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MECHANISTIC VIEWS OF STEREOSELECTIVE SYNTHESIS OF TRI- AND TETRA-SUBSTITUTED ALKENES, PART I; THE ORGANIC CHEMISTRY NOTEBOOK SERIES, A DIDACTICAL APPROACH, Nº 3

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ABSTRACT

As underlined in two previous papers in: "The Organic Chemistry Notebook Series, a Didactical Approach", the presentation of synthesis works in a verbal and graphical succinct manner, needs a didactical approach. Isomerically pure tri- and tetra-substituted alkenes are difficult to obtain as shown in several publications. We used a series of reactions to synthesize tri- and tetra-substituted alkenes as reviewed by W. Carruthers, and we have proposed didactical and mechanistic views for the reviewed reactions.

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ANALYSIS AND MECHANISTIC PROPOSALS

As academics we are concerned with the didactical importance of covering the needs of debutant students in organic synthesis. This is a third study in: "The Organic Chemistry Notebook Series, a Didactical Approach" [1,2]. The present article is an analytical and didactical approach to stereoselective synthesis of tri- and tetra-substituted alkenes as reviewed by W. Carruthers [3]. Tri- and tetra-substituted alkenes are difficult to obtain. Authors [3,4] signaled that the substrate α-chloro-aldehyde or –ketone, in its way to alkene, finds its critical step when reacting with Grignard reagent. Also, the most reactive conformation for the substrate is when the carbonyl group and the carbon-chlorine are antiparallel dipoles [3,4]. This conformation allows an addition of Grignard reagent very stereo-selectively and from the side less hindered by R^1 and R^2 groups, on the α-carbon atom with respect to carbonyl [3,4]. The nucleophilic attacking group R^4 orients itself in an *anti* disposition with respect to the most hindering group between R^1 and R^2 [3,4]. The derived chlorohydrin is then submitted to stereoselective reactions to afford the alkene where three of the double bond substituents come from the alfa-chloro-aldehyde, -ketone and the fourth one comes from Grignard reagent [3,4]. Figure 1 shows the corresponding mechanistic view.

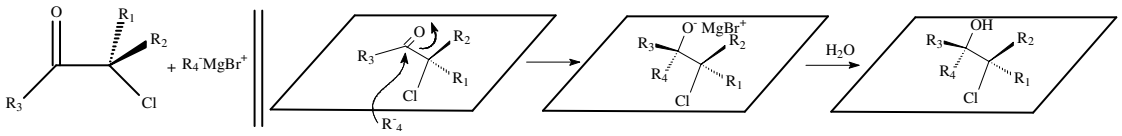

Figure 1. *Halohydrin by nucleophilic attack (R^4) over C=O of α-chloro-aldehyde, -ketone*

As an example let us examine the synthesis of (*E*)-3-methyl-2-pentene [3,4] (Figure 2), and let us propose the corresponding mechanistic view (Figure 3).

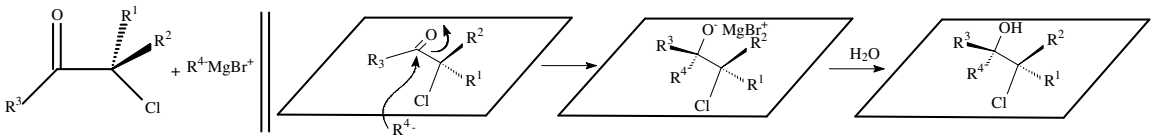

Figure 2. *Synthesis of (E)-3-methyl-pentene as reviewed by W. Carruthers* [3]

