach to Reduction of α, β-Unsaturated Ketones via Zinc-mediated Single Electron Transfer (SET) Process: A Preliminary Review

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Abstract
Dissolving metal reductions involving single electron transfer (SET) from metal to carbonyl compounds are unique and furnish wide range of products. In this review reduction of zinc metal to carbonyl functions under different reaction conditions have been re-examined and explicate by SET-mediated pathways. This review attempt to provide a compact discussion of old, never reviewed, almost forgotten and new SET methodologies and mechanisms employed in organic synthesis.

Key words: *Clemmensen reduction, zinc, α ,β-unsaturated ketones*

Introduction

Though most of the organic reactions are known to proceed by two-electron transfer pathways, biological and radical chemistry generally rely on single-electron transfer (SET) process. Radicals can be generated following various methods including the SET. They are highly reactive intermediates and form valuable products. For example, during the last century, massive demand for synthetic rubber needed the replacement of conventional industrial production of polymers by radical polymerization procedure (Walling, C., 1987). Similarly in academia, single electron transfer (SET) reactions initiated many interesting research fields such as electrochemistry, electron transfer catalysis promoted by various metals or organometallics, supramolecular chemistry, conducting organic materials, electron transfer in biological systems etc. Several books and reviews are available covering above mentioned topics individually. A single review published in 2014 provides an exception covering almost all aspects of SET reactions including the mechanisms and the applications of it in organic transformations, material science, supramolecular and polymer synthesis (Zhang, N. et. al., 2014). In this present review I will only emphasize particularly on SET reactions of enone systems assisted by zinc metal at different reaction conditions leading to reduction or reductive dimerization which was not discussed earlier.

Carbon-carbon bond formation is the backbone of organic chemistry. Among the numerous procedures available for C-C bond construction, reductive dimerization of carbonyl compounds by active metals is one of the most suitable routes to synthesize C-C bond. In 1834, Faraday first reported the preparation of organic compounds at electrodes involving single electron transfer (SET) process. The reaction involved a C-C bond formation (Scheme 1) (Faraday, M., 1834).
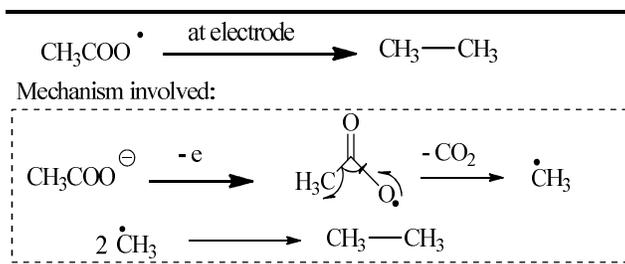
Scheme 1. First SET reaction for formation of ethane

Since then, there have been many applications of SET in organic synthesis by Wurtz (Wurtz, A., 1855), Sandmeyer (Sandmeyer, T., 1884), Barbier (Barbier, P.C.R., 1899), Clemmensen (Clemmensen, E., 1913) and others during last century which are well documented in literature (Zhang, N. et. al., 2014). Among them, Clemmensen reduction is one of the most studied area.
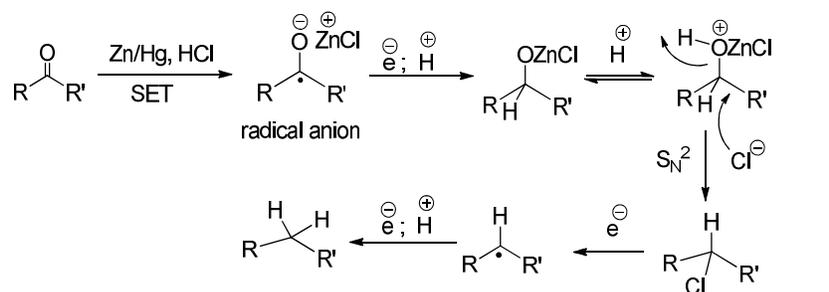
Clemmensen Reduction

