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THE PREPARATION OF GRIGNARD REAGENTS VIA THE HYDROMAGNESATION REACTION AND THEIR USES IN ORGANIC SYNTHESIS

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Summary

Titanium compounds catalyze the exchange of Grignard reagents having β-hydrogen(s) with unsaturated hydrocarbons, thus providing a convenient method of preparing alkyl-, allyl- or vinyl-Grignard reagents from olefins, conjugated dienes or acetylenes, respectively. Because of the versatility of Grignard reagents, this hydromagnesation reaction has become a powerful synthetic tool for utilization in organic syntheses.

With the advent of hydroboration of unsaturated hydrocarbons [1], numerous attempts have been made to develop hydrometallation reactions especially for their utilization in organic synthesis. Such efforts have included hydroalumination [2], hydrosilylation [3] and hydrozirconation [4]. Since Grignard reagents are one of the most versatile reagents in organic syntheses, there has been a great deal of interest in their preparation via the hydromagnesation reaction. However, magnesium hydride, HMgX (X = halogen), is not readily available, and thus the literal hydromagnesation reaction has not been developed [5]. But, fortunately, transition metal compounds catalyze the exchange of alkyl-Grignard reagents having β-hydrogen(s) with olefins, conjugated dienes or acetylenes, thereby providing a convenient method for the preparation of alkyl-, allyl- or vinyl-Grignard reagents, respectively. In this reaction, alkyl-Grignard reagents RMgX can be formally regarded as HMgX + olefins from which HMgX adds to unsaturated hydrocarbons, and hence this reaction is commonly known as the hydromagnesation reaction.

This short review attempts to cover the contributions which have been made in the field of hydromagnesation reactions, and their uses in organic synthesis.

1. The hydromagnesation reaction of olefins

In 1962 Cooper and Finkbeiner reported that the addition of a catalytic amount of $TiCl_4$ to an ether solution of n-PrMgBr and a certain olefin brings about a

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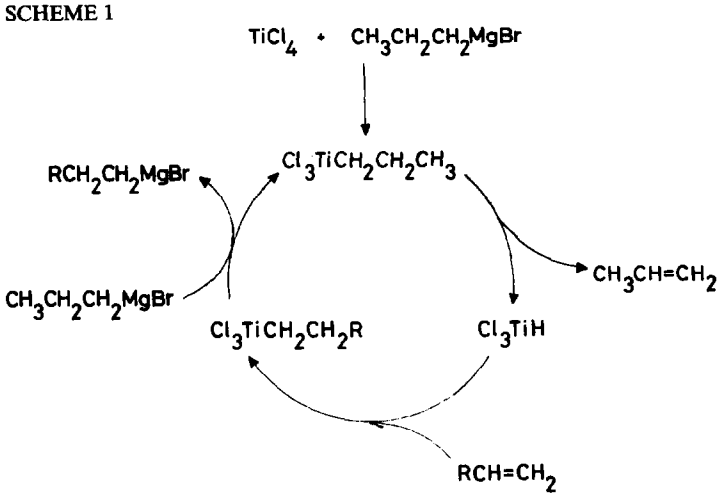
displacement reaction, producing propylene and a new Grignard reagent from the added olefin [6]. Cp_2TiCl_2 ($Cp = \eta^5$-C_5H_5), $Ti(O\text{-}i\text{-}Pr)_4$, $ZrCl_4$ and VCl_4 were also found to be effective catalysts.

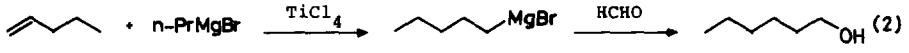
$$RCH{=}CH_2 + n\text{-}PrMgBr \xrightarrow{TiCl_4} RCH_2CH_2MgBr + CH_3CH{=}CH_2 \quad (1)$$

These authors suggested for this reaction the reaction mechanism shown in Scheme 1. In the first step, a propyltitanium compound is formed, which undergoes β-hydrogen elimination to yield a titanium hydride and propylene. Insertion of the carbon–carbon double bond into the Ti–H bond then affords a new alkyltitanium compound. Next titanium and magnesium exchange takes place affording a new Grignard reagent and propyltitanium compound, thereby closing the catalytic cycle.

SCHEME 1

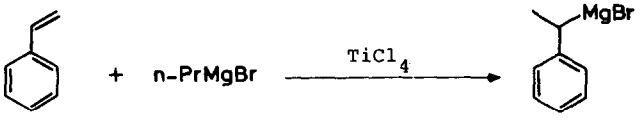


A large number of olefins having a terminal vinyl group were treated in this way with n-PrMgBr, and the reaction mixture was then treated with typical Grignard substrates such as CO_2, O_2 or HCHO. Products corresponding to the Grignard reagent derived from the olefin were isolated in 20–60% yields. A typical example is shown in eq. 2.