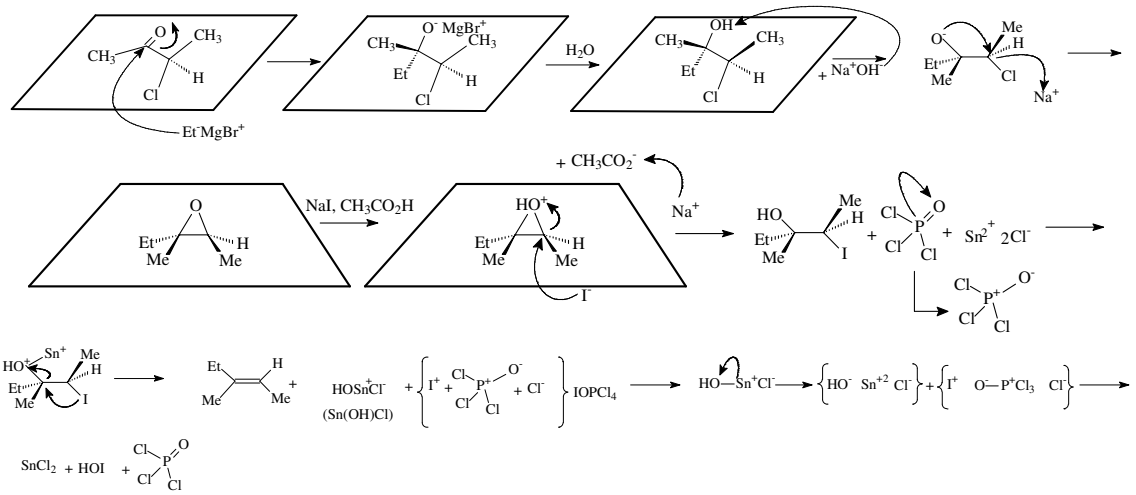

Figure 3. *Synthesis of (E)-3-methyl-pentene, mechanistic view*

Similarly, a series of stereo-selective reactions with methylmagnesium iodide (Grignard reagent) onto substrate 2-chloropentane-3-one gave rise to (*Z*)-3-methyl-2-pentene [3,4] as shown in the mechanism of Figure 4. These reaction series are an elegant way to obtain pure stereo-isomers.

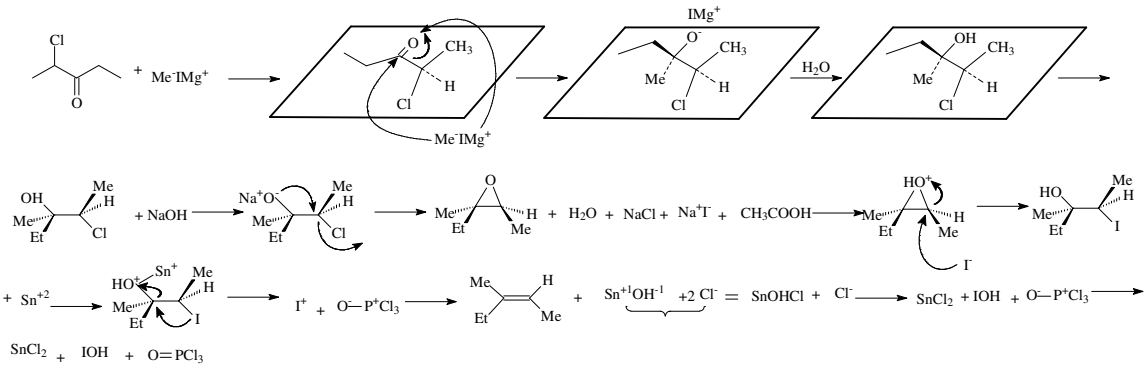

Figure 4. *Synthesis of (Z)-3-methyl-2-pentene, mechanistic view*

A different reaction to afford the stereo-specific obtaining of 2- or 3-alkylated allylic alcohol from a propargylic alcohol is achieved by reduction of propargylic alcohol into β- or γ-iodoallylic alcohols with aluminium hydride reagent (modified) and ulterior reaction of the reduction product with iodine [3,5], Figure 5.

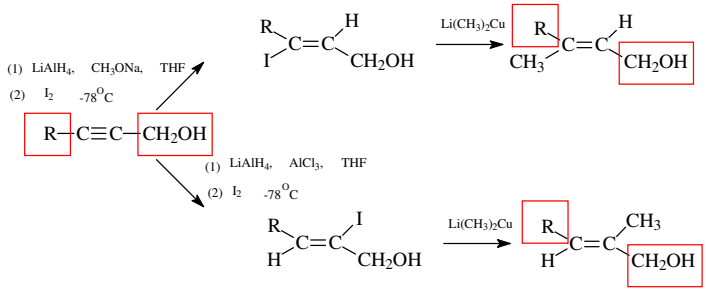

Figure 5. *Synthesis of 3- or 2-alkylated allylic alcohols where the susbtituents, originally present in the propargyl alcohol, are* trans *to each other; reviewed by W. Carruthers* [3]

Reduction is done with presence of NaOMe and the final product is only γ-iodoallylic alcohol. If reduction is carried out with $LiAlH_4$ in the presence of $AlCl_3$, final iodination gives final β-iodoallylic alcohol exclusively.

