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Pinacol Coupling of Aliphatic Aldehydes Promoted by Niobium (III) Reagent

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Key Words : Nb(III) reagent; Pinacol coupling; Acetalization; Stereoselectivity.

Abstract : *$NbCl_3$ (DME) was found to be a useful reagent for the intermolecular pinacol coupling of aliphatic aldehydes . The high anti diastereoselectivity of this reaction (dl / meso ≥ 9 / 1) did not depend on the variation in the aldehyde alkyl chain. With respect to intramolecular pinacolization, the loss of the stereoselectivity observed is consistent with the mechanism involving an insertion of the oxo-group into the metal-carbon bond of the intermediate niobiooxirane.*

The reductive coupling of carbonyl compounds to give vicinal diols or alkenes makes up an important group of carbon-carbon bond forming reactions. Whereas the McMurry reaction[1] to yield alkenes is essentially limited to a strongly oxophilic low-valent titanium species, its first pinacol-forming step can be acomplished with a variety of metal reducing agents.[2] However, none of the pinacol reagents presently known are universally applicable. There is a continuous search for the methods which will allow stereocontrolled construction of the vicinal diol unit.[3]

We have recently found[4] that a highly stereoselective carbonyl coupling of aromatic aldehydes and ketones may be promoted by the niobium(III) compound $NbCl_3$(DME) (DME : 1,2-dimethoxyethane). These reductions lead, depending upon the reaction conditions, to either alkenes or diols. Moreover, acetals can also be formed from the intermediate niobiopinacols owing to the Lewis acidity of the reagent used. For example, both alkene (E-stilbene) and acetal (threo-2,4,5-triphenyl-1,3-dioxolane) were formed stereospecifically starting from two equivalents of benzaldehyde, at room temperature. On the other hand, threo-hydrobenzoin was obtained as the sole product by reacting the equimolar mixture of

benzaldehyde and $NbCl_3$(DME) at -10°C. A somewhat different course of these reactions, in comparison with the Ti(0) induced reductive coupling, appears to be due to a lower oxophilicity together with an enhanced Lewis acidity of the Nb(III) reagent. The $NbCL_3$(DME) mediated coupling may be thought to proceed via a mechanism different[4] from that proposed for the McMurry reaction.[5]

This characteristic prompted us to extend our study to the aliphatic carbonyl compounds, with the aim of testing the synthetic utility and limitations of the method. The experiments reported below, using $NbCl_3$(DME) for the inter- and intramolecular coupling of some aliphatic aldehydes, have mechanistic implications as well in regard to the product stereochemistry.

Results and Discussion

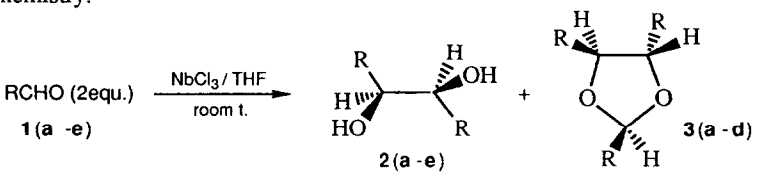
The aliphatic carbonyl compounds and particularly ketones are generally harder to reduce than aromatic ones. Nevertheless, both aliphatic aldehydes and ketones react under the effect of the strong reducing power of Ti(0). We noticed that, unlike in the Ti induced reactions, only aldehydes undergo a notable coupling by the milder reducing agent $NbCl_3$(DME). The relatively short reactional time needed for the Nb(III) induced coupling of aliphatic aldehydes (see below) can allow their chemoselective transformation in the presence of an aliphatic ketone function.[6]

When $NbCl_3$(DME) and 2 equiv of n-hexanal (**1b**) in THF were allowed to react under argon at room temperature a mixture of diol **2b** (dl/meso = 9/1) and acetal **3b** (dl / meso + meso' = 93/7) were recovered after basic workup (Scheme 1, Table 1).

Also for other aliphatic aldehydes (**1a**, **c-e**) the reductive coupling is stopped at the pinacol stage. Heating did not give rise either to the alkene formation, and only a lowering of the overall yield was detected. Such a result contrasts with the course of the reactions in which aromatic aldehydes were used as substrates. Obviously, conjugation can be considered as an essential driving force of the pinacol deoxygenation step in the Nb(III) mediated carbonyl coupling. We confirmed this by an experiment using cinnamic aldehyde as substrate; in the latter only alkene i.e. (1E, 3E, 5E)-1,6-diphenyl-1, 3, 5 - hexatriene was isolated in excellent yield (90%).