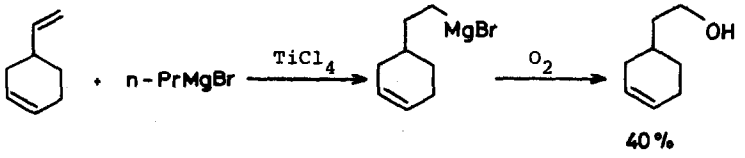
45%

Only terminal Grignard reagents are obtained from 1-alkenes, but styrene yields α-phenylethylmagnesium bromide predominantly.



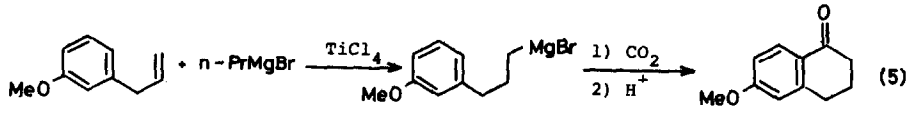
The exchange reaction takes place only with terminal vinyl groups ($RCH{=}CH_2$); internal double bonds and vinylidene groups ($RR'C{=}CH_2$) are unaffected. This fact

somehow restricts the synthetic utility of the reaction, but at the same time it allows the selective reaction of one double bond in unconjugated dienes, as exemplified by eq. 4.



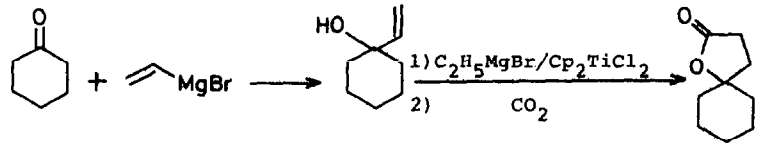
(4)

The olefin exchange reaction is a useful process for the preparation of Grignard reagents in cases where the olefin is available but the corresponding halide is not. Kagan and co-workers used it to prepare methoxytetralone from methoxyallylbenzene [7].



(5)

Eisch and Galle developed a two-step synthesis of γ- and δ-lactones from aldehydes or ketones which involves the addition of vinyl- or allyl-Grignard reagents to the appropriate carbonyl substrates, and Cp_2TiCl_2-catalyzed hydromagnesation of the resulting alkenols followed by carbonylation [8].



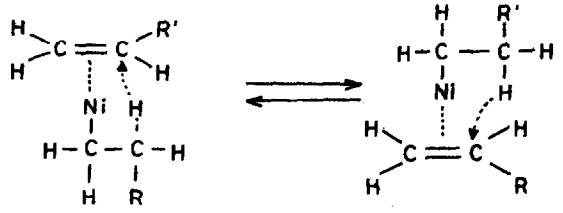
(6)

Markó and co-workers obtained analogous results using $NiCl_2$ as a catalyst. Olefins having a terminal vinyl group and an alkyl-Grignard reagent, in the presence of $NiCl_2$, lead to the primary alkyl-Grignard reagent, whereas styrene gives the secondary Grignard reagent [9].

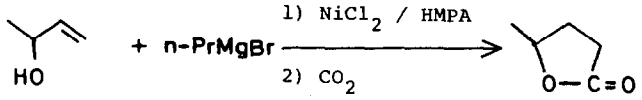
$$n\text{-}C_8H_{17}MgBr + CH_3CH{=}CH_2 \xrightarrow{NiCl_2} C_8H_{16} + CH_3CH_2CH_2MgBr \qquad (7)$$

It has been suggested that the alkyl-olefin exchange takes place via β-hydrogen transfer from an alkyl group to a π-complexed olefin within an alkylnickel-olefin complex (Scheme 2).

SCHEME 2



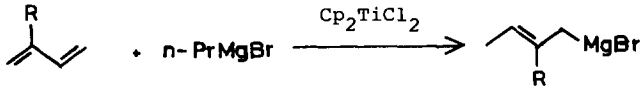
Nickel-catalyzed hydromagnesation reactions of allylic alcohols have been investigated [10].



(8)

2. The hydromagnesation reaction of conjugated dienes

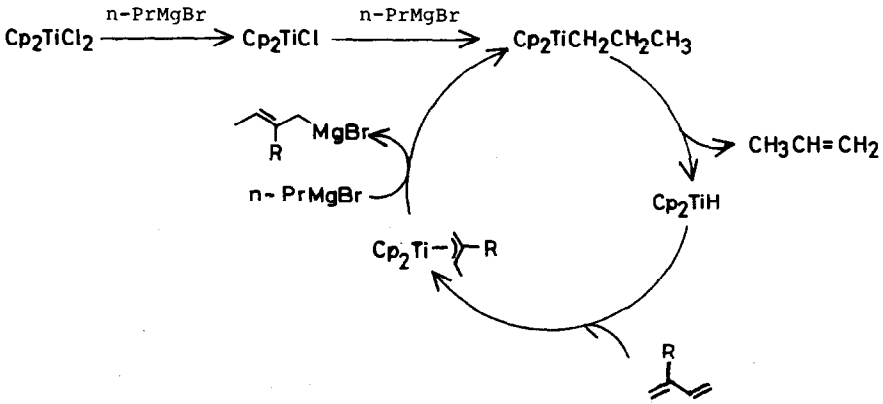
Although $TiCl_4$ is an excellent catalyst in the exchange reaction of olefins with an alkyl-Grignard reagent, it is not effective in the reaction with conjugated dienes. If Cp_2TiCl_2 is used as the catalyst instead of $TiCl_4$, however, the reaction occurs readily at room temperature, producing allylic Grignard reagents [11]. The reaction proceeds quantitatively with butadiene and 2-alkyl substituted 1,3-butadienes, but not with 4-alkyl substituted 1,3-dienes such as 1,3-pentadiene. The reaction with 2-alkyl substituted 1,3-butadienes takes place regioselectively to afford exclusively the following allylic Grignard reagents.



