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VINYL-COPPER DERIVATIVES XII : STEREOSPECIFIC SYNTHESIS OF ALLYLIC AMINES BY AMINOMETHYLATION OF ORGANOCOPPER REAGENTS

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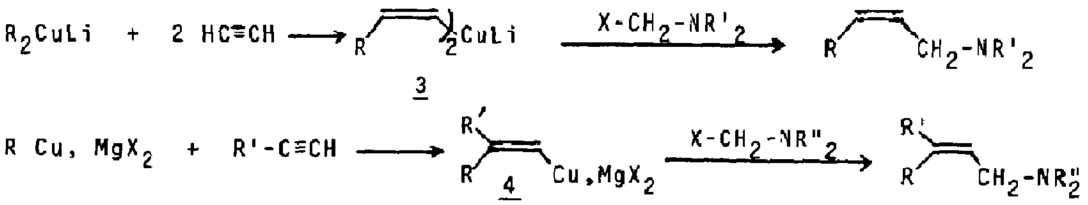
The carbocupration or hydroalumination of alkynes followed by aminomethylation yields allylic amines. The stereochemical integrity of the alkenyl moiety is completely retained in both cases.

The reaction of various organometallic derivatives (Li, Mg, Zn) with Mannich reagents $X\text{-}CH_2\text{-}NR_2$ (X=OR, SR, halogen) is known to afford the aminomethylation product[1]. We wish to report in this communication that organocuprate reagents behave similarly :

$$Hept_2CuLi \quad + \quad 2\ \underset{\underline{1}}{nBu\text{-}O\text{-}CH_2\text{-}NEt_2} \xrightarrow{Ether} 2\ Hept\text{-}CH_2\text{-}NEt_2 \qquad 72\ \%$$

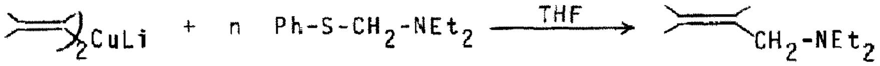
$$Hept_2CuLi \quad + \quad 2\ \underset{\underline{2}}{Ph\text{-}S\text{-}CH_2\text{-}NEt_2} \xrightarrow{THF} 2\ Hept\text{-}CH_2\text{-}NEt_2 \qquad 92\ \%$$

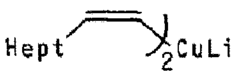
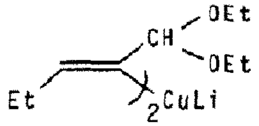
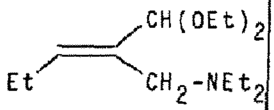
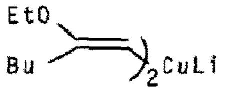
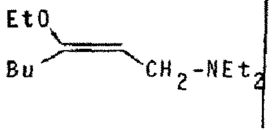
In this reaction, <u>*both*</u> alkyl groups of the cuprate reagent react as well. We have applied this reaction to alkenyl-copper[2] and cuprates[3] reagents, obtained stereospecifically by the carbometallation of alkynes. This reaction should lead to stereospecifically substituted tertiary allylic amines :



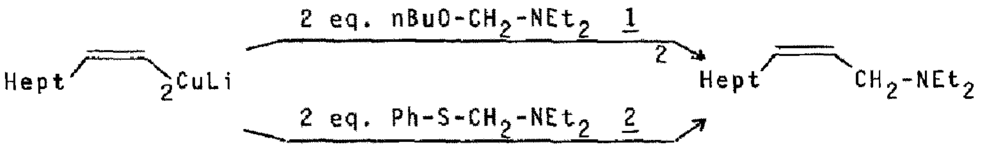
Indeed, with cuprates 3, this one-pot procedure gave the expected product either with the α-aminoether 1[1a] or with the α-aminothioether 2[1c].

Table 1



Entry	Cuprate	n equiv.	Product [5]	Yield[a]	Eb °C/mm Hg
1	 [c]	2		78%[b]	125°/15
2	"	1,5	"	95%	
3	 [d]	2		79%	73°/0.01
4	 [e]	1,65		74%	70°/0.05

a/ Isolated yield based on the α-aminothioether added ; b/ In Et_2O solvent the yield is 70% ; c/ Prepared in situ according ref.3a,b ; d/ Prepared in situ according ref.3c, modified by the addition of 2 eq. of $HC{\equiv}C\text{-}CH(OEt)_2$ to 1 eq. of Et_2CuLi, under the same experimental conditions ; e/ Prepared in situ according ref.2b, modified as above.



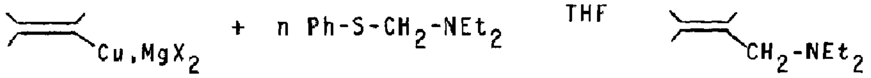
Et_2O : 52%
THF : 31%

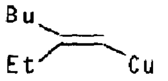
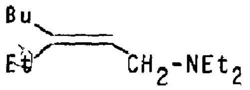
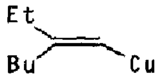
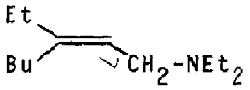
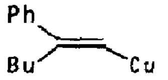
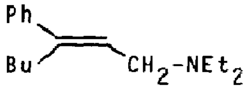
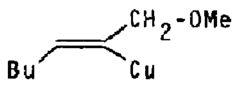
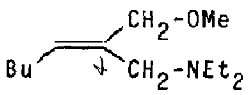
Et_2O : 70%
THF : 78%

The best yields are obtained with α-aminothioether 2 and *both* alkenyl groups of the cuprate react as well. On the other hand, vinyl-copper 4 reacts very sluggishly[4] with 1 but more easily with 2. Since 2 is easily prepared and in quantitative yield[1c], we have used this Mannich reagent for the synthesis of various allylic amines.

