Zinc Mediated Allylation of Aldehydes and Ketones with Cinnamyl Chloride in Aqueous Medium
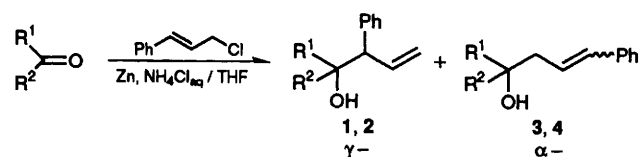
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The Zn mediated reactions of cinnamyl chloride with aldehydes and ketones in THF–NH₄Cl(aq) give—besides α- and γ-addition products—phenyl propenes and dicinnamyls, indicating the presence of radical intermediates in the reaction.

Allylation of carbonyl compounds with allylic organometallic compounds, or by allylic halides assisted by metals, to produce homoallylic alcohols has become an important synthetic reaction. The main emphasis has been on finding methods for stereocontrolled synthesis of acyclic starting materials for the preparation of, among others, macrolide and polyether antibiotica.[1] Some allylations can be performed in aqueous media, rendering them especially attractive for allylation of aldehydes and ketones containing acidic hydrogens or less reactive carbonyl groups like those of esters and amides.[2] Zn mediated addition of allylic halides to aldehydes and ketones in aqueous media was introduced by Luche and coworkers some years ago,[3,4] and has become a well established method for the synthesis of homoallylic alcohols.[5–9] However, the mechanism of the reaction and the stereochemistry of the products have gained little attention. Although by-products have been observed in the reactions,[3] they have not been identified.

We reacted some selected aldehydes and ketones with cinnamyl chloride in THF–NH₄Cl(aq) in the presence of Zn metal, in order to elucidate the regio- and stereo-chemical course of the reactions and to gain more knowledge of the reaction mechanisms and the structures of the by-products. The reactions were performed by adding cinnamyl chloride to a stirred mixture of saturated NH₄Cl(aq), THF, Zn powder and the carbonyl compound. The ratio of THF to NH₄Cl(aq) was 1 : 10. The halide to carbonyl compound ratio was 2 : 1 and 2.5 : 1 in the aldehyde and ketone reactions, respectively. The halide to Zn ratio was 1 : 1. Moreover, argon was blown through the NH₄Cl(aq) solution prior to mixing of reactants and reactions took place under an argon atmosphere. The reaction mixtures were analysed by GC/MS and ¹H NMR spectroscopy. The reactions gave mixtures of homoallylic alcohols 1–4 (Scheme 1 and Table 1).

In the reactions between cinnamyl chloride and aldehydes, rearrangement of the allylic group leads to diastereomeric γ-products 1 and 2. The reactions of ketones gave mixtures of α-isomers 3 and 4, as well. When the size of the alkyl group in the phenyl ketone was increased, the α/γ-product ratio increased and with R¹ = Buᵗ (entry 8) only the α-adduct with an (E)-configuration was formed. Increasing steric hindrance also reduced the overall yields of the addition products. An increase of the cinnamyl chloride excess did not increase the yields of homoallylic alcohols. We noticed, however, that the exclusion of air from the reaction mixture increased the yields of alcohols. Phenyl propenes 5a–c and 'dicinnamyls' 6a–c (Scheme 2) were formed in all reactions. Moreover, some of the aldehyde reaction mixtures (entries 2 and 3) contained small amounts of pinacols 7. The amounts of 5 and 6 increased when the halide excess was increased. We also noted that in an experiment without aldehyde (ketone) all cinnamyl chloride was consumed and compounds 5 and 6 were formed quantitatively.