(9)

Based on the known reaction that hydrotitanation of isoprene with Cp_2TiH gives $Cp_2Ti(\eta^3$-1,2-dimethylallyl) [12], the following mechanism (Scheme 3) was proposed for this highly regiospecific exchange reaction.

SCHEME 3

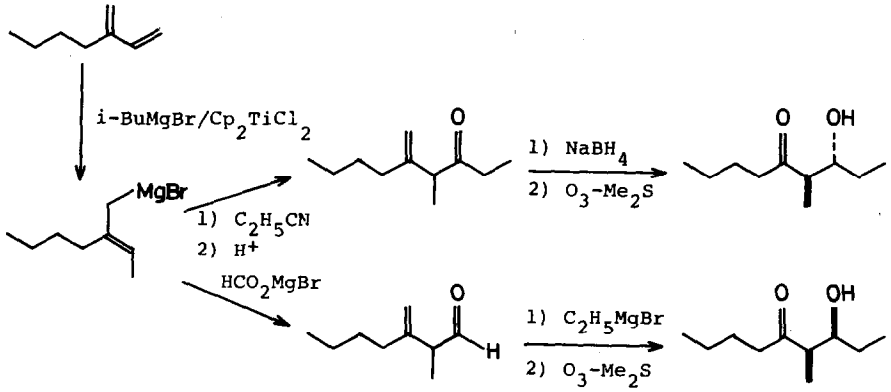


The present reaction is a useful process for preparation of allylic Grignard reagents of the type shown in eq. 9, because preparation of allylic Grignard reagents by direct metalation of allylic halides frequently suffers from the tendency of the resulting Grignard reagents to couple with the remaining halides, forming 1,5-alkadienes.

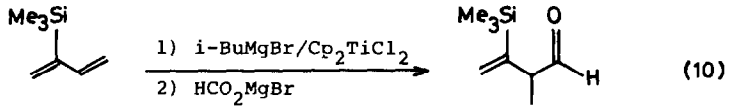
Recently it has been shown that α-methyl-β-methylidenecarbonyl compounds react highly selectively with nucleophiles to afford "Cram" products [13–16]. A combination of this finding with the hydromagnesation reaction of 2-alkyl-1,3-butadienes offers a practical and efficient method for stereo- and regio-controlled aldol synthesis [13]. As exemplified in Scheme 4, hydromagnesation of 2-butyl-1,3-butadiene, prepared by nickel-catalyzed coupling of butylmagnesium bromide and

chloroprene [17], followed by treatment with propionitrile or the magnesium salt of formic acid yields the corresponding α-methyl-β-methylidene alkyl ketone or aldehyde, respectively. Reaction of the α-methyl-β-methylidene alkyl ketone thus prepared with $NaBH_4$ and subsequent ozonolysis provides the *anti*-aldol, while its diastereoisomer is obtained by the reaction of the α-methyl-β-methylidene aldehyde with C_2H_5MgBr followed by ozonolysis.

SCHEME 4

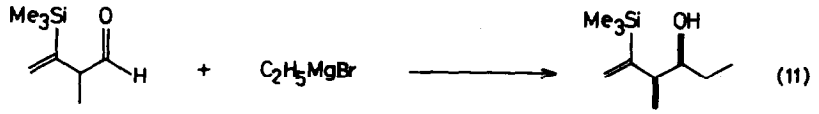


Hydromagnesation of 2-trimethylsilyl-1,3-butadiene and subsequent reaction with HCO_2MgBr affords 2-methyl-3-trimethylsilyl-3-butenal [14].

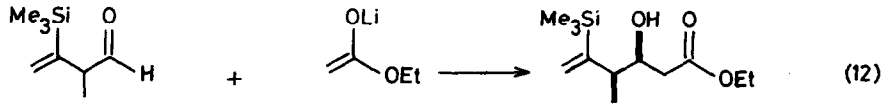


(10)

This aldehyde reacts with Grignard reagents [14] or enolate anions [15] with high diastereofacial preference, thus providing a highly selective method for β-methylhomoallyl alcohol derivatives, the preparation of which has attracted much interest in relation to the synthesis of macrolide and ionophore antibiotics [18].