The resulting iodo compounds with LiR_2Cu afford the corresponding substituted allylic alcohol, where the original substituents of the propargyl alcohol, are now *trans* to each other (Figure 5) [3,5]. The explicit mechanism for these reactions are shown on Figure 6 and 7. Figure 6 shows the mechanism for the synthesis of β-iodinated, allylic alcohol.

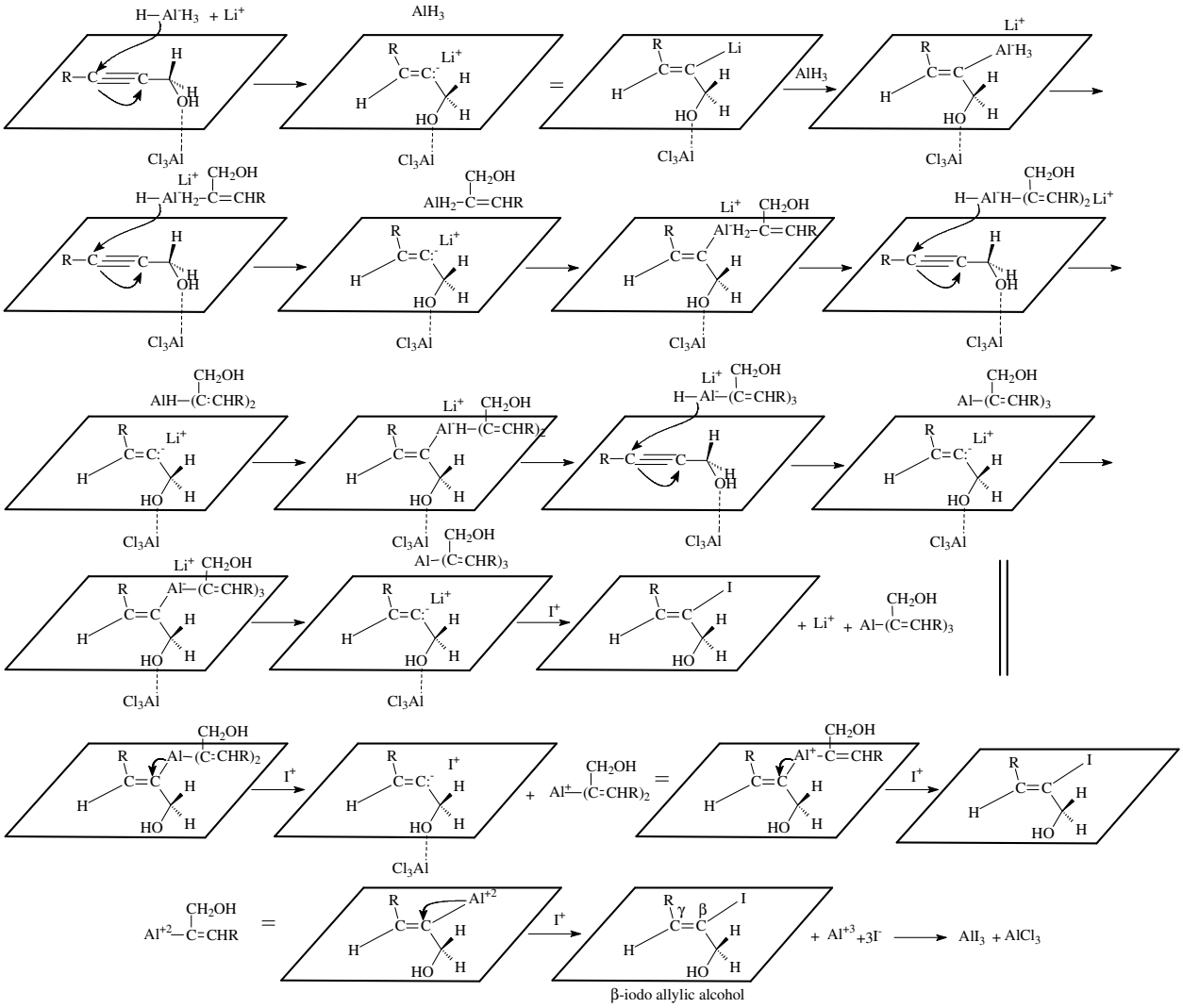

Figure 6. *Synthesis of β-iodinated allylic alcohol, mechanistic view*

For the γ-iodinated allylic alcohol, $NaOCH_3$ is employed (Figure 5) [3,5]. The corresponding mechanism is shown in Figure 7.

