A Dual Regiocontrol in the Copper-catalysed Grignard Reaction with Primary Allylic Acetates

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The reaction of primary allylic acetates with Grignard reagents in the presence of catalytic amounts of Li_2CuCl_4 can be regiochemically controlled to give either α- or γ-substitution of the allylic acetoxy group.

Metal-catalysed nucleophilic substitutions of allylic substrates are important reactions in organic synthesis.[1] Transition metals such as palladium,[2] nickel,[3] copper,[4,5] iron,[6] molybdenum,[7] and tungsten[8] are known to promote the nucleophilic substitution of allyic carboxylates (Scheme 1). From a synthetic point of view it is of great importance to be able to control the regiochemistry of these reactions (path a or b) and this question has been addressed by several research groups.[2,7—12]

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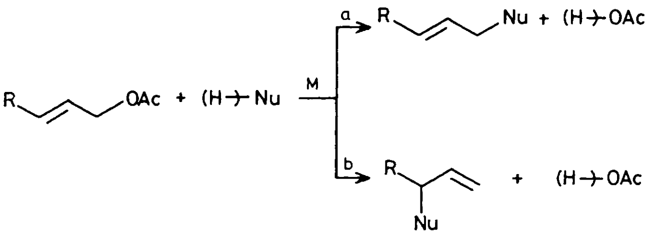
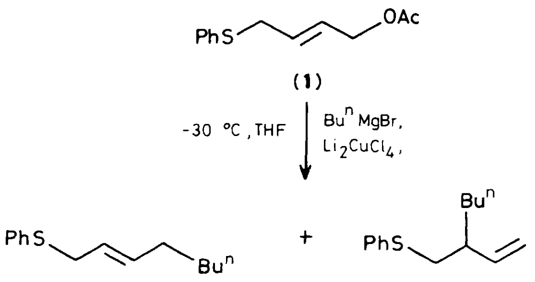
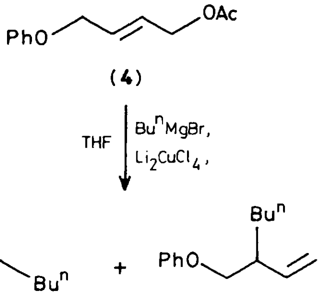


Scheme 1



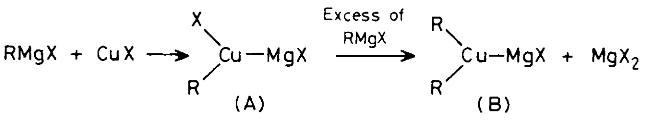
(1) (2) (3)

Addition time of RMgX/min	Mol % Li_2CuCl_4	Ratio (2):(3)
2	2	75:25
20	2	62:38
40	2	53:47
20	5	23:77
40	5	13:87

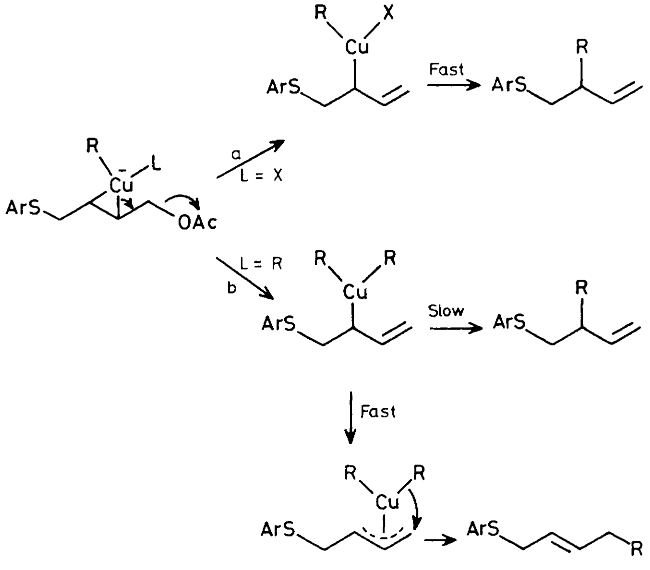


(4) (5) (6)

	Addition time of RMgX/min	Mol % Li_2CuCl_4	Ratio (5):(6)
−30 °C	1.5	2	96: 4
	40	2	82:18
	40	5	75:25
0 °C	20	5	44:56
	40	5	38:62
	150	5	14:86



Scheme 2. X = Cl, Br.



