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The intramolecular reductive cyclization of cyclic enones

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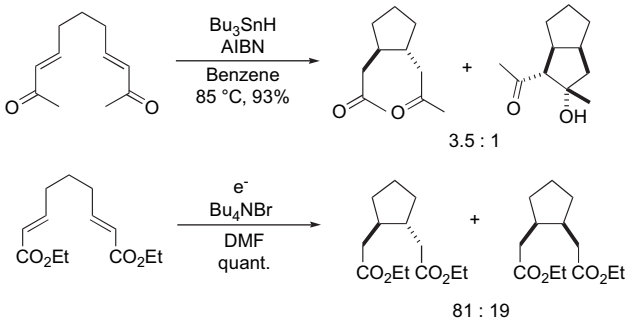
Abstract—The reductive cyclization (electrohydrocyclization reaction) of tethered cyclic enones has been investigated under electrochemical, metal-mediated, and photochemical conditions. The tricyclic products are generally formed with excellent stereoselectivity, particularly if at least one of the enones is β,β-disubstituted.

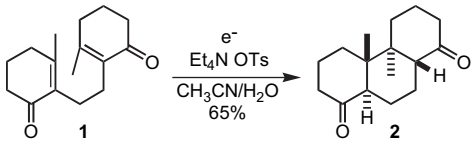
1. Introduction

The hydrodimerization reaction is a highly important reaction, particularly for the preparation of monomers for use in the synthesis of a variety of polymeric compounds.[1] A great deal of research has been conducted on the development of a variety of electrochemical and metal-mediated conditions to effectively conduct these intermolecular reactions. At the same time, relatively little attention has been focused on the development of the intramolecular version of this reaction (the electrohydrocyclization, hereafter called the reductive cyclization).[2] Indeed, the majority of these studies have explored the cyclization of simple tethered acyclic enones or enoates, such as those seen in Scheme 1.[3] While interesting, such focus ignores the vast potential of the reductive cyclization.



Scheme 1. Acyclic enone/enoate cyclizations.[2c,g]

The earliest exception to this trend of using acyclic systems is the reductive cyclization of **1** reported by Mandell and co-workers in 1976 (Scheme 2).[3a] Under controlled potential conditions, this reaction afforded trans/anti/trans tricycle **2** as a single isomer in 65% yield (81% brsm). Thus, four new stereocenters were established with complete stereocontrol. Rather surprisingly, there has been little effort to expand the scope of this transformation in the passing decades. Our efforts to remedy this situation and study the influence of ring size and β-substitution are the focus of this manuscript.[4]



Scheme 2. Mandell's reductive cyclization.

2. Results and discussion

The first challenge was the development of a general and efficient route to a range of cyclization precursors. Mandell's route to **1** featured a Kolbe dimerization of 3-methyl-2-cyclohexen-1-one-2-acetic acid, itself accessible in three steps from ethyl acetoacetate. We felt that a more efficient route would be the dimerization of functionalized allylic halides such as **3** (Scheme 3). The basis for this plan was a report by Chan and Ma that allylic and benzylic halides could be cleanly homo-coupled using a combination of manganese metal and copper(I) chloride.[5] Although it was not clear if such a reaction would work in the presence of a ketone, the fact that allylic acids had been successfully coupled gave this route promise.

Keywords: Hydrodimerization; Electrohydrocyclization; Electrosynthesis; Samarium diiodide; Cyclization; Stereoselectivity.
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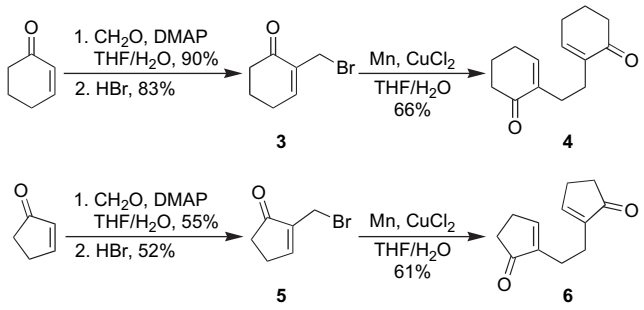
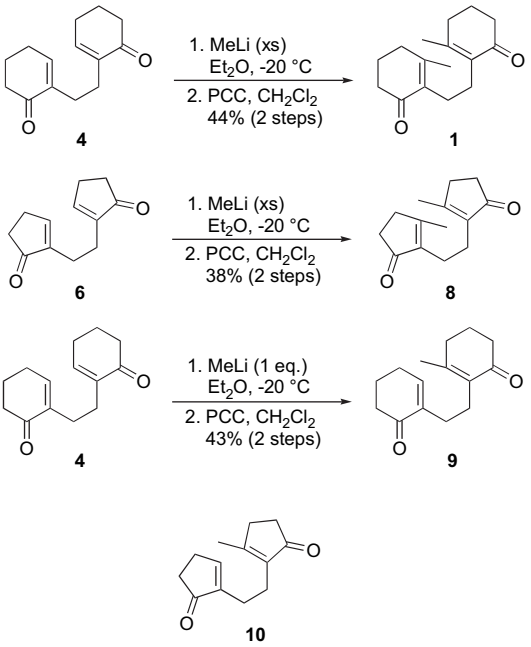