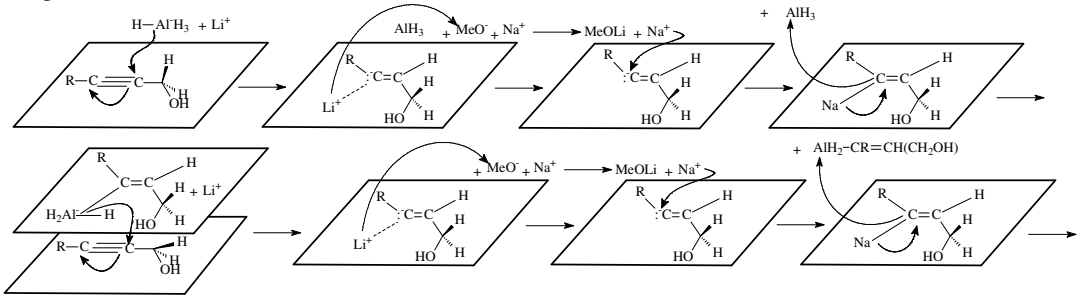

Figure 7. *Synthesis of γ-iodinated allylic alcohol, mechanistic view*

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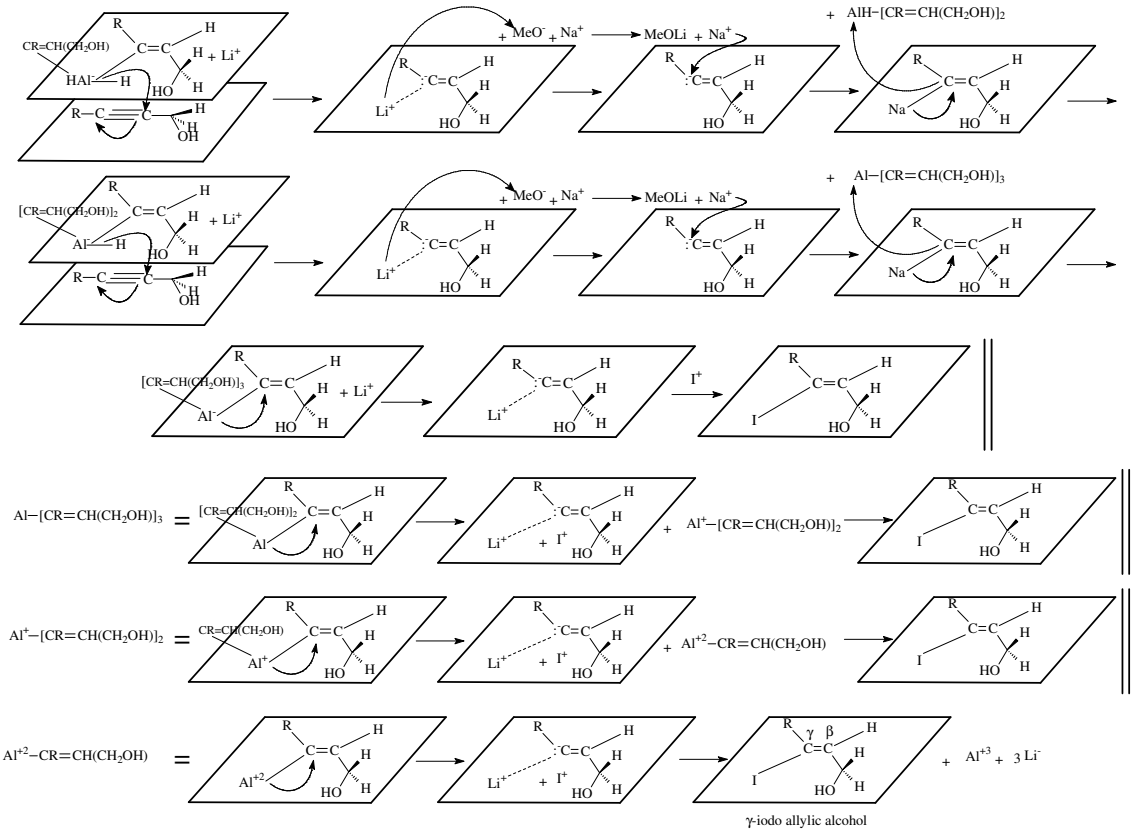