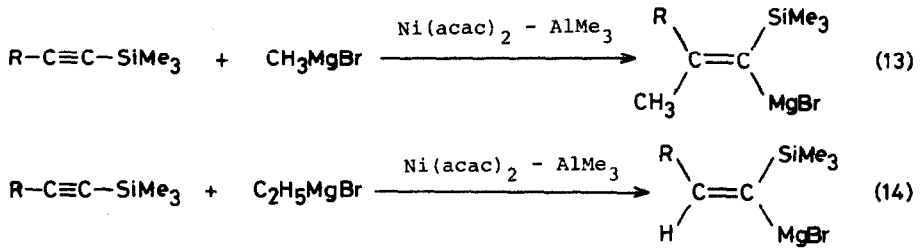
(11)



(12)

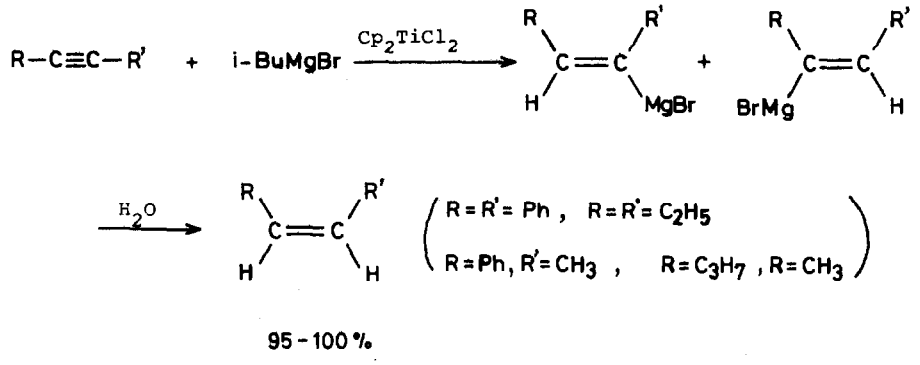
3. The hydromagnesation reaction of acetylenes

Carbomagnesation of silylacetylenes with CH_3MgBr catalyzed by nickel compounds proceeds stereo- and regio-selectively (eq. 13). When this reaction was carried out using C_2H_5MgBr instead of CH_3MgBr, the hydromagnesation product was obtained in 50% yield along with 30% of the dimerization product of silylacetylenes (eq. 14) [19].

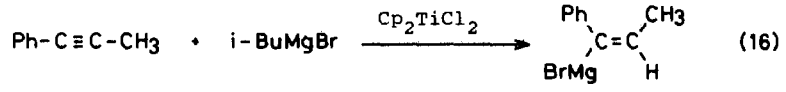


Colomer and Corriu reported that diphenylacetylene reacted with C_2H_5MgBr in the presence of Cp_2TiCl_2 to provide, after hydrolysis, a 70% yield of *trans*-stilbene and a 30% yield of a mixture of *cis*-stilbene and 1,2-diphenylethane [20]. Although this result suggested low stereoselectivity of the Cp_2TiCl_2-catalyzed hydromagnesation reaction of acetylenes, we reinvestigated this reaction and found that it proceeds highly selectively.

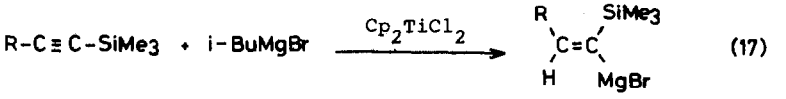
Disubstituted acetylenes react with i-BuMgBr in the presence of a catalytic amount of Cp_2TiCl_2 in ether at room temperature to produce (*E*)-alkenyl Grignard reagents in excellent yields and thus, after hydrolysis, *cis*-olefins of high purity can be obtained [21].



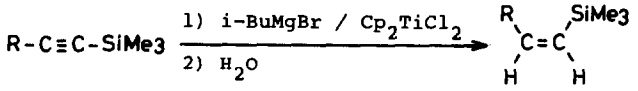
The reaction occurs with low regioselectivity for unsymmetrical dialkylacetylenes, but it takes place with high regioselectivity for alkylarylacetylenes, with the magnesium being placed at the carbon containing the aryl group.



The hydromagnesation of 1-trimethylsilyl-1-alkynes also proceeds highly selectively; previously, we reported that the reaction proceeded with about 95% selectivity [21]; however, it has now become clear that if the reaction is carried out at 25°C for 6 h, the selectivity is almost 100%. Thus the reaction offers a selective and operationally simple route to various vinylsilanes which are versatile synthetic intermediates.

