Organometallic Chemistry

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Unsaturated Fatty Alcohol Derivatives as a Source of Substituted Allylzirconocene**

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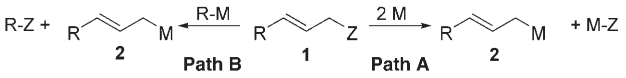
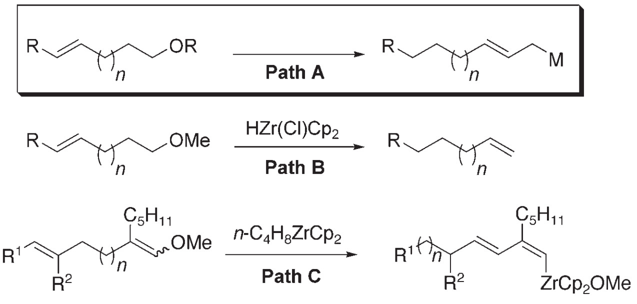
The development and use of allylic organometallic reagents has been an underlying theme of modern organic synthesis.[1] A plethora of methods currently exists for the preparation of diversely substituted allylic organometallic moieties **2** by the displacement of pre-prepared allyl reagents **1** (Scheme 1). The Z group can be a halogen (Cl, Br, I),[1e] chalcogen (O, S, Se, Te),[2] metalloid (Pb, Sn),[3] or hydrogen,[2a,4] but also carbon (in particular tertiary carbinol).[5a–c] The source of the metal can be the element (M) itself (Scheme 1, Path A), which undergoes an oxidative insertion into the C−Z bond. However, cross-contamination of the product with the Wurtz coupling adduct always occurs (the longer the alkyl chain R in **1**, the more abundant the Wurtz coupling product). Alternatively, the source of the metal can be an organometallic derivative or a metallic salt (Scheme 1, Path B).[5d] However, all of these methods required a presynthesized allyl substrate **1** that has to be prepared independently in as few steps as possible.



Scheme 1.

Alternatively, allylic organometallic derivatives can also be prepared by carbo- and hydrometallation of allenes and dienes.[6] As one of the major challenges in synthesis nowadays is to assemble target molecules—here, namely, allylic organometallic derivatives—from readily available starting materials in a one-step procedure and in a simple and straightforward manner, we have recently been working on a totally different approach based on a four-component reaction with concomitant creation of chiral quaternary centers.[7] However, the most ideal solution would be to prepare allylic organometallic derivatives of type **2** from unsaturated fatty alcohol derivatives, which are naturally present in large quantities from fatty acids, through a hypothetical successive tandem isomerization–elimination reaction of the internal double bond (Scheme 2, Path A). In this regard, hydrometallation reactions (such as hydroalumination, hydroboration, and hydrozirconation) followed by an isomerization of internal olefins is a known way of rendering unactivated methyl hydrogen atoms accessible to substitution.[8] Moreover, hydrozirconation of internal aliphatic olefins with terminal oxygen-, sulfur-, or nitrogen-containing functionalities has already been investigated and leads to an elimination reaction of the functional group after rearrangement of the zirconium moiety towards the carbon atom that bears the heteroatoms (Scheme 2, Path B).[9] On the other hand, if one equivalent of 1,2-dicarbanionic species[10] would be available and react in this process with the same unsaturated system, the final product should contain an organometallic derivative and therefore Path A would be a realistic route.



Scheme 2.