Since its discovery in 1913, the Clemmensen reaction (Clemmensen, E., 1913) had found wide applications for the conversion of variety of ketones and aldehydes to the corresponding methylene groups. Usual methodology was to reflux the carbonyl compound for several hours in presence of amalgamated zinc, in non-polar solvents like toluene or ethanol type polar reaction medium, with 40%

aqueous hydrochloric acid when deoxygenation of the carbonyl function was achieved. But, due to the harsh reaction conditions, scope of this reaction with polyfunctional carbonyl compounds was limited.
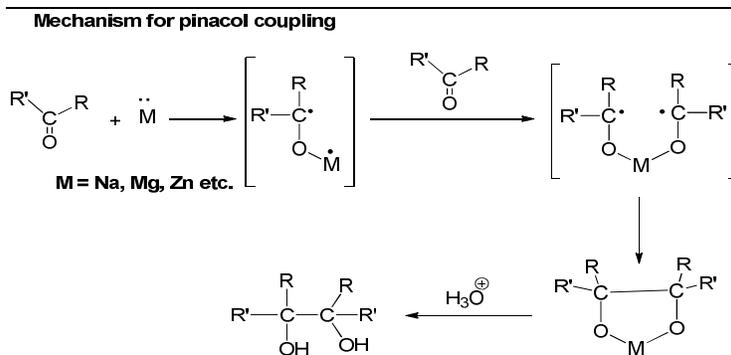
Mechanism
Despite numerous studies so far, little is known about the mechanism of the Clemmensen reaction. Brewster (Brewster, J.H., 1954), Nakabayashi (Nakabayashi, T., 1960, Fürstner, A. et. al., 1988, Schreibmann, A.A.P., 1970, Hekmatshoar, R. et. al., 2001) and other researchers like M. L. Di Vona and V. Rosnati (Di Vona, M.L., Rosnati, V., 1991) had recognized several general characteristics of this reduction reaction suggesting a stepwise mechanism implicating an organo-zinc intermediate. It had been shown that presence of zinc was essential as other metals of comparable reduction potential had evinced poor reactivity. Generally the "radical anion mechanism" engaging a SET process from metal to carbonyl carbon is discussed (Scheme 2).


Scheme 2. Proposed mechanism of Clemmensen reduction

Nakabayashi (Nakabayashi, T., 1960) observed that an electrochemical reduction (pinacol coupling) procedure competed with the Clemmensen reaction, though the two reactions had no common intermediate (Scheme 3). For the pinacol coupling reaction, the first step required one-electron reduction of the carbonyl group by a reducing agent such as Mg (Fürstner, A. et. al., 1988) or Al (Schreibmann, A.A.P., 1970) or Zn (Hekmatshoar, R. et. al., 2001) to a ketyl radical anionic species. Two ketyl groups would participate in a coupling reaction yielding a vicinal diol after acidic work up (Scheme 3).

Scheme 3. Mechanism of pinacol coupling

However, in the year 1986, J. Burdon et. al. had established the formation of a zinc-carbene intermediate during Clemmensen reaction from deuterium labeling experiments as depicted in Scheme 4.
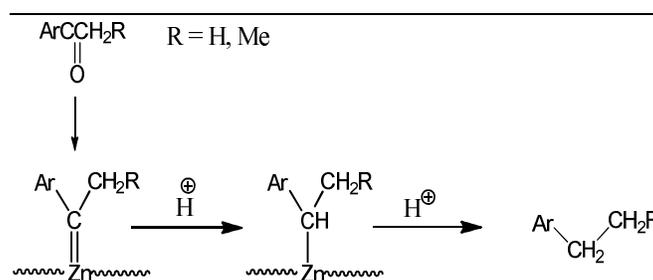

Scheme 4. Clemmensen reduction involving a zinc-carbene intermediate

Scope and limitations
The Clemmensen reduction normally allows the deoxygenation of aldehydes or ketones to produce the corresponding hydrocarbon. However, 1,3- and 1,4-diketones rarely provide usual Clemmensen reduction products. For instance, in case of 1,3-diketones,

intramolecular pinacol coupling to cyclopropanediols **2** was the favored initial product, which subsequently rearranged rapidly to a mixture of α- and β-hydroxyketones (Scheme 5) (Buchanan, J.G.St.C. et. al, 1969).
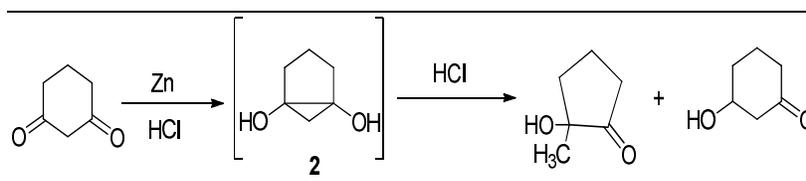
Scheme 5. Clemmensen reduction of 1,3-diketones