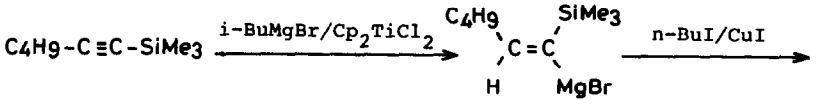


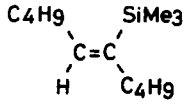
The hydromagnesation of silylacetylenes followed by hydrolysis provides a simple method for the preparation of (*Z*)-1-trimethylsilyl-1-alkenes [21,22]. From one of our recent findings [23], it should be noted, however, that sometimes under hydrolysis conditions, isomerization of (*Z*)-1-trimethylsilyl-1-alkenes to (*E*)-isomers takes place; the exact hydrolysis conditions under which this isomerization occurred are yet to be standardized.



(18)

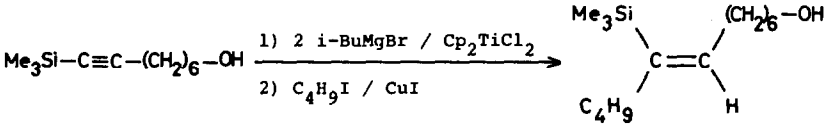
Reactions of the vinyl Grignard reagents obtained from silylacetylenes with methyl iodide or allyl halides, or alkyl iodides in the presence of CuI afforded the corresponding 1,2-dialkylvinylsilanes [24].





(19)

The utility of this reaction sequence was illustrated by the synthesis of a sex pheromone of the false colding moth (eq. 20) and dihydrojasmone (eq. 21).



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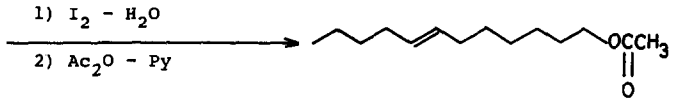
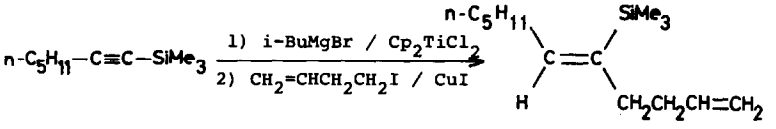
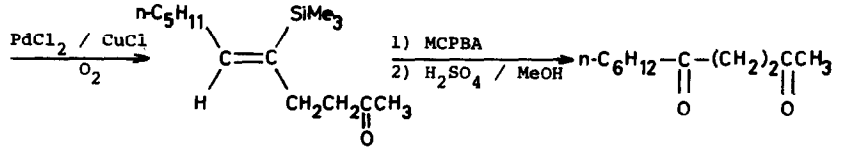
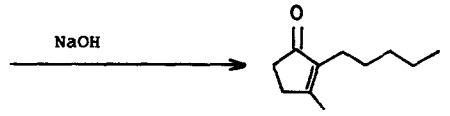


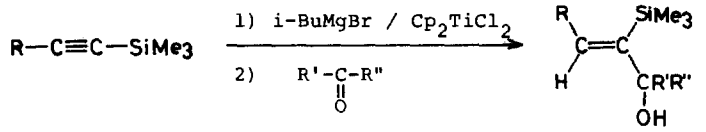






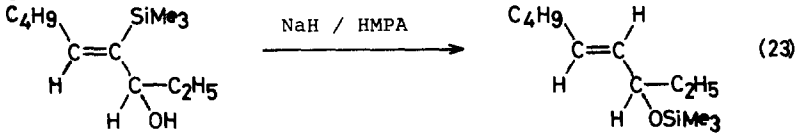
(21)

Since the hydromagnesation of silylacetylenes followed by treatment with aldehydes or ketones affords various β-trimethylsilylallyl alcohols in excellent yields, their reactions have been investigated [25,26].



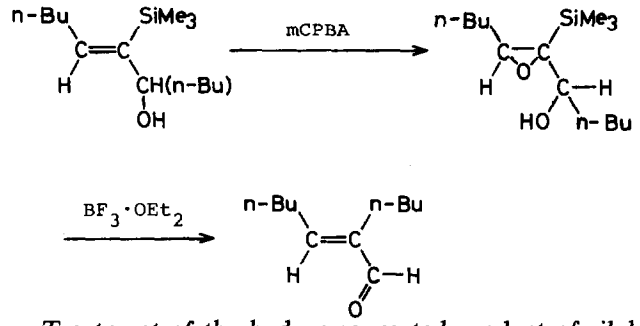
(22)

Treatment of β-trimethylsilylallyl alcohols with NaH in HMPA (or KH in THF) results in a facile 1,3-silyl group shift from carbon to oxygen, thereby offering a convenient synthesis of allyl silyl ethers [25], useful precursors of silyl enol ethers [27] and allylic alcohols.

