Zirconocene-mediated Preparation of Precursors for Estratriene Synthesis

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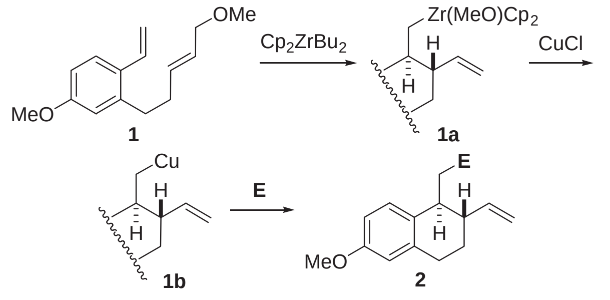
Zirconium-mediated cyclization of an allyl-ene compound afforded organozirconium intermediate, which after alkylation (allylation and acylation) afforded either dienes or unsaturated ketones. These are considered to be precursors further elaboration of which should yield functionlized steroids.

Zirconocene-based C–C forming reactions constitute a powerful tool for organic synthesis.[1] The underlying strategy for many of such processes is based on the use of compounds bearing double or triple bonds that after the reaction with "reduced zirconocene" (Negishi reagent) yield zirconacycles. These can be used in reactions with various electrophiles either directly[2] or after transmetallation to obtain a more reactive organometallic compound (e.g. with CuCl to give organocopper compounds).[3,4]

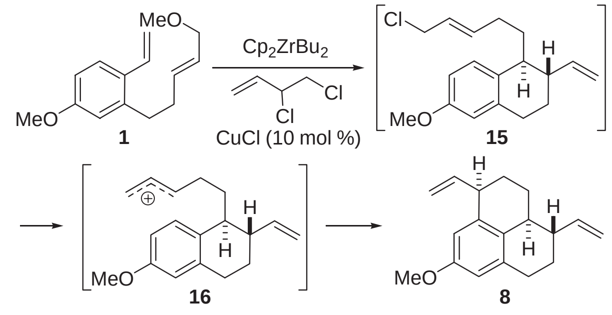
Recently, we have reported a new approach to estratriene derivatives that utilized sequential reactions based on the repetitive use of the Negishi reagent.[5] One of the most important steps was B-ring closure together with generation of a suitable starting material for the C-ring formation. The reaction relied on the cyclization of non-conjugated diene containing terminal allylic ether **1** followed by a reaction with 2-methylallyl chloride in the presence of a catalytic amount of CuCl affording a new diene. During the course of the study we found that the B-ring closure proceeded with excellent trans selectivity, which was important for generation of other stereochemical centers. Although both steps proceeded uneventfully in good yield, from the synthetic point of view it was interesting to study the above-mentioned reaction also with other carbon electrophiles, because they could be used for synthesis of other estratriene derivatives.

All the reactions were run analogously to previously reported procedure: non-conjugated diene containing terminal allylic ether **1** was cyclized with Cp_2ZrBu_2 to organozirconium intermediate **1a**.[6] Then followed addition of the corresponding carbon electrophile and a catalytic amount of CuCl (usually 10 mol % with respect to the substrate) giving **2**. The addition of CuCl was essential for the transmetallation of the unreactive Zr–C bond in **1a** to the more reactive organocopper species **1b** (Scheme 1). The repetition of the reaction with 2-methylallyl chloride confirmed its efficiency yielding the corresponding product **3** again in high 93% yield (Table 1, Entry 1). The reaction with allyl chloride proceeded also well giving diene **4** in good 79% yield (Entry 2). The use of halogenated allyl halides such as 2,3-dichloropropene and 2,3-dibromopropene resulted in the formation of the corresponding halodienes **5** and **6** in 84 and 83% yields, respectively (Entries 3 and 4). Alkylation of **1b** with 3-chlorobutene afforded product **7** (80%) as 2/1 mixture of trans/cis isomers (Entry 5). Interesting result was obtained in the reaction with 3,4-dichlorobutene (Entry 6). Although it proceeded with high conversion as a product was isolated only tricyclic compound **8** in 45% yield. The reactions with bifunctionalized allyl halides, ethyl 2-(bromomethyl)acrylate and 3-chloro-2-(chloromethyl)propene, afforded **9** and **10** in 76 and 61% yields, respectively (Entries 7 and 8). Small amount (6%) of the doubly alkylated product **10a** was also isolated. Selective S_N2' substitution was observed in the reactions with 2-butenyl chloride and 3-bromopropyne. The former gave product **11** (74%) as 1:1 diastereoisomeric mixture (Entry 9) and the latter allene **12** in 71% yield (Entry 10). The reaction of the organocopper intermediate **1b** proceeded in a similar manner also with acyl halides, benzoyl and propanoyl chloride (Entries 11 and 12). In both cases the corresponding ketones **13** and **14** were obtained in good yields of 72 and 69%, respectively. Since the stereochemistry in positions 7 and 8 is controlled by the cyclization step, all products were obtained with excellent trans stereoselectivity (>98%).