Scheme 3. Preparation of cyclization substrates.

In the event, allylic bromide **3** was prepared from cyclohexenone by a Baylis–Hillman reaction with formaldehyde,[6a] followed by treatment of the allylic alcohol with hydrogen bromide (Scheme 3). With the desired allylic bromide in hand, the homo-coupling proceeded cleanly to afford cyclization substrate **4**. No product was observed from reaction at the ketone, the lower yield being the result of the instability of the allylic bromide, particularly when stored neat. A similar pathway, starting with cyclopentenone, was also effective for the preparation of five-membered ring cyclization precursor **6**. In this case, the lower yields of both steps are likely the result of increased volatility of the products, the very sluggish Baylis–Hillman reaction,[6b] and the even greater sensitivity of bromide **5**.

For methyl-substituted substrates, bis-enones **4** and **6** proved to be satisfactory starting materials (Scheme 4).[7] Thus, treatment with excess methyllithium afforded the corresponding tertiary alcohols, which were subjected to oxidative rearrangement to afford the desired cyclization substrates **1** and **8**. Unsymmetrical substrate **9** was also prepared in this manner by the treatment of **4** with a single equivalent of methyllithium, followed by oxidative rearrangement of the resulting tertiary alcohol. Curiously, attempts to prepare **10** using similar conditions failed, affording only a mixture of **8** and **6**.

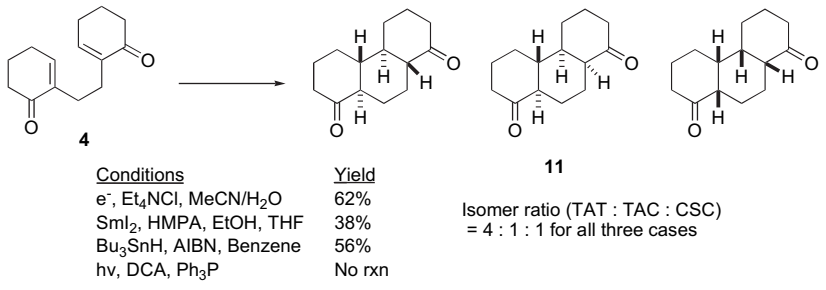
With the desired cyclization substrates in hand, the reductive cyclization could be studied (Scheme 5). Beginning with cyclization substrate **4**, the reductive cyclization was explored under simple electrochemical conditions using a tin cathode and a platinum anode.[4] These conditions resulted in the formation of an inseparable mixture of three isomers of product **11**, the major isomer being trans/anti/trans (TAT). Although the isolated yield of **11** was modest, the reaction itself was quite clean by TLC, showing only



Scheme 4. Preparation of methyl-substituted substrates.

the formation of **11** and some polymeric by-products at the base of the TLC plate.[8] The stereochemistry of the products was confirmed to be that shown in Scheme 5 by the conversion of bis-ketones **11** into the corresponding perhydrophenanthrenes under Wolff–Kishner conditions.[9] The ^{13}C spectra of these phenanthrenes were then compared with the data for the various isomers reported in the literature.[10] It is worth noting that there could have been epimerization of the stereocenters α to the ketones during the Wolff–Kishner reduction, but this does not appear to have occurred to any significant extent, since the same isomeric ratio is observed both prior to and after the Wolff–Kishner reduction.

As another avenue of exploration, we were interested in what effect a change in cyclization conditions might have on the outcome of the reaction. In particular, there have been reports using metal-mediated conditions (SmI_2 or Bu_3SnH)[2g,h] and even photochemical conditions.[2d,e,f] For the most part, though, these different reports have examined different substrates, so there was little clear evidence to suggest what, if any, differences in yield and/or selectivity might be observed. To that end, the cyclization of compound **4** was examined under two metal-mediated conditions and Pandey's photochemical conditions (Scheme 5). For the



Scheme 5. Cyclization of substrate **4**.