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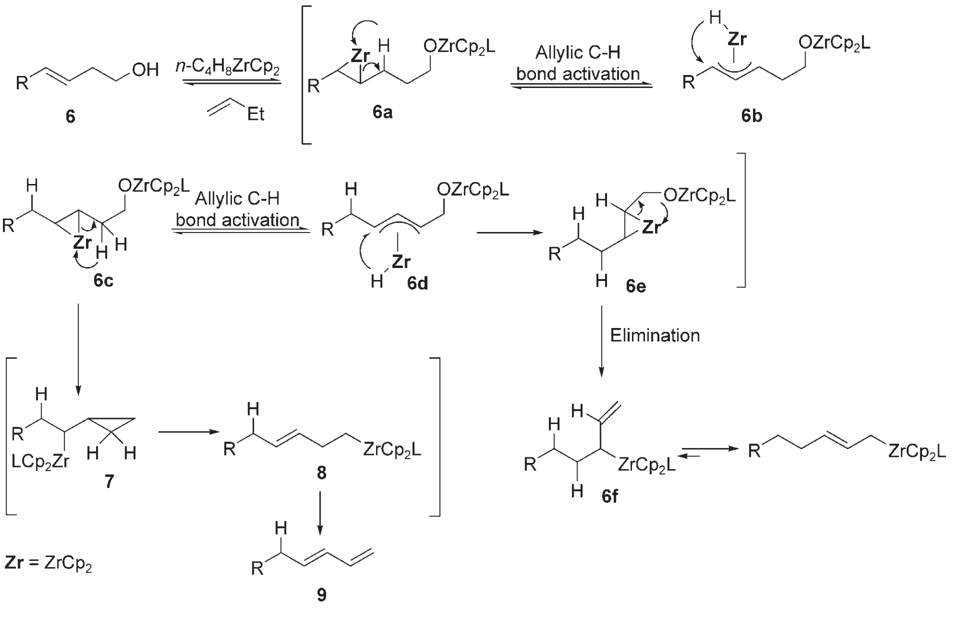
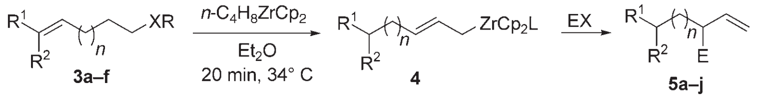


Scheme 3.

We previously reported that simple nonconjugated unsaturated enol ethers react smoothly with (1-butene)$ZrCp_2$ (Negishi reagent; Cp = cyclopentadienyl)[10] to lead to polysubstituted dienyl zirconocene derivatives as single geometrical isomers (Scheme 2, Path C).[11] This approach to stereoisomerically pure dienyl metals was based on a tandem allylic C–H bond-activation–elimination sequence, and the mechanism has since been mapped out by deuterium-labeling experiments.[12] Thus, we reasoned that internal aliphatic olefins of type **3**, which bear a leaving group at the terminal position, should undergo a tandem isomerization–elimination reaction with the Negishi reagent in a one-pot operation to give the corresponding substituted allylzirconocene derivatives **4**, which may further react with classical electrophiles (Table 1).

Table 1: Preparation of allylzirconocene derivatives from unsaturated fatty alcohol derivatives.



Entry	R^1	R^2	*n*	XR	Alkene **3**	EX	Product	Yield [%][a]
1	H	C_5H_{11}	0	OCH_3	**3a**	HCl	**5a**	80
2	H	C_5H_{11}	0	Cl	**3b**	HCl	**5a**	20
3	H	C_5H_{11}	0	OH	**3c**	HCl	**5a**	80
4	C_5H_{11}	H	0	OCH_3	(*E*)-**3a**	HCl	**5a**	60
5	C_5H_{11}	H	0	OCH_3	(*E*)-**3a**	NCS	**5b**	66
6	H	C_5H_{11}	0	OH	**3c**	NCS	**5b**	65
7	H	C_5H_{11}	0	OH	**3c**	PhCHO[b]	**5c**	65
8	H	C_5H_{11}	1	OH	**3d**	NCS	**5d**	65
9	H	C_5H_{11}	1	OH	**3d**	PhCHO[b]	**5e**	73
10	C_4H_9	H	2	OH	**3e**	NCS	**5d**	65
11	C_4H_9	H	2	OH	**3e**	PhCHO[b]	**5e**	73
12	H	C_8H_{17}	6	OH	**3f**	HCl	**5f**	72
13	H	C_8H_{17}	6	OH	**3f**	NCS	**5g**	65
14	H	C_8H_{17}	6	OH	**3f**	PhCHO[b]	**5h**	76

[a] Isolated yield after purification by column chromatography (silica gel) and based on the starting materials **3a–f**. [b] *Anti*/*syn* ratio = 82:18 to 88:12.