Figure 7. *Synthesis of γ-iodinated allylic alcohol, mechanistic view (Cont.)*

The γ-iodinated and β-iodinated allylic alcohols are easily transformed by action of lithium dimethylcuprate over substrates to afford 2-, 3-alkylated allylic alcohols as shown in Figure 8.

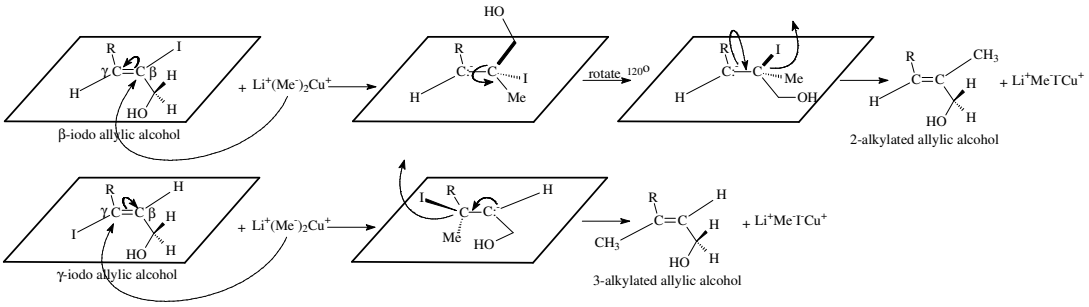

Figure 8. *Transformation of β-, γ-iodinated allylic alcohols into 2-, 3-alkylated allylic alcohols; mechanisms*

This method found application in the stereo-specific C=C bond formation in the synthesis of trisubstituted derivatives. This was the case for the key step in the synthesis of the *dl*-C18 *Cecropia* juvenile hormone, as reviewed by W. Carruthers [3,6], Figure 9.

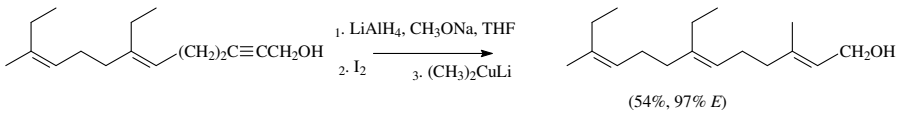

Figure 9. *Key step in the synythesis of dl-C18 Cecropia juvenile hormone; reviewed by W. Carruthers* [3]

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Figure 10 is the mechanism corresponding to the key step in the synthesis of *dl*-C18 *Cecropia* juvenile hormone.