The results support a radical mechanism for the Zn mediated cinnamylation of aldehydes and ketones in THF–NH₄Cl(aq). As formation of organozinc compounds in water does not seem probable, the phenyl propenes (5, Scheme 2) could form by combination of cinnamyl radicals with hydrogen radicals formed by the reaction of Zn with protons. The three different 'dicinnamyls' (6, Scheme 2) were probably formed by coupling of cinnamyl radicals. The formation of pinacol type adducts 7 shows that ketyl radicals probably are formed. However, the formation of ketyl radicals does not seem to be the initial step in the reaction as only small amounts of pinacols are formed even if the allylic halide is omitted.[4]

We therefore suggest that the allylation is initiated by the formation of an allylic radical which then adds to the carbonyl group of the aldehyde (ketone). The addition would result in formation of an alkoxide radical which immediately adds an electron released from the metal and forms the alcohol. According to Luche and coworkers,[4] this process should affect the pH value of the reaction solution. As a matter of fact we observed an increase from pH 5 before the reaction started to pH 7 at the end of the reaction. The yield increase on exclusion
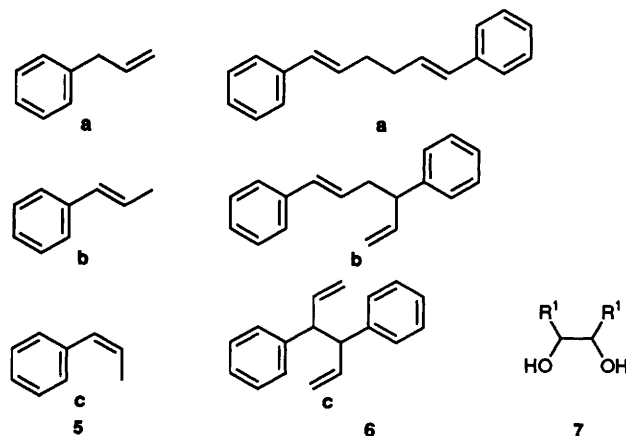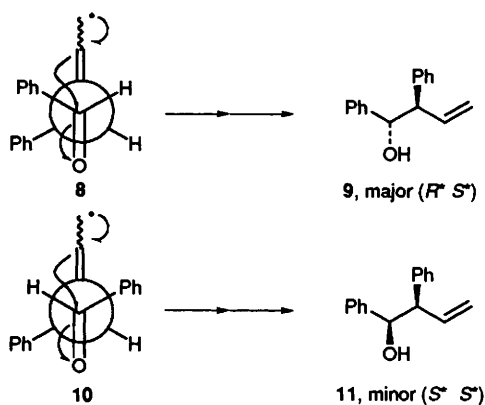
Scheme 1

Table 1 Normalised and total yields of homoallylic alcohols in the Zn mediated reactions of cinnamyl chloride with aldehydes and ketones in THF–NH₄Cl(aq). Yields were determined by GC and ¹H NMR spectroscopy

Entry	R¹	R²	1,2 Major	1,2 Minor	3,4 (Z)-	3,4 (E)-	Total yield (%)
1	Et	H	73	27	—	—	98
2	Buᵗ	H	86	14	—	—	54
3	Ph	H	85	15	—	—	71
4	Fur	H	63	37	—	—	36
5	Me	Ph	92	6	Trace	2	63
6	Et	Ph	94	5	Trace	1	35
7	Prⁱ	Ph	52	32	Trace	16	59
8	Buᵗ	Ph	—	—	—	100	6

Scheme 2

of air also indicated the presence of radicals. In our opinion, at least the initial reaction, the formation of the allylic radicals, takes place on the surface of the metal.

The stereochemistry of the addition products could also give information about the mechanisms. However, the relative stereochemistry of the γ-isomers has yet been unambiguously established only for the benzaldehyde adducts. The major isomer had the R*S* and the minor had the S*S* configuration.[10] Assuming a similar non-cyclic transition state as in polar allylations,[11] two possible transition states in the formation of the diastereomeric γ-adducts from the reaction of benzaldehyde with cinnamyl chloride could be 8 and 10 (Scheme 3). The transition state 8 would be favoured and lead

to the major isomer as the synclinal relationship of the phenyl groups leads to favourable π–π interaction[12] and is also favoured in the products, as shown by molecular modelling.[13] The stereochemistry of the transition state, however, probably depends on the substituents in the carbonyl compounds and can be topologically different for the different reactant pairs.

Scheme 3

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