Scheme 3. X = Cl, Br.

When a non-stabilized carbon nucleophile has to be used in substitution of an allylic acetate (*cf.* Scheme 1), copper is one of the few metals that can be applied. Dialkylcuprates[4] and more recently copper-catalysed Grignard reactions have been used with success.[5]

During our work on copper-catalysed Grignard coupling with allylic acetates we observed that the regiochemistry drastically changes with reaction conditions. In this communication we report that it is possible to control the nature of the catalytic species by variation of the addition time of the Grignard reagent, the temperature, and the amount of catalyst used, which leads to total regiocontrol of the reaction.

Reaction of the allylic acetate (**1**) with Bu^{n}MgBr in the presence of catalytic amounts of Li_2CuCl_4‡[13] resulted in displacement of the acetoxy group by the butyl group either in an S_N2 or S_N2' fashion (α- or γ-substitution). The regiochemical outcome of the reaction is strongly dependent on the reaction conditions. Thus a rapid addition of the Grignard reagent to a solution of allylic acetate (**1**) and Li_2CuCl_4 in tetrahydrofuran (THF) at −30 °C gave mainly attack at the terminal carbon by the butyl group. If the addition time of the Grignard reagent was prolonged, the product from γ-attack increased. An increase in the amount of catalyst also resulted in an increase of the γ-attack product. With an addition time of 40 min and a catalytic amount of 5 mol% the α:γ ratio was 13:87.

With the less reactive substrate (**4**) the same variations of reaction conditions at −30 °C gave a less drastic regiochemical change. In this case the variation from 1.5 min, 2% of catalyst to 40 min, 5% of catalyst at −30 °C led to a moderate change of the α:γ ratio from 96:4 to 75:25. However by increasing the temperature to 0 °C it was possible to change the regioselectivity towards mainly γ-attack.

The observations may be rationalized by assuming the presence of a monoalkylcopper complex (A) and a dialkylcopper complex (B) in the reaction mixture (Scheme 2),‡[13] the former of which reacts to give the γ-product[10,14] and the latter to give the α-product (Scheme 3).[10a,10b,15] In support of this assumption the reaction of (**1**) with preformed Bu$^n{}_2$CuLi yielded (**2**):(**3**) in a ratio of 96:4. Thus, with a reactive substrate, or if the Grignard reagent is added slowly, most of

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‡ Li_2CuCl_4 is convenient to use since it is soluble in most solvents and it is rapidly reduced *in situ* to a copper(I) species by the Grignard reagent even at −78 °C.[13]

the reaction occurs *via* complex (A), whereas with a less reactive substrate or if the Grignard reagent is added quickly most of the reaction occurs *via* complex (B). This phenomenon would also account for the lower $\alpha:\gamma$ ratios obtained from allylic halides than from allylic acetates.§ The lower propensity of complex (B) for γ-attack could be accounted for by slower reductive elimination in the absence of an electron-withdrawing halogen ligand,¶ allowing time for rearrangement to a π-allyl system (Scheme 3).[10d,11] A common intermediate is frequently assumed in copper-catalysed Grignard coupling reactions,|| but our results suggest that this may not always be the case.

There is one previous example of regiochemical reversal in a copper-catalysed Grignard reaction of an allylic substrate. A primary allylic derivative of benzothiazol-2-thiol afforded mainly α-attack in diethyl ether–THF 1:2 but exclusively γ-attack in diethyl ether.[16] Very recently Goering *et al.* reported that by changing the copper catalyst to copper cyanide it was possible to direct the Grignard coupling with allylic carboxylates towards exclusively γ-attack.[11]

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§ There are many examples reported in the literature but without explanations; see for example: M. Schmid, F. Gerber, and G. Hirth, *Helv. Chim. Acta,* 1982, **65**, 684.

¶ It is known that electron-withdrawing ligands accelerate reductive elimination: T. Yamamoto, A. Yamamoto, and S. Ikeda, *J. Am. Chem. Soc.,* 1971, **93**, 3350, 3360.

|| For example in the Li_2CuCl_4-catalysed cross-coupling of alkyl halides with Grignard reagents a monoalkyl copper species has been assumed (*cf.* ref. 13). For the corresponding reactions of allylic oxygen derivatives a dialkylcopper species is usually assumed: Y. Gendreau and J. F. Normant, *Tetrahedron,* 1979, **35**, 1517.

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