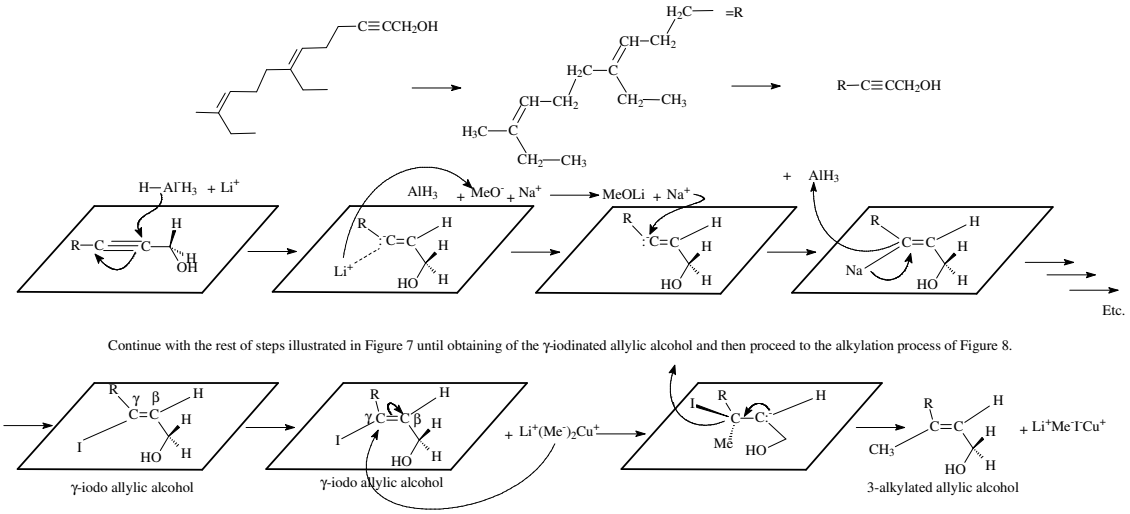

Figure 10. *Key step in the synthesis of dl-C18 Cecropia juvenile hormone; mechanism*

Organocopper and organoborane reagents are employed to obtain stereoselectively tri- and tetra-substituted alkenes by addition on alkynes [3,7]. Organocuprates lead to $\beta\beta$-dialkylacrylic esters by reaction with $\alpha\beta$-acetylenic esters (Figure 11) [3]. The structure of each stereoisomer depends on the temperature and the solvent [3]. High yield of β,β-dialkylacrylic ester is achieved at -78°C in THF [3]. Contrasting with reactions employing propargyl alcohols, this reaction produces alkenes in which the substituents in the acetylenic precursor are *cis* to each other in the alkene [3].

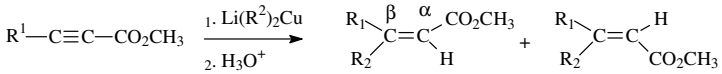

Figure 11. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocuprates; reviewed by W. Carruthers* [3]

The mechanistic views conducting to alkenes by this method are exposed in Figure 12.

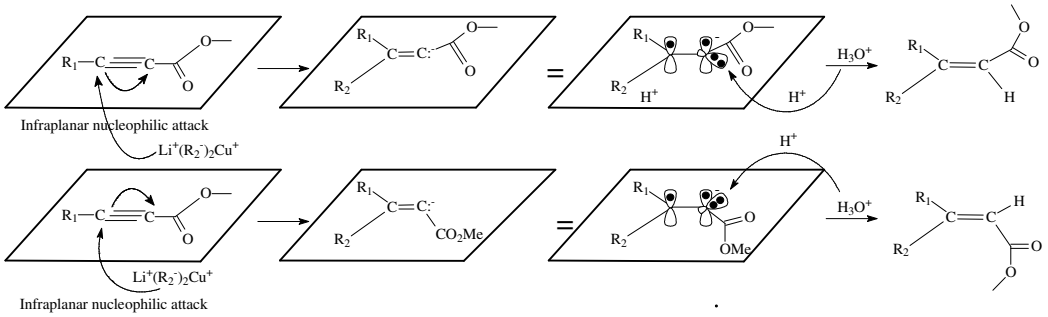

Figure 12. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocuprates; mechanism*

Organocopper(I) reagents add readily to terminal alkynes giving rise to 1-alkenylcopper(I) compounds [3]. These organocopper(I) reagents are RCu.Alkyl copper(I) compounds that can be obtained from Grignard reagents and an equimolar quantity of copper(I) bromide or copper(I) bromide-dimethylsulphide complex [3]. Copper adds to the alkyne on the terminal carbon, adding the alkyl group of the alkylcopper(I) reagent, in a *syn* manner [3]. This kind of products, alkenylcopper(I) compounds, react with electrophiles like alkyl halides, $\alpha\beta$-unsaturated ketones and epoxides to afford trisubstituted alkenes with almost complete retention of configuration [3,7,8]. See Figure 13. The elaborated mechanism is shown in Figure 14.

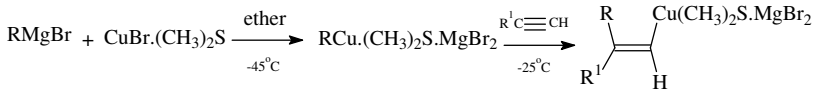

Figure 13. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocopper(I) reagents; reviewed by W. Carruthers* [3]