The mechanistic pathway was supported by using acetic anhydride as the reaction medium when cyclopropanediol intermediate was trapped as diacetate. As an example for 1,4-diketone, the strained diketone 3 took long reaction hours to undergo internal pinacol coupling leading to cyclobutanediol as shown in Scheme 6 (Wenkert, E. et. al., 1970).
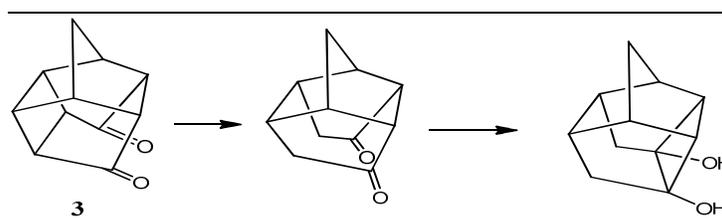
**Scheme 6.** Clemmensen reduction of strained1,4-diketones

Modified Clemmensen reduction of α,β-unsaturated ketones
In case of reduction of α,β-unsaturated ketones, a wide array of products, ranging from corresponding saturated ketone, hydrocarbons and pinacols, are obtained. In addition, reductive dimeric compounds are also isolated due to coupling between the radicals formed on β-carbons (Buchanan, J.G.St.C. et. al., 1969). A review on Clemmensen type reduction of structurally diverse α, β-unsaturated ketones under variety of reaction conditions (Davis, B.R. et. al., 1966) is presented below.

Reduction of 2-arylcyclohex-2-en-one 4, and of arylidene cyclopentanone **5**, with zinc and anhydrous HCl in ether in the presence of acetic anhydride yielded mixture of bicyclic cyclopropanol acetates which rearranged to saturated ketones, 6 and 7 (Scheme 7) (Elphimoff-Felkin, I. et. al., 1975).
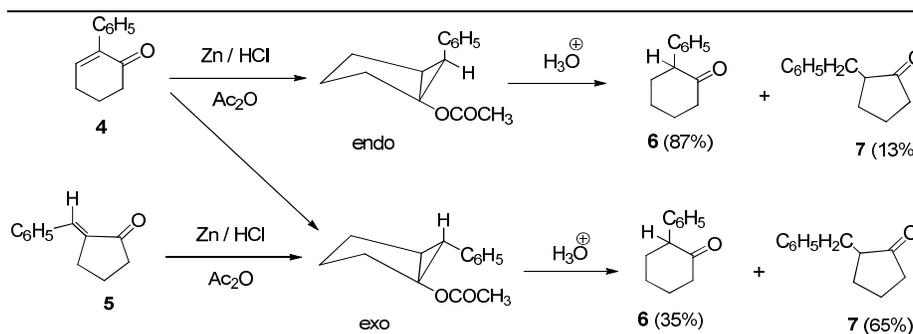
Scheme 7. Modified Clemmensen reduction of enone system

In 1990, S. K. Talapatra et. al. had reported the formation of both reductive dimers and rearranged products from the substrates 8, 9, 10 and 11 employing two variants of Clemmensen reaction conditions. They have altered the amount of conc. HCl using toluene as solvent. Under condition-l, the total quantity of the required acid was added in four installments in the ratio 7:2:2:2 while under condition-2, only the first installment of the acid was added. Both reactions were carried out for 24 hr. The product distributions from compounds 8, 9, 10 and 11 under these two conditions are presented in Figure l.