Although the formation of compound **8** was initially rather puzzling, we later realized that it was formed from allyl chloride **15**, the formation of which was confirmed by analysis of the reaction mixture, as a result of standard work-up and purification procedure, which included column chromatography on silica

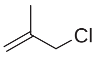
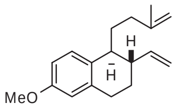
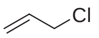
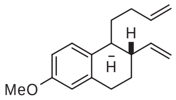
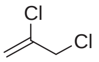
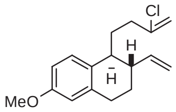
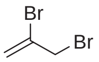
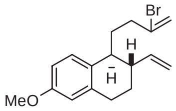
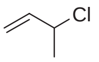
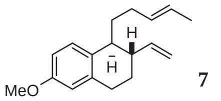
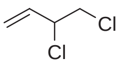
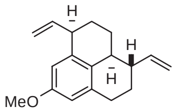
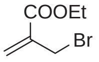
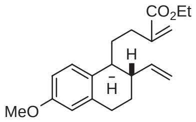
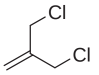
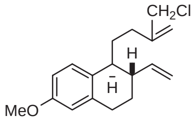
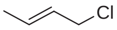
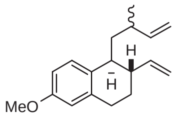
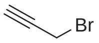
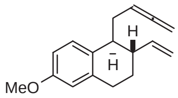
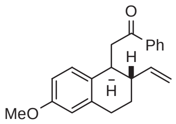
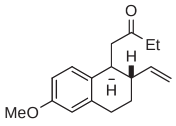


Scheme 1. Cyclization of **1** and reaction with electrophiles.



Scheme 2. Formation of **8**.

Table 1. Zr-mediated cyclization and alkylation of **1**

Entry	Electrophile	Product	Yield/%[a]
1		 **3**	93
2		 **4**	79
3		 **5**	84
4		 **6**	83
5		 **7**	80[b]
6		 **8**	45[c]
7		 **9**	76
8		 **10**	61
9		 **11**	74[d]
10		 **12**	71
11	PhCOCl	 **13**	72
12	EtCOCl	 **14**	69

[a] Isolated yields. [b] Trans/cis 2/1. [c] Isolated as a single diasteroisomer. [d] 1:1 diasteroisomeric mixture.

gel. Thus, we assume that allyl chloride **15** could undergo solvolysis to generate an allylic cation **16**, which owing to the favorable spatial arrangement with an electron-rich aromatic ring undergoes an intramolecular aromatic electrophilic subtitution to give **8** (Scheme 2).[8]

In summary, the presented results show that the reaction of intermediate **1b** with various electrophiles afforded products that could serve as potential intermediates for synthesis of modified steroids. In this regard, of special interest are compounds **3** and **4** which are considered to be crucial intermediates for zirconocene-based synthesis of estrone derivatives. In addition, the basic framework of compound **8** resembles the structure of pseudopterosins[7] that were isolated from sea whips *Pseudopterogorgia elisabethae* and have antiinflammatory and analgesic properties. Perhaps the above-mentioned results can serve as an inspiration for its alternative synthesis. Experiments along this line are under investigation.

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