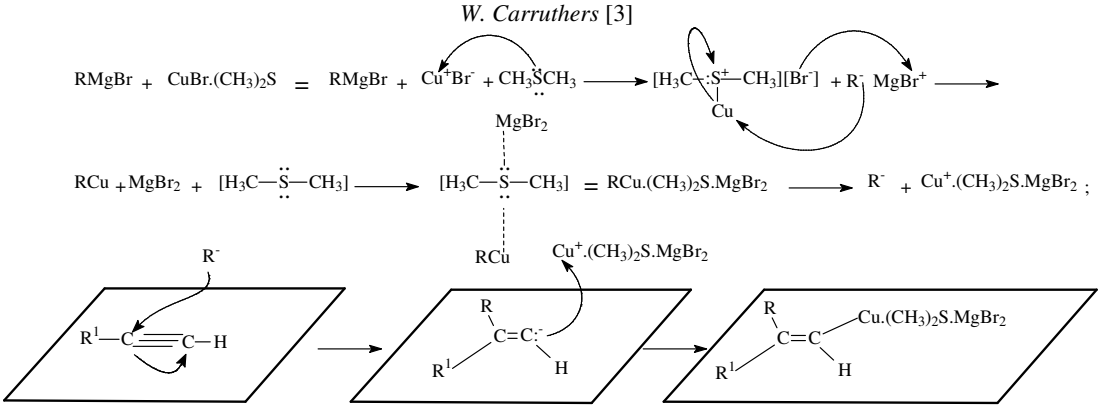

Figure 14. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocopper(I) reagents; mechanistic view*

The method was employed as shown in the examples of Figure 15.

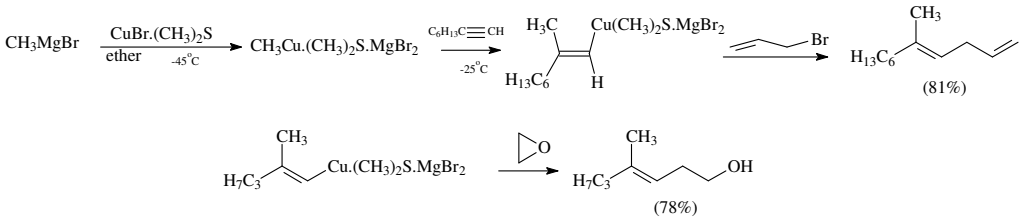

Figure 15. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocopper(I) reagents, other examples; reviewed by W. Carruthers* [3]

The corresponding mechanistic views are exposed in Figures 16 and 17.

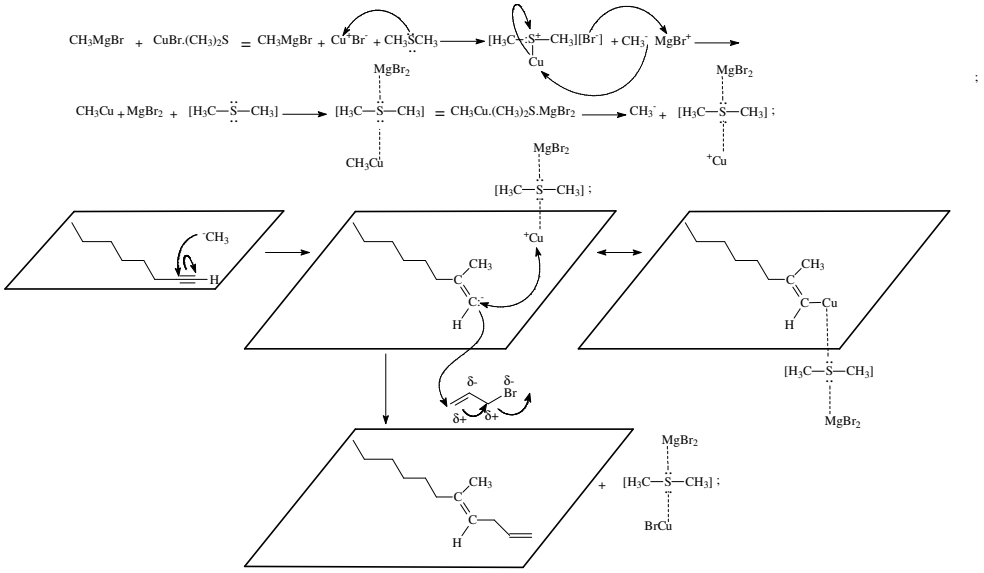

Figure 16. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocopper(I) reagents, other examples; mechanistic views*

