Tetrahedron Letters, Vol. 34, No. 49, pp 7943-7946, 1993
Printed in Great Britain

0040-4039/93 $6.00 + 0
Pergamon Press Ltd

Stereoselective Alkynylation of Chiral Benzaldehyde Chromium Tricarbonyl Complexes. Synthesis of Optically Active Alkynyl Alcohols

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Abstract: *Addition of lithium acetylides and ethynyl magnesium bromide to chiral ortho substituted benzaldehyde tricarbonylchromium complexes* ***1 - 3*** *gives alkynyl alcohols* ***4 - 7*** *in good yields and with complete stereoselection.*

Enantiomerically pure alkynyl alcohols represent an important class of compounds which are very useful intermediates in the preparation of various organic molecules[1-3], however access to them is not always straightforward. A number of stereoselective syntheses of these alcohols have so far been reported[4,5], including chemical[6] or enzymatic[7] catalyzed reactions (although enzymatic systems have failed to produce optically active 1-arylalkynyl alcohols).[8]

The use of chiral tricarbonyl(η^6arene)chromium complexes in the highly stereoselective synthesis of many classes of compounds is well demonstrated.[9-13] Since the diastereofacial nucleophilic additions to chiral benzaldehyde tricarbonylchromium complexes is usually highly selective,[10] we examined the possibility of exploiting these compounds in the asymmetric synthesis of arylalkynyl alcohols.

Our interest in complexed arylalkynyl alcohols is connected with their further synthetic applications,[14,15] and particularly with their potential transformation into chiral β-oxoalkylesters by means of ruthenium catalysed reactions with carboxylic acids.[16]

In this communication, we report that the addition of both lithium acetylides and ethynyl magnesium bromide to *ortho*-substituted benzaldehydetricarbonylchromium complexes **1-3** gives access to the alkynyl alcohols **4a-d** and **6a-c** respectively in good yields and high diastereoselection (Scheme 1).

Complexed alkynyl alcohols **4a-d** were prepared according to the following procedure: *n*-BuLi (1.4 mmol, 0.88 ml of a solution 1.6 M in THF) was added to a solution of (trimethylsilyl)acetylene or ethyl propynoate (1.4 mmol.) in THF (2 ml) at -78°C under N_2 atmosphere. After 5 min, a solution of complexes **1-3**[17] (1.1 mmol.) in THF (3 ml) was added dropwise. The yellow mixture was stirred for 1 h at -78°C, and then quenched with saturated aqueous NH_4Cl. Standard work-up and purification of the oily residue by flash

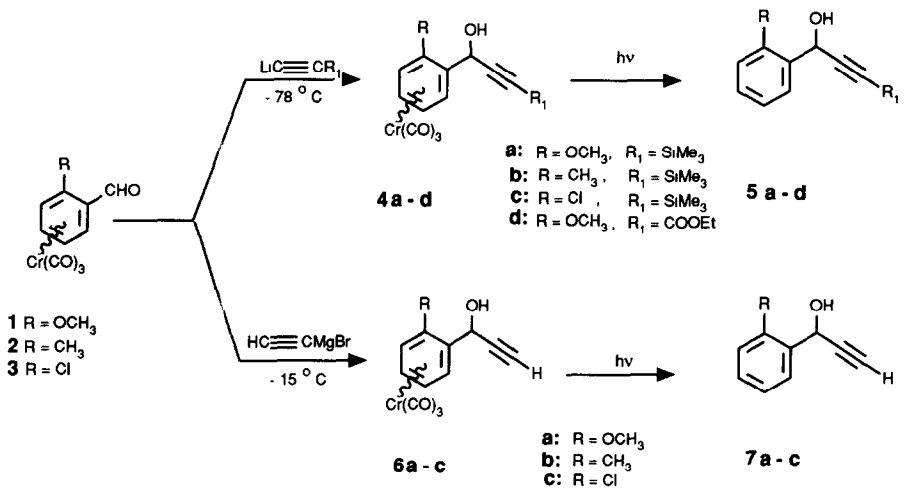
column chromatography gave analytically pure complexed alcohols **4a-d** in good yields and with complete diastereoselection (see Table). The trimethylsilyl group can be eliminated from compounds **4a-c** by stirring them for 30 min. with 0.1 N methanolic sodium hydroxide;[4] complexed alcohols **6a-c** were thus isolated in 90% yields after chromatography (eluent, diethyl ether: petroleum ether, 2:1).