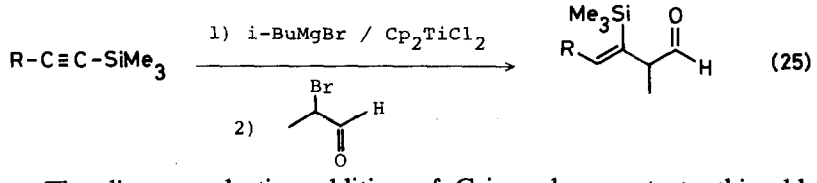


(23)

Epoxidation of β-trimethylsilylallyl alcohols followed by treatment of the resulting β′-hydroxy-α,β-epoxysilanes with $BF_3 \cdot OEt_2$ results in the rearrangement of the epoxysilane skeleton followed by the Peterson olefination, leading to α,β-unsaturated carbonyl compounds [28].

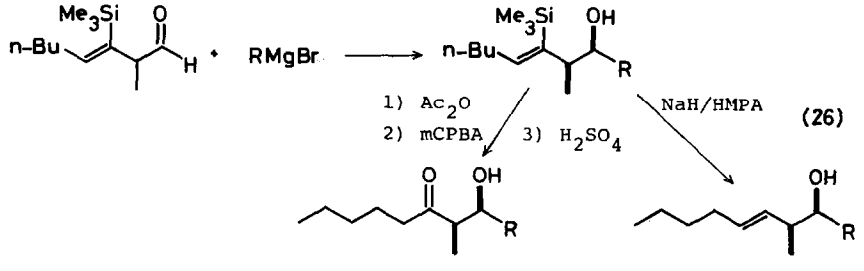


Treatment of the hydromagnesated product of silylacetylenes with 2-bromopropanal gives 2-methyl-3-trimethylsilyl-3-alkenyl aldehyde [14].



(25)

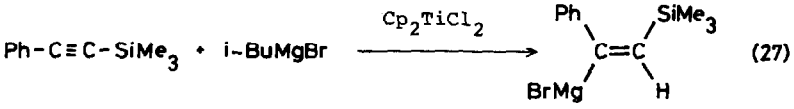
The diastereoselective addition of Grignard reagents to this aldehyde affords 2-methyl-3-trimethylsilyl-3-alkenyl alcohols, which can be subsequently converted to



(26)

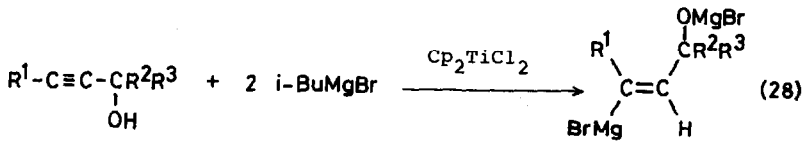
syn-β-methylhomoallyl alcohols and *syn*-β-hydroxy-α-methyl ketones, useful intermediates for the synthesis of macrolide antibiotics.

Phenylsilylacetylene is also hydromagnesated selectively; however, in this case, the magnesium is always placed at the carbon bonded to the phenyl group [21].



(27)

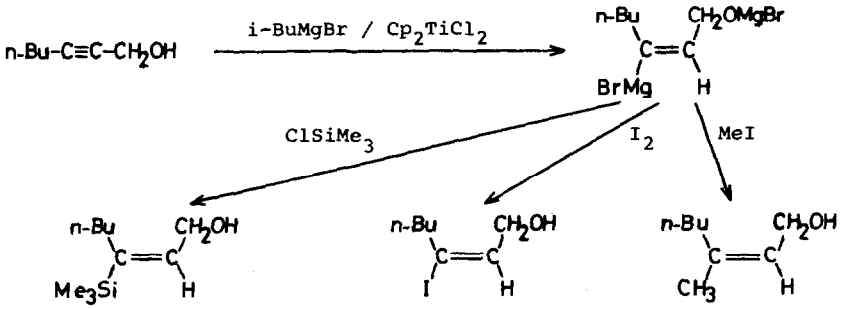
Cp_2TiCl_2-catalyzed hydromagnesation of propargylic alcohols with two equivalents of i-BuMgBr proceeds with 100% selectivity to give the Grignard reagents shown in eq. 28 [29].



(28)

The *syn*-addition pathway of this reaction is noteworthy because hydroalumination of propargylic alcohols with $LiAlH_4$ [30] or the addition of organocopper compounds [31] or Grignard reagents in the presence of a copper(I) salt [32] to propargylic alcohols follows the *anti*-pathway. This reaction provides a convenient way to various γ,γ′-disubstituted allyl alcohols as is exemplified by Scheme 5, which shows the synthesis of 3-(*E*)-iodoallyl alcohol [29], 3-(*E*)-trimethylsilylallyl alcohol [33] and 3-(*Z*)-methylallyl alcohol [29].