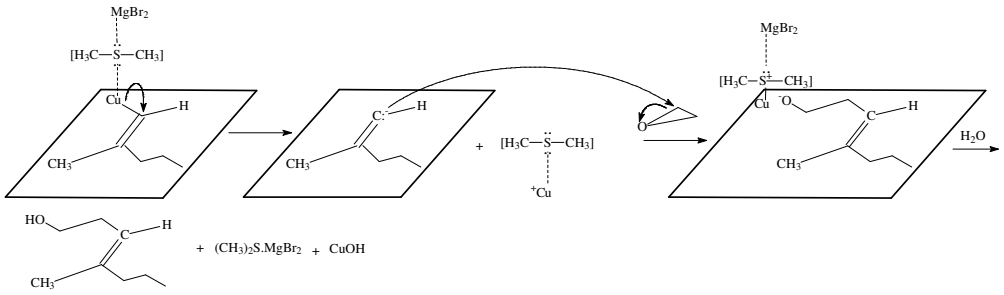

Figure 17. *Trisubstituted alkenes stereoselectively obtained from alkynes by addition of organocopper(I) reagents, other examples; mechanistic views*

Alkenyl iodides also react in the presence of $Pd(PPh_3)$ as catalyst to give conjugated dienes [3,9], Figure 18.

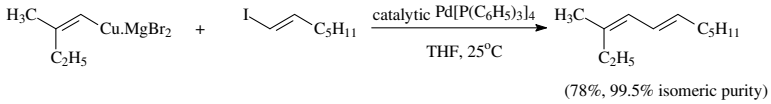

Figure 18. *Alkenyl iodide catalyzed by $Pd[P(C_6H_5)_3]_4$ to afford conjugated diene; reviewed by W, Carruthers* [3]

The corresponding mechanism is exposed in Figure 19.

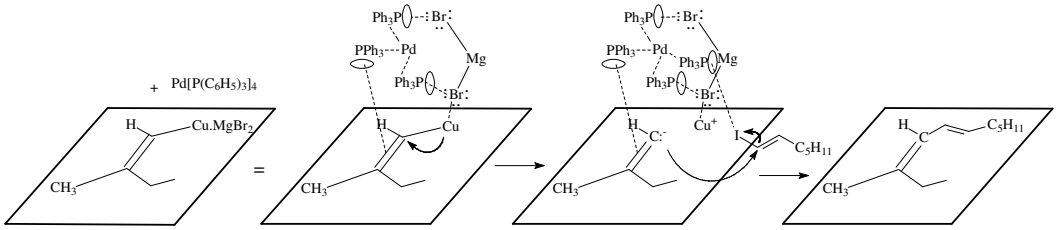

Figure 19. *Alkenyl iodide catalyzed by $Pd[P(C_6H_5)_3]_4$ to afford conjugated diene; mechanism*

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REFERENCES

1. Bravo, J. **2005**, *Bol. J. of Chem*., *23*, 1-10. (http://www.bolivianchemistryjournal.org, 2005).
2. Bravo, J.A., Mollinedo, P., Peñarrieta, J.M., Vila, J.L. **2013**, *Bol. J. of Chem*., *30*, 24-41 (http://www.bolivianchemistryjournal.org, 2013)
3. Carruthers, W. Some Modern Methods of Organic Synthesis, Cambridge University Press, 3rd ed., **1987**, Worcester, U.K., pp. 148-156.
4. Conforth, J.W., Conforth, R.H., Mathew, K.K. **1959**, *J. Chem. Soc*., 112.
5. Corey, E.J., Katzenellenbogen, J.A., Posner, G.H. **1967**, *J. Am. Chem. Soc*., *102*, 1433.
6. Corey, E.J., Katzenellenbogen J.A., Gilman N.W., Roman, S.A., Erickson, B.W. **1968**, *J. Am. Chem. Soc*., *90*, 5618.
7. Carruthers, W. In Comprehensive Organometallic Chemistry, eds. Wilkinson, G., Stone F.G.A., Abel, E.W., Vol. 7, Pergamon Press, **1982**, Oxford, U.K., pp. 716.
8. Marfat, A., McGuirk, P.R., Helquist, P. **1979**, *J. Org. Chem*., *44*, 3888.
9. Jabri, N., Alexakis, A., Normant, J.F. **1982**, *Tetraedron Lett*. *23*, 1589.