The reaction of **1** with lithium ethyl propynoate was more conveniently quenched with trimethylsilylchloride at -78 °C,[18] giving the O-silylated derivative of alcohol **4d** in quantitative yield.

Alternatively, alcohols **6a-c** can be directly obtained by adding ethynylmagnesium bromide (1.3 mmol. 0.5M solution in THF) to a stirred THF solution (2ml) of compounds **1-3** at -15 °C. The reaction mixture is stirred for 1h at the same temperature and then worked up following the same procedure used for compounds **4**. It is worth noting that, when the Grignard reagent was used, no reaction occurred at temperatures below -15 °C, but complexed alcohols **6** were again obtained with complete diastereoselection. Compounds **4a-d** and **6a-c** were then decomplexed to alcohols **5a-d** and **7a-c** (80% average yield) by exposure of their CH_2Cl_2 solutions for 2-3 h to atmosphere and sunlight.[19]

For a sound evaluation of the above results, we repeated the reaction with lithium trimethylsilylacetylide and ethynylmagnesium bromide on optically pure complex 1*S*-**1**[20] ($[\alpha]_D$= +1015°, *c*= 0.2, $CHCl_3$); products **4a** and **6a**[21] were isolated as pure enantiomers (**4a**: $[\alpha]_D$= -100.4°, *c*= 0.96, $CHCl_3$; **6a**: m.p.= 79-81 °C, $[\alpha]_D$= -187.4°, *c*= 1.94, $CHCl_3$). After decomplexation, enantiomerically pure[22] 3-phenyl-1-(trimethylsilyl)-2-propyn-1-ol **5a** ($[\alpha]_D$= +13.8°, *c*= 0.9, $CHCl_3$) and α-ethynyl -2-methoxy-benzenemethanol **7a** ($[\alpha]_D$= +25.3°, *c*= 1.8, $CHCl_3$) were obtained in good yields.

Scheme 1



Table

Product[a]	*m.p.(°C)*[b]	*Yield(%)*	*d.e.*[c]
4a	oil	78	≥98
4b	oil	72	≥98
4c	93-94	75	≥98
4d	oil	75	≥98
6a	52-53	90	≥98
6b	80-82	89	≥98
6c	68-69	78	≥98

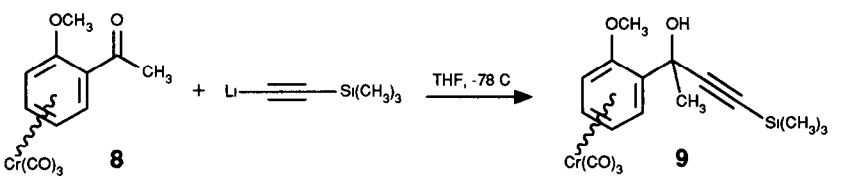
[a] All new compounds gave analytical and spectroscopic data according with their assigned structure. [b] From hexane/diisopropylether,2/1. [c] From ^{1}H NMR 300 MHz

Similarly, starting from 1*S*-**2**[20] ($[\alpha]_D$= +650°, *c*= 0.2, $CHCl_3$) and 1*R*-**3**[17] ($[\alpha]_D$= -1075°, *c*= 0.2, $CHCl_3$) we obtained enantiomerically pure **4b**[23] ($[\alpha]_D$= -13.4°, *c*= 0.8, $CHCl_3$) and **4c**[23] ($[\alpha]_D$= +20.9°, *c*= 0.8, $CHCl_3$), and the corresponding **5b** ($[\alpha]_D$= +15.3°, *c*= 0.8, $CHCl_3$) and **5c** ($[\alpha]_D$= +11.4°, *c*= 0.8, $CHCl_3$) were recovered in 80% yields after decomplexation and preparative thin-layer chromatography.