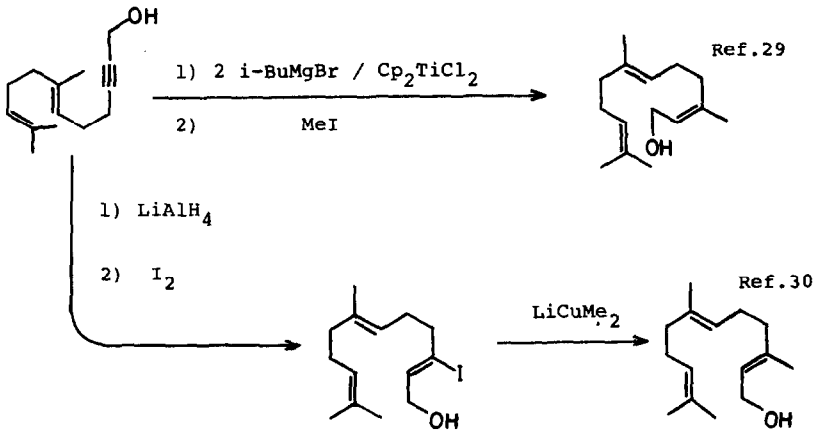
SCHEME 5



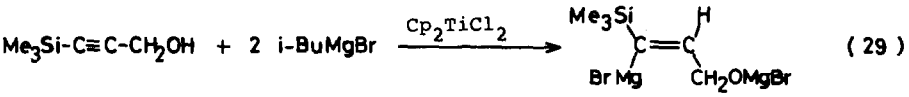
The most interesting fact is that this reaction provides a method of preparing terpenes or related substances, the stereochemistries of which are opposite to those obtained via the hydroalumination-iodination-alkylation method developed by Corey starting with the same propargylic alcohols; thus Scheme 6 shows the preparation of (*E*,*Z*)- and (*E*,*E*)-farnesol by using these two procedures.

Hydromagnesation of 3-trimethylsilylpropargyl alcohol follows the *syn*-pathway, usually observed with disubstituted acetylenes and propargylic alcohols to yield the corresponding (*Z*)-alkenyl Grignard reagents, which, however, isomerize rapidly

SCHEME 6

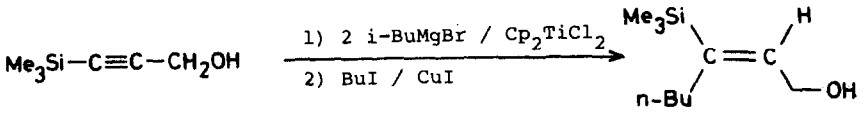


into their stereoisomers under the reaction conditions. Thus, 6 h-reaction of 3-trimethylsilylpropargyl alcohol with i-BuMgBr at 25°C afforded the (*E*)-alkenyl Grignard reagent quantitatively [34].



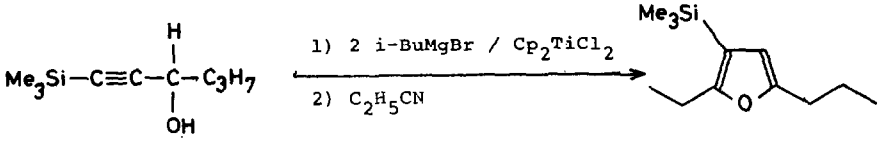
(29)

By using this reaction, (*E*)-3-trimethylsilyl-2-alken-1-ols, the halides of which act as alkylative equivalents of alkyl vinyl ketones, can be readily prepared as shown in eq. 30.



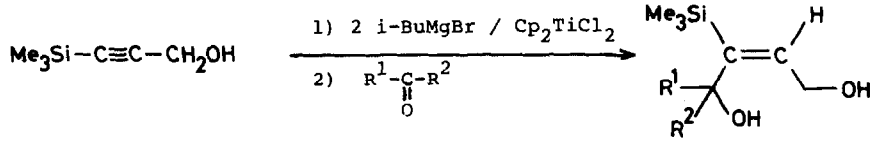
(30)

Hydromagnesation of 3-trimethylsilylpropargyl alcohols followed by treatment with nitriles affords 3-furanyltrimethylsilane [35].



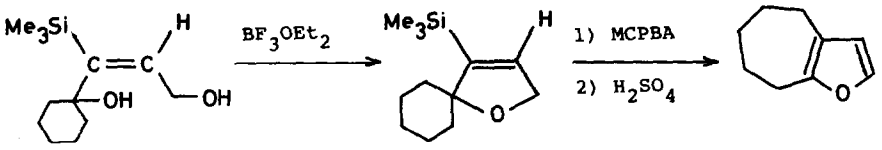
(31)

(*E*)-3-Trimethylsilyl-2-alken-1,4-diols are prepared from 3-trimethylsilylpropargyl alcohol via hydromagnesation and subsequent reaction with aldehydes or ketones [36].



(32)

The diols thus prepared are readily dehydrated to 3-trimethylsilyl-2,5-dihydrofurans by treatment with $BF_3 \cdot OEt_2$ which can be converted to furans through epoxidation and subsequent treatment with H_2SO_4 [36].



In summary, hydromagnesation reactions provide a convenient and selective method of preparing various Grignard reagents. Because of the versatility of these reactions, continued rapid development of this powerful synthetic tool is very likely in the near future.