Similarly to the aromatic series[4] acetal **3b** was formed as a second product when an excess of n-hexanal was used. Only for pivalic aldehyde (**1e**) no acetal was detected. This result corroborates our previous observations, concerning the role of a steric control at C-4 and C-5 in niobiopinacol to avoid the attack of the carbonyl compound. The acetalization step may be strongly limited by decreasing both the quantity of the aldehyde and the temperature. In this manner, only traces of acetals were observed when the equimolar quantities of

aldehydes and $NbCl_3$(DME) were allowed to react at -10°C. In the last case, only diols were obtained in significant yields (from 75% for n-hexanal to 42% for propanal) and with similar stereochemistry.



Scheme 1

Table 1

RCHO (**1a-e**)	R	Diol (**2a-e**) dl/meso (yield)*	Acetal (**3a-d**) dl/meso+meso' (y)*
1a	Et	9 / 1 (19%)	94 / 6 (55%)
1b	n-pentyl	9 / 1 (25%)	93 / 7 (59%)
1c	iso-Pr	88 / 12 (30%)	87 / 13 (51%)
1d	s-pentyl	9 / 1 (22%)	9 / 1 (53%)
1e	t-Bu	> 95 / 5 (71%)	—

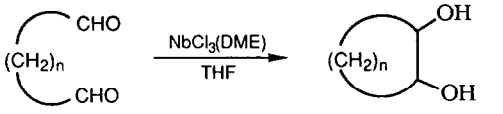
(*) isolated yields based on starting aldehyde

Table 1 lists the yields and ratios of dl/meso diastereomers of diols and acetals obtained from aldehydes **1a-e**. The generally high stereoselectivity (dl/meso = 9/1) observed agrees with the mechanism proposed[4], i.e. the insertion of the oxo-group into the metal-carbon bond of the initially formed metalloxirane **I**, leading to metallopinacol **II** (Scheme 3, entry 1).

Several aspects need expanding. As can be seen in Table 1, the diastereoselectivity does not vary in a significant manner with the variation in the alkyl chain. Only the substitution at the α-position by two methyl groups (**1e**) slightly enhance the dl/meso ratio. The constantly predominant formation of the dl (anti) isomer seems to be consistent with the mechanism involving the niobiooxirane intermediate. Indeed, the geometric separation and relative flexibility of the two reacting species would assume a subtle control on the way to the transition state, so that no alkyl substituent discrimination occurs. As a result, the thermodynamically favoured dl - isomer was obtained invariably as a major product. Otherwise, an alternative mechanism might involve the kinetically controlled dimerization of anion radicals *on the common surface of the metal*, similarly to the Ti(0) induced carbonyl coupling.[5] In such a case however, the stereochemistry of the pinacol product would depend on the steric bulk of the aldehyde alkyl groups, owing to the metal-bridging control.[7]

The solvent used (THF, DME, PhMe, CH_2Cl_2) had little effect upon the yield of pinacol products, while the stereoselectivity depended on it. Of all solvents tested THF give the best diastereomeric ratio (dl/meso). Changing the solvent from polar to nonpolar seems to result in the decreasing of stereoselectivity. In the case of isobutanal (**1d**) for exemple, a decreasing of the dl/meso ratio is observed from 9/1 in THF to 85/15 in DME, and to about 3/1 in PhMe/DME = 1/1 and in CH_2CH_2. The marked inversion of this trend with regard to THF and DME using the low-valent titanium reagent ($TiCl_3/Li$)[8] was noteworthy in this respect.

In several recent reports, cyclic pinacols were obtained by the intramolecular coupling of dicarbonyl compounds. These reactions were achieved in the presence of low-valent titanium,[9] samarium diiodide,[10] or vanadium (II) reagent.[11] The cis/trans ratio of the cyclic pinacols appears to depend upon the ring size. The predominance of a cis stereochemistry in the formation of the vicinal diols with the medium ring size (6-8) has been mentioned. For example, only cis-1,2-cyclohexanediol was obtained and the cis/trans ratio was equal to 7/3 for 1,2-cyclooctanediol using $TiCl_3$ /Zn-Cu as reductant.[9] On the other hand, the predominance of a trans stereochemistry was observed for the ring sizes greater than ten.



1f (n=4) **2f** (cis / trans = 9 / 11)

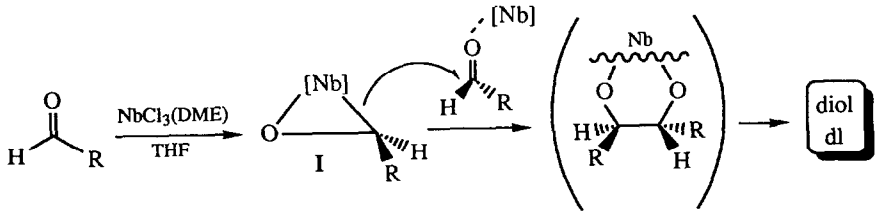
1g (n= 6) **2g** (cis / trans = 1 / 1)

Scheme 2