In the same year, V. Rosnati et. al. (Rosnati, V. et. al., 1990) carried out a parallel study of the Clemmensen reaction of benzophenone, benzhydryl chloride and dichlorodiphenylmethane in AcOH as solvent and TFA as substitute for mineral acid with LiCl as a source of chloride ions. They suggested new hypotheses about the mechanism of this reduction. The kinetic data indicated electron transfer (ET) from zinc metal to the substrate forming an organo-zinc radical 12, which was reduced by zinc (either bound or free) in presence of the proton source via the intermediacy of a four-membered, cyclic transition state (Scheme 8). They had also observed that the destiny of 12 was dependent on the experimental conditions. For example, carbon-carbon bond formation was favored in presence of aprotic solvents.
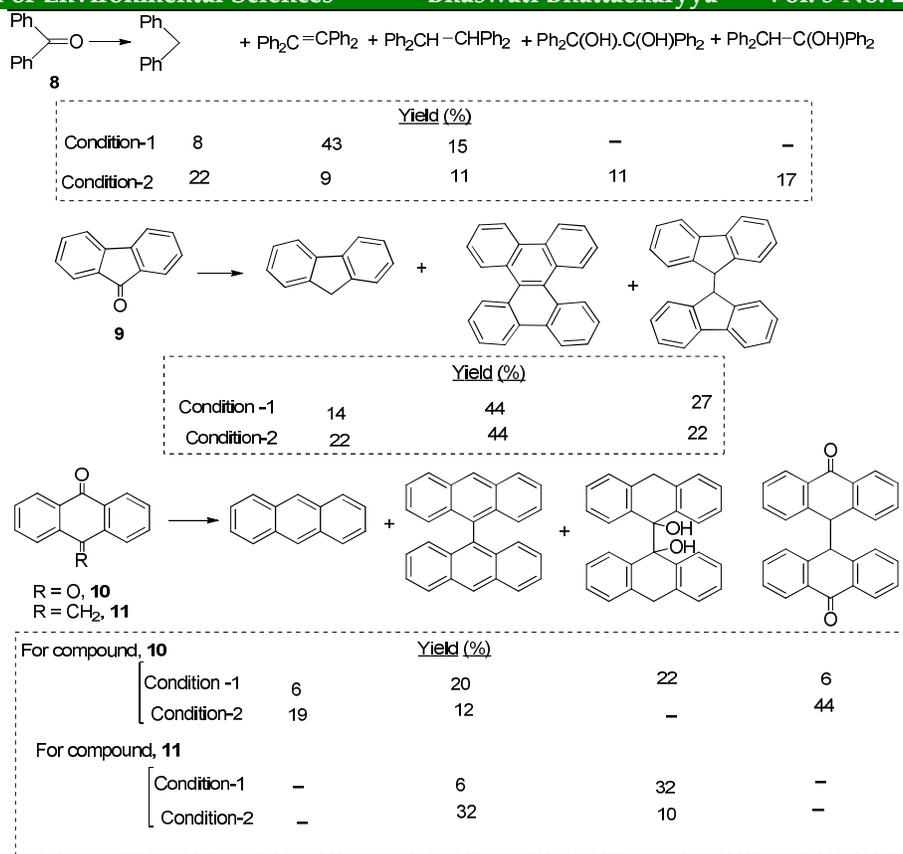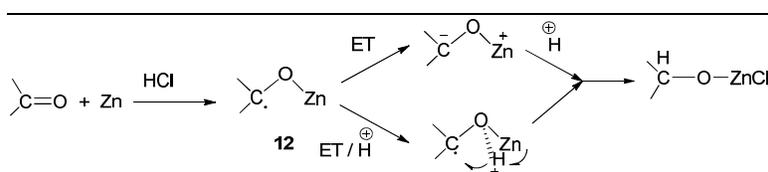
Figure l. Products of Clemmensen reduction of compounds 8, 9, 10 and 11

**Scheme 8.** Suggested mechanistic pathway of Clemmensen reaction

The same group investigated the reduction of identical set of substrates with Zn powder or amalgamated Zn employing different reaction conditions viz. in anhydrous AcOH (both in presence and absence of dry HCl), in refluxing AcOH or stirring at 10-25 °C and employing TFA instead of HCl (Di Vona, M.L. and Rosnati, V., 1991). Product distributions varied and isolation of reductive dimers indicated the formation of carbon radical species.

In 1994, they have examined the effect of ring strain while studying the reduction of 1,2-dibenzoylcycloalkanes (Di Vona, M.L. et. al., 1994). Zn/Hg reductions of *trans*-1,2-dibenzoylcyclobutane 13, *trans*-1,2-dibenzoylcyclopentane 14 and *trans*-1,2-dibenzoylcyclohexane 15 were carried out under three different conditions *viz*. using neat AcOH, in anhydrous AcOH/LiCl and with 7M HCl. Product distributions from the reduction of 13 and the pathways were summarized in Scheme 9. However, reduction of the substrates 14 and 15 yielded respective mixtures of products under each of those reaction conditions. The results indicated that ring strain was the decisive factor for the reductive cleavage of these cycloalkane rings.