We were pleased to observe that this reaction proceeds, but the yield of this transformation was highly dependent on the nature of the leaving group XR. When a good leaving group was used, such as a chlorine atom (Table 1, entry 2), the yield of the terminal alkene **5a**, after hydrolysis, was very low (diene **9** formed as the major product; see Scheme 3). However, alkoxy functions such as the methoxy group (Table 1, entry 1) led to the corresponding allylzirconocene derivatives in good isolated yields after hydrolysis. As alcohol moieties are the logical precursors for the alkoxy groups and as many derivatives of unsaturated fatty acids that contain a terminal hydroxy functionality are commercially available, we decided to concentrate our effort on the most challenging isomerization–elimination reactions of ω-alkenols **3c–f**. In these cases, either two equivalents of the Negishi derivatives were used (the deprotonation of the alcohol precedes the isomerization) or the alkenols were first deprotonated by the addition of one equivalent of *n*BuLi or Et_2Zn. Although the exact nature of the ligand L on the zirconium after the tandem deprotonation–isomerization reaction of the alkenols **3c–f** with (1-butene)$ZrCp_2$ is still unclear, we believe that oligomeric zirconium alcoholates are formed.[13] In all cases the reaction was rapid: only 20 minutes treatment at 34 °C in Et_2O was enough to transform non-allylic alkenol into allylzirconocene derivatives. The stereochemistry of the initial double bond had no effect on the isomerization–elimination processes as *Z*- or *E*-configured double bonds could be used indifferently (compare entries 1 and 5, Table 1). The formation of the new allylic organometallic products **4** was checked by reactions with *N*-chlorosuccinimide or benzaldehyde.[2h] In the latter cases, *anti*-homoallylic alcohols formed predominantly and the diastereoselectivity (*anti*/*syn* = 82:18 to 88:12) closely parallels the isomeric composition of these substituted allylzirconocenes reagents, as determined by low-temperature NMR spectroscopic studies,[14] which suggests that the reaction proceeds through a six-membered chair transition state.

This isomerization–elimination reaction was not limited to (3*Z*)-nonenol (**3c**) with a two-carbon-atom tether. Indeed,

3d–f (with three-, four-, and eight-carbon-atom tethers, respectively) also underwent this tandem reaction (Table 1, entries 8–14) in 20 minutes at 34 °C. This migration–elimination reaction can be rationalized by the following mechanism on a three-carbon-atom tether (Scheme 3): (1-Butene)$ZrCp_2$ reacts first with the remote double bond of **6** to form a zirconacyclopropane derivative **6a**. Then, through allylic C–H bond activation,[12] the η^3-allyl intermediate **6b** is formed, and after hydrogen migration the zirconacyclopropane **6c** is produced. By repeating the same sequence, the zirconacyclopropane **6e** is finally obtained before its β elimination[15] into the allylzirconocene intermediate **6f**. When a good leaving group is used as in **3b** (Table 1, entry 2), the major side product thus obtained may be rationalized by the zirconium-mediated conversion of homoallylic species into cyclopropane derivatives, as shown by Szymoniak and co-workers,[16] followed by dehydrozirconation into diene **9**.[9] Therefore, when the zirconium alcoholate is used as leaving group, the allylic C–H bond activation of **6c** into **6d** is faster than the 1,3-elimination reaction (**6c** into **7**).

In conclusion, (1-butene)$ZrCp_2$ easily transforms (20 minutes at 34 °C) unsaturated fatty alcohol derivatives into allylzirconocene complexes through a tandem allylic C–H activation–β-elimination reaction. The reaction seems to be independent of the chain length between the unsaturated system and the alcohol moiety. Extension of this new preparative route to more elaborated structures is currently under investigation.

Experimental Section

A solution of *n*-butyllithium in hexanes (4.8 equiv) was added dropwise to a stirred solution of bis(cyclopentadienyl)zirconium dichloride (2.4 equiv) in dry Et_2O (15 mL) at −78 °C under argon atmosphere. The temperature of the solution was allowed to reach −5 °C and was then maintained for 5–6 min. The reaction mixture was then cooled to −50 °C, and the alkenol **3c** (1 equiv) in Et_2O (5 mL) was added dropwise to the solution, keeping the temperature at −50 °C. When the addition was complete, the cooling bath was removed and the reaction mixture was rapidly warmed to room temperature. The solution was then heated and maintained at 34 °C for 20 min to form the allylzirconocene intermediate (monitored by GC of hydrolyzed aliquots), which is ready for further use[17] or, alternatively, can be hydrolyzed with 1N HCl after cooling the solution to room temperature. After hydrolysis, the layers were separated and the aqueous phase was extracted four times with diethyl ether. The combined organic extracts were washed successively with a saturated solution of sodium bicarbonate, brine, and then dried over $MgSO_4$. The obtained residue was finally purified by column chromatography on silica gel to give the functionalized alkenes as reported in Table 1.

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