Consistent with the well known model of stereoselection observed with this kind of complex,[10] we can reasonable assume that for compounds **1-3** the sense of induction is the same as usual. To confirm it, additional experiments are in progress to determine the absolute configuration of these alkynyl alcohols.

Finally, as a logical extension of this work, we examined the reaction of lithium trimethylsilyl acetylide with a ketone: the (2-methoxyacetophenone)tricarbonylchromium **8** (Scheme 2).

Scheme 2



Complexed alcohol **9** was obtained in very good yields (90%) and with complete diastereoselection using 2 equivalents of lithium acetylide. The reaction with a stoichiometric amount of lithium trimethylsilylacetylide gave product **9** only in 50% yields, probably because of the formation of the enolate of **8**. This hypothesis is supported by the recovery of partially deuterated starting ketone **8** when the reaction mixture is quenched with D_2O.

In conclusion, the use of chiral tricarbonylchromium complexed benzaldehydes enables an efficient and highly stereoselective synthesis of arylalkynyl alcohols. Moreover, we have shown that a complexed acetophenone derivative also easily leads to the corresponding propargyl alcohol with complete stereoselection. Some of the newly prepared optically active complexed and uncomplexed propargylic alcohols are useful intermediates in the synthesis of various organometallic and organic molecules such as allenes. Further studies are in progress.

We thank MURST and the CNR "Piano Finalizzato Chimica Fine II" for their financial support.

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19. All new compounds gave analytical and spectroscopic data in agreement with the proposed structures.
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21. ^{1}H-NMR data for compounds **4a**,**6a** ($CDCl_3$, 300 MHz), δ ppm: **4a**: 0.05 (s, 9H, $Si(CH_3)_3$), 2.50 (d, 1H, OH, J=4.3 Hz), 3.75 (s, 3H, OCH_3), 4.90 (t, $1H_{arom}$, J_o=6.3 Hz), 5.04 (d, $1H_{arom}$, J_o=6.8 Hz), 5.44 (d, 1H, CH, J=4.3 Hz), 5.60 (t, $1H_{arom}$, J_o=6.8 Hz), 6.00 (d, $1H_{arom}$, J_o=6.3 Hz); **6a**: 2 40 (d, 1H, OH, J=4.4 Hz), 2.58 (d, 1H, ≡CH, J=2.1 Hz), 3.79 (s, 3H, OCH_3), 4.90 (t, $1H_{arom}$, J_o=6.2 Hz), 5.04 (d, $1H_{arom}$, J_o=6.6 Hz), 5.49 (dd, 1H, CH, J_1=2.1 Hz, J_2=4.4 Hz), 5.57 (t, $1H_{arom}$, J_o=6.6 Hz), 6.02 (d, $1H_{arom}$, J_o=6.2 Hz).
22. Enantiomeric purities were determined on a JASCO HPLC(880-PU pump, 870-UV detc.) with a 10 μm Baker Bond Chiracel OD column; eluent: hexane/ethanol 8/1, flow rate 0.5 ml/mın.
23. ^{1}H-NMR data for compounds **4b**,**c** ($CDCl_3$, 300 MHz), δ ppm: **4b**: 0.10 (s, 9H, $Si(CH_3)_3$), 2.20 (d, 1H, OH, J=4.8 Hz), 2.28 (s, 3H, CH_3), 5.14 (d, $1H_{arom}$, J_o=6.3 Hz), 5.20 (t, $1H_{arom}$, J_o=6.3 Hz), 5.31 (d, 1H, CH, J=4.8 Hz), 5.39 (t, $1H_{arom}$, J_o=6.4 Hz), 5.90 (d, $1H_{arom}$, J_o=6.4 Hz); **4c**: 0.18 (s, 9H, $Si(CH_3)_3$), 2.40 (d, 1H, OH, J=4.7 Hz), 5.11 (dt, $1H_{arom}$, J_m=2.2 Hz, J_o=4.7 Hz), 5.45 (m, 3H, $2H_{arom}$ + CH), 5.92 (d, $1H_{arom}$, J_o=6.3 Hz).

(Received in UK 20 July 1993; accepted 1 October 1993)