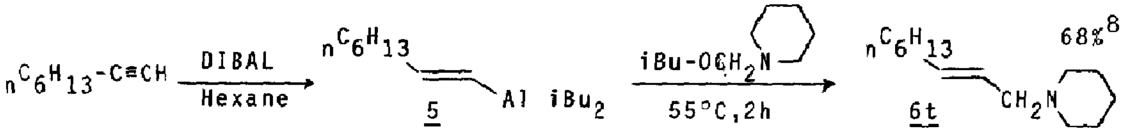
As seen form the tables, functionnalized alkenyl-copper and cuprates derivatives can be used (see entry 3, 4 and 9). This reaction gives an easy and straithforward access to various functionnalized allylic amines ; moreover the stereoisomeric purity of the C=C double bond is at least 99.9%[6] as determined by capillary gas chromatography (OV 101 column, 50 m). In order to compare our *cis* allylic amines with their *trans* counterparts, we have synthetized the latter via an analogous new reaction : we have found that alkenyl alane 5 and alanates[7] also react with α-aminoethers :

Table II



Entry	Vinyl-copper	n equiv.	Product [5]	Yield [a]	Eb °C/mm Hg
5	 [c]	1		53% [b]	104°/15
6	" [c]	0,75	"	71%	
7	 [c]	0,70		87%	104°/15
8	 [d]	0,80		66%	102°/0.01
9	 [e]	1		70%	70°/0.01

a/ Isolated yield based on the α-aminothioether ; b/ In Et_2O solvent the yield is 42% ; c/ Prepared in situ according ref.2a ; d/ Prepared in situ according ref.2c ; e/ Prepared in situ according ref.2d, modified by the use of 2 eq. Me_2S under the same experimental conditions.



The reaction of the organometallic (Al or Cu) occurs with retention of configuration. Amine 6t and its *cis* analog 6c display on C^{13} NMR the following signals : δ ppm ($CDCl_3$) 6t : 134.2 and 126.8 (C=C), 61.8 (CH_2-N)
" " 6c : 132.8 and 126.5 (C=C), 56.0 (CH_2-N)
which are in complete agreement with the known values [9].
We are presently extending this method to various other Mannich reagents and we are applying it to the synthesis of some natural products.

Typical procedure :

A solution of alkenyl-copper (50 mmol) or cuprate reagent (25 mmol) is cooled to -40°C at which temperature 50 ml of THF are added (if the carbometallation had been performed in Et_2O). The appropriate amount of 2 is added and the mixture is allowed to warm to room temperature, stirred 3-4h, then hydrolysed, at -10°C, with 60 ml NH_4Cl sat. sol. and 20 ml NH_4OH conc. sol. After filtration and extraction with ether, the organic phases are dried on K_2CO_3. Evaporation of the solvents afforded the crude product which is distilled through a 10 cm Vigreux column.

Aknowledgements : We thank the C.N.R.S. (ERA 825) for financial support.

References and notes -

1 - a/ M. Robinson, R. Robinson, J. Chem. Soc. 123 (1923) 532
    b/ J. Ficini, H. Normant, Bull. Soc. Chim. Fr. (1957) 1454
    c/ L. Miginiac, B. Mauzé, Ibid (1968) 2544
    d/ R. Golse, M. Bourhis, J.J. Bosc : C.R. Acad.Sci.Paris Série C 287 (1978) 585
    e/ C.D. Poulter, J.L. Roberts, P.S. Borromeo : Tetrahedron Lett.(1977)1299
    f/ T.A. Bryson, G.H. Bonitz, C.J.Reichel,R.E.Dardis, J.Org.Chem.45(1980)524
2 - a/ J.F. Normant, G. Cahiez, M. Bourgain, C.Chuit, J. Villieras, Bull. Soc. Chim. Fr. (1974) 1656
    b/ A. Alexakis, J. Cahiez, J.F. Normant, J. Villieras, Ibid (1977) 693
    c/ H. Westmijze, J. Meijer, H.J.T. Bos, P. Vermeer, Rec.Tr.Chim. Pays-Bas 95 (1976) 299
    d/ J.F. Normant, A. Alexakis, J. Villieras, J.Organomet.Chem.57(1973)C99
    e/ A. Alexakis, J.F. Normant,J. Villieras,J.Molecular Catl.1(1975/76)43
3 - a/ A. Alexakis, J.F. Normant, J. Villieras,Tetrahedron Lett.(1976)3461
    b/ A. Alexakis, G. Cahiez, J.F. Normant, J.Organomet.Chem.177(1979)293
    c/ A. Alexakis, A. Commerçon, J. Villieras, J.F. Normant, Tetrahedron Lett.(1976) 2313
4 - The reaction has to be run at -10°C due to the thermal instability of 4. On the contrary the α-aminothioether 2 has a stabilizing effect on 4, thus allowing a higher reaction temperature.
5 - All new products gave satisfactory spectroscopic and analytical data.
6 - The carbometallation of alkynes has been shown to afford products of 99.9% steric purity. See : A. Alexakis, G. Cahiez, J.F. Normant : Tetrahedron Lett. (1980) 1433. See also : A. Marfat, P.R. Mc Guirk, P. Helquist : J. Org. Chem. 44 (1979) 3888
7 - Comparable yield is obtained with the alanate of 5 in Et_2O
8 - We have observed the unusual transfer of the iBu rest to an extent of 6% affording the product iBu-CH_2-N Et_2
9 - J.B. Stothers, ^{13}C NMR Spectroscopy, Academic Press, 1972, New York

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