In the year of 2005, another group of researchers (Kapoor, K.K. et. al., 2005) studied zinc dust mediated reductive dimerisation and cyclisation of benzylidene acetophenone derivatives, 19 in presence of catalytic amount of mercury(II)chloride isolating substituted cyclopentanols 20 as depicted in Scheme 10.

The role of mercury(II)chloride seemed to be that of a Lewis acid facilitating the SET. The proposed mechanism is described in Scheme 11.

The same group in 2007 (Kapoor, K.K. et. al., 2007) had explored similar type of cyclodimerisation of α,β-unsaturated aryl ketones under a different reagent system i.e.1:4 (v/v) mixtures of saturated aqueous NH₄Cl and tetrahydrofuran at room temperature producing 3,4-*trans*-diarylcyclopentanols in good yields.
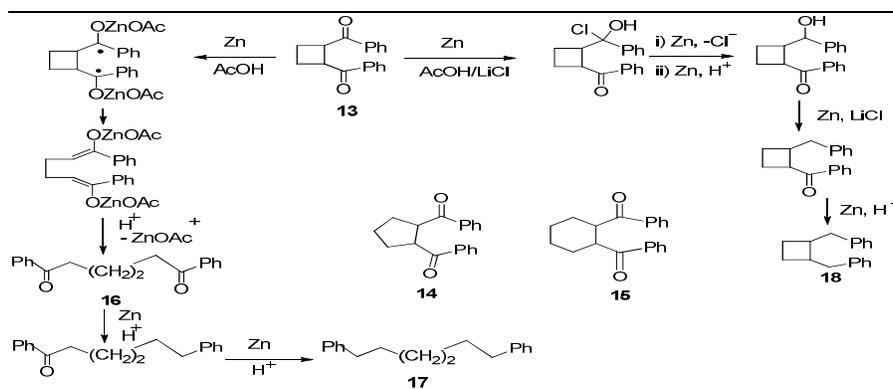
Scheme 9. The Zn reduction of **13** in AcOH and AcOH/LiCl
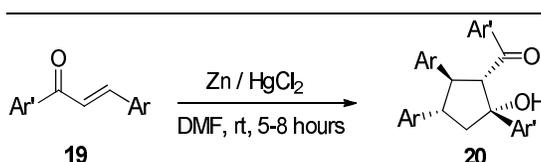
Scheme 10. Zinc mediated reductive dimerisation and cyclisation of α,β-unsaturated ketones
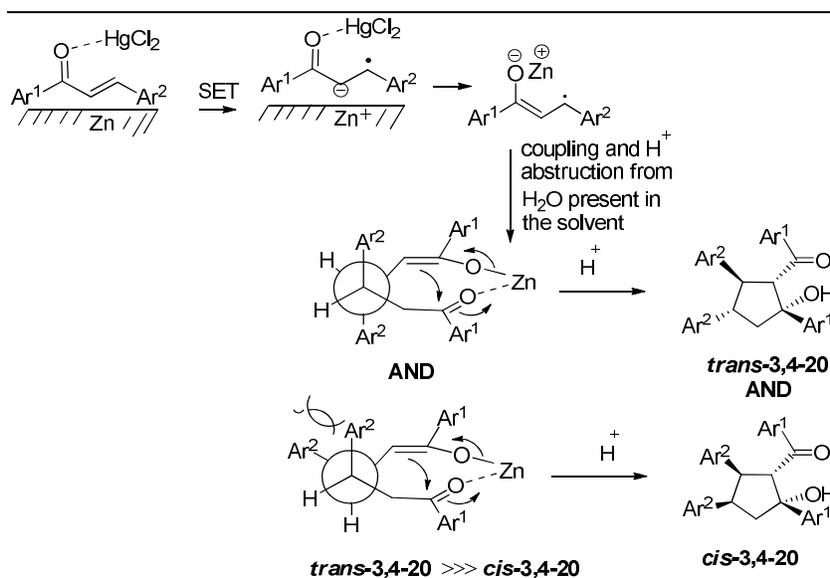
Scheme 11. Proposed mechanism of zinc mediated reductive cyclodimerisation of α,β-unsaturated ketones

