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Intramolecular Carbometallation of Secondary Organozinc Reagents.

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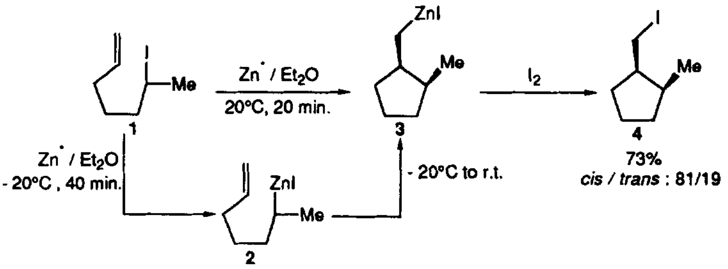
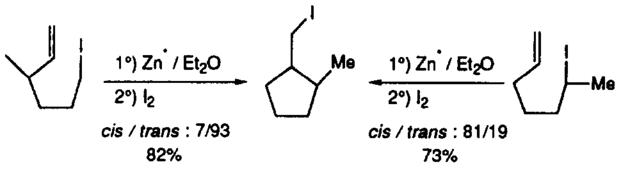
Abstract: The intramolecular carbocyclization of secondary organozinc derivatives allows the preparation of *cis*-substituted cyclopentylmethylzinc derivatives in an easy and straightforward way.

Recently, a number of synthetic methods have been introduced which employ anionic cyclizations for the construction of 5-membered rings[1]. However, a severe limitation is observed when ω-ethylenic *secondary* organometallic reagents are used. Treatment of ω-ethylenic secondary iodides with t-BuLi at -78°C leads mainly to Wurtz type coupling and elimination products[2]. Furthermore, the stereoselectivity of the cyclization is a function of the order of mixing the reagents. On the other hand, the intramolecular addition of secondary Grignard reagents[3] requires harsh conditions. A notable exception is the case of α-alkoxylithium, α-aminolithium derivatives[4], and the metalla-ene reactions[5]. We have recently reported[6] that the intramolecular cyclization reaction of ω-alkenyl primary organozinc reagents leads to cyclopentylmethylzinc derivatives in a totally regiospecific 5-exo-trig cyclization, with a good chemical yield, even in the presence of a highly sensitive function.

We now report our preliminary results in the area of cyclizations of ω-alkenyl *secondary* organozinc[7] reagents. Treatment of 6-iodo-1-heptene **1** with Rieke's zinc[8] in ether, as previously described[6], quantitatively leads to the cyclized organozinc iodide species **3** in less than 20 min[9] as shown by iodinolysis of the reaction mixture :



At lower temperatures, we have observed a clean and rapid insertion of activated zinc metal into the carbon-iodine bond leading to the acyclic zinc derivative **2** in 95% yield (as shown by hydrolysis) contaminated by 5% of cyclized product. The formation of the linear organozinc iodide **2** and its subsequent cyclization by simple warming of the reaction mixture to room temperature can be taken as a hint to the absence of a one electron tranfer process in this cyclization. The stereoselectivity (*cis/trans* = 81/19) has been attributed by comparison with an authentic sample prepared according to our preliminary report^6 :

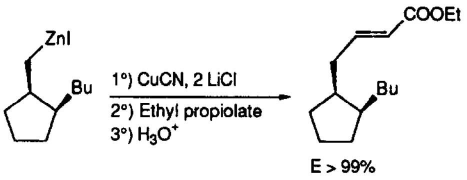


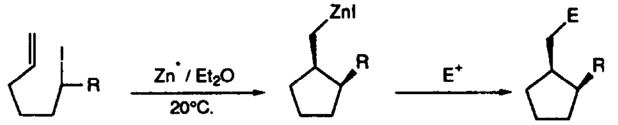
The *cis* stereoselectivity observed is attributed to steric interactions which favor a geometry in which the substituent preferentially occupies an outside position in the chair like transition state. The pronounced *cis* stereoselectivity of the reaction is opposite to the *trans* stereoselectivity observed by Bailey^3, Broka^4, and Richey^5. It may be that organolithium and organomagnesium cyclizations, in contrast to the zinc one, proceed through a rather "product like" transition state. The highly covalent nature of the carbon-zinc bond as well as the favorable intramolecular association of the zinc atom with the double bond^{10} may explain the *cis* stereoselectivity observed here.

The scope of this cyclization is quite broad: alkyl groups can be primary, secondary, tertiary as well as a phenyldimethylsilyl derivatives as reported in the table.

In the case of **5b** (entry 3) the diastereoisomeric ratio can be improved to *cis/trans* = 80/20^{11}, by a slow warming to room temperature of the linear organozinc derivative^{12}.

Transmetallation of a cyclic organozinc iodide^{13} to copper followed by addition of ethyl propiolate leads to the corresponding ethylenic ester :

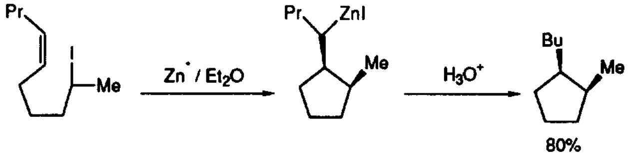




Entry	R	Time[a]	E+	Product[b] (Yield %)	*cis/trans*[c] ratio
1	Me	20 mn	I_2	**4** E=I (73)	81/19
2	nBu	20 mn	H_3O^+	**5a** E=H (60)	73/27
3	nBu	20 mn	I_2	**5b** E=I (68)	73/27
4	iPr	2 h	I_2	**6** E=I (78)	73/27[d]
5	t-Bu	3 h	I_2	**7** E=I (60)	62/38[d]
6	SiPhMe$_2$	overnight	H_3O^+	**8** E=H (68)	66/34[d]

a) Necessary time for the transformation of linear organozinc iodide into the cyclic derivative. b) Yield of isolated product by chromatography on silica gel. c) The cis/trans ratio was determined by ^1H and ^{13}C NMR spectroscopy[11]. d) The stereochemistry has been deduced from the preceding exemples.

A very promising result is that the secondary organozinc derivative undergoes a smooth carbocyclization in ether at room temperature into a 1,2-disubstituted double bond to afford a new secondary zinc iodide in 80% yield after hydrolysis, with a 68/32 *cis/trans* ratio :



Since the corresponding lithium or magnesium derivatives do not cyclise in acceptable yields[3-5], this peculiarity of the zinc reagents opens a new route in cyclization reactions. The cyclization onto unactivated 1,2 disubstituted alkenes has been mostly restricted so far to radicals[14], to Π-allyl palladium derivatives[2], or aluminum derivatives[15]. We are currently exploring the scope and limitations of this reaction.

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