References

1 H.C. Brown, Organic Syntheses via Boranes, John Wiley & Sons, New York, 1975.
2 For olefins: F. Sato, in Y. Ishii and M. Tsutsui (Eds.), Fundamental Research in Homogeneous Catalysis, Vol. 2, Plenum, New York, 1978, p. 81. For acetylenes: E. Negishi, J. Organomet. Chem. Libr., 1 (1976) 93.
3 M. Kumada, K. Tamao and J. Yoshida, J. Organomet. Chem., 239 (1982) 115.
4 J. Schwartz, Pure Appl. Chem., 52 (1980) 733.
5 Titanium compound catalyzed hydromagnesation of olefins and acetylenes with MgH_2 has been reported: E.C. Ashby and T. Smith, J. Chem. Soc., Chem. Commun., (1978) 30; see also E.C. Ashby and R.D. Ainské, J. Organomet. Chem., 250 (1983) 1.
6 G.D. Cooper and H.L. Finkbeiner, J. Org. Chem., 27 (1962) 1493; H.L. Finkbeiner and G.D. Cooper, ibid., 27 (1962) 3395.
7 A. Horeau, L. Menager and H. Kagan, Bull. Soc. Chim. Fr., (1971) 3571.
8 J.J. Eisch and J.E. Galle, J. Organomet. Chem., 160 (1978) C8.
9 L. Farady, L. Bencze and L. Markó, J. Organomet. Chem., 10 (1967) 505; 17 (1969) 107; L. Farady and L. Markó, ibid., 28 (1971) 159.
10 H. Felkin and G. Swierczewski, Tetrahedron, 31 (1975) 2735.
11 F. Sato, H. Ishikawa and M. Sato, Tetrahedron Lett., 21 (1980) 365.
12 H.A. Martin and J. Jellinek, J. Organomet. Chem., 12 (1968) 149.
13 F. Sato, Y. Takeda, H. Uchiyama and Y. Kobayashi, J. Chem. Soc., Chem. Commun., (1984) 1132.
14 F. Sato, M. Kusakabe and Y. Kobayashi, J. Chem. Soc., Chem. Commun., (1984) 1130.
15 F. Sato, M. Kusakabe, T. Kato and Y. Kobayashi, J. Chem. Soc., Chem. Commun., (1984) 1331.
16 K. Suzuki, E. Katayama and G. Tsuchihashi, Tetrahedron Lett., 25 (1984) 2479.
17 K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato and M. Kumada, Bull. Chem. Soc. Jpn., 49 (1976) 1958; A. Hosomi, M. Saito and H. Sakurai, Tetrahedron Lett., (1979) 429.
18 S. Masamune and W. Choy, Aldrichimica Acta, 15 (1982) 47; D.A. Evans, ibid., 15 (1982) 23.
19 B.B. Snider, M. Karras and R.S.E. Conn, J. Am. Chem. Soc., 100 (1978) 4624.
20 E. Colomer and R. Corriu, J. Organomet. Chem., 82 (1974) 367.
21 F. Sato, H. Ishikawa and M. Sato, Tetrahedron Lett., 22 (1981) 85.
22 T. Hirao, N. Yamada, Y. Oshiro and T. Agawa, Chem. Lett., (1982) 1997.
23 F. Sato, unpublished observations.
24 F. Sato, H. Watanabe, Y. Tanaka, T. Yamaji and M. Sato, Tetrahedron Lett., 24 (1983) 1041.
25 F. Sato, Y. Tanaka and M. Sato, J. Chem. Soc., Chem. Commun., (1983) 165.
26 K. Yamamoto, T. Kimura and Y. Tomo, Tetrahedron Lett., 25 (1984) 2155.
27 H. Suzuki, Y. Koyama, Y. Morooka and T. Ikawa, Tetrahedron Lett., (1979) 1415.
28 F. Sato, Y. Tanaka and H. Kanbara, J. Chem. Soc., Chem. Commun., (1983) 1024.
29 F. Sato, H. Ishikawa, H. Watanabe, T. Miyake and M. Sato, J. Chem. Soc., Chem. Commun., (1981) 718.

30 E.J. Corey, J.A. Katzenellenbogen and G.H. Posner, J. Am. Chem. Soc., 89 (1967) 4245.
31 J.G. Duboudin, B. Jousseaume, A. Alexakis, G. Cahiez, J. Villieras and J.F. Normant, C.R. Acad. Sci. Ser. C, 285 (1977) 29.
32 J.G. Duboudin and B. Jousseaume, J. Organomet. Chem., 168 (1979) 1.
33 J. Kang, W. Cho and W.K. Lee, J. Org. Chem., 49 (1984) 1838.
34 F. Sato, H. Watanabe, Y. Tanaka and M. Sato, J. Chem. Soc., Chem. Commun., (1982) 1126.
35 F. Sato and H. Katsuno, Tetrahedron Lett., 24 (1983) 1809.
36 F. Sato, H. Kanbara and Y. Tanaka, Tetrahedron Lett., 25 (1984) 5063.