The work (Dhara, K.P. et. al., 2012) in 2012, on zinc amalgam mediated reduction of α,α′-(E,E)-bis(benzylidene) cycloalkanones 21 and 22 in acidic medium revealed that ring size exerted profound influence not only on the rate and extent of reduction to yield the respective monomeric reduction products but also on the mode of C-C coupling between the β,β-benzylic carbons constructing the reductive dimers. In case of α,α′-(E,E)-bis (benzylidene) cyclopentanone 21, reduction of only one of the two exocyclic olefinic bonds on the five-membered ring ketone took place to form the product 23 whereas both exocyclic bonds around the cyclohexanone ring of α,α′-(E,E)-bis (benzylidene)cyclohexanone 22 were reduced to produce symmetrical product 24. Simultaneously, substrates 21 and 22 yielded coupled dimers 25 and 26 respectively with varying degrees of reductions. ^{1}H- and ^{13}C-NMR data and their mass spectral studies indicated that both types of dimers possessed symmetry in their molecular architecture. Single crystal X-ray diffraction analyses of the compounds 25 and 26 confirmed that while the former existed as *erythro* isomer in its *staggered* conformation with respect to the coupled β,β-benzylic C-C bond, the latter was present as its *threo* configurational isomer where smallest hydrogen atoms remained in *anti* relationship to each other with larger identical groups in *gauche-butane* relationship between themselves (Scheme 12). A common feature of the product ratio between reduced monomer and reductive dimers for both cross-conjugated enones 21 and 22 was the predominance of the former over the latter. This observation was attributed to the presence of proton source in the reaction medium.
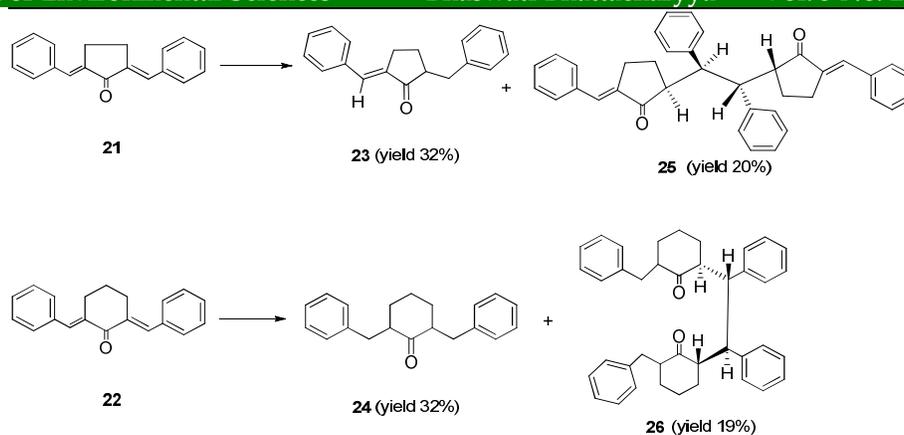
Scheme 12. Zinc-amalgam/acetic acid reduction products of bis(benzylidene)cycloalkanones

Scheme 13 presented plausible mechanistic pathways for the Zn-Hg mediated reduction of α,α'-(*E,E*)-bis(benzylidene)cycloalkanones. An electron was transferred from metal surface to the conjugated β-benzylic carbon forming the stable benzyl radical 21´ which extracted stability from extensive delocalization of electron encompassing both phenyl rings. Other than usual reduction steps to form 23 and 24, C-C coupling between two radicals 21´ yielded the reductive dimers 25 and 26.
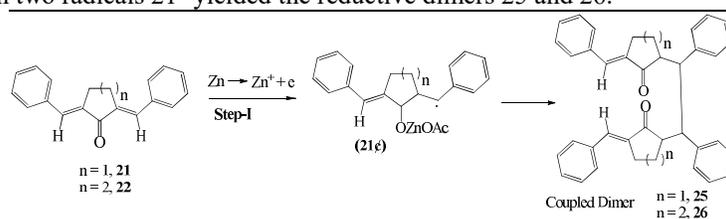
Scheme 13. Mechanism for the reduction of α,α'-(*E,E*)-bis(benzylidene)cycloalkanones

Concluding remarks

In this review the mechanisms of some traditional reduction reactions of zinc metal under different reaction conditions have been re-examined and explained by SET mechanism. The review briefly discussed the new synthetic methods developed on the basis of SET mechanisms engaging enone systems, assisted by zinc metal, which provides a wide range of different products e.g. fully or partially reduced monomers, inter- or intramolecular pinacols to cyclopropanediols, rearranged product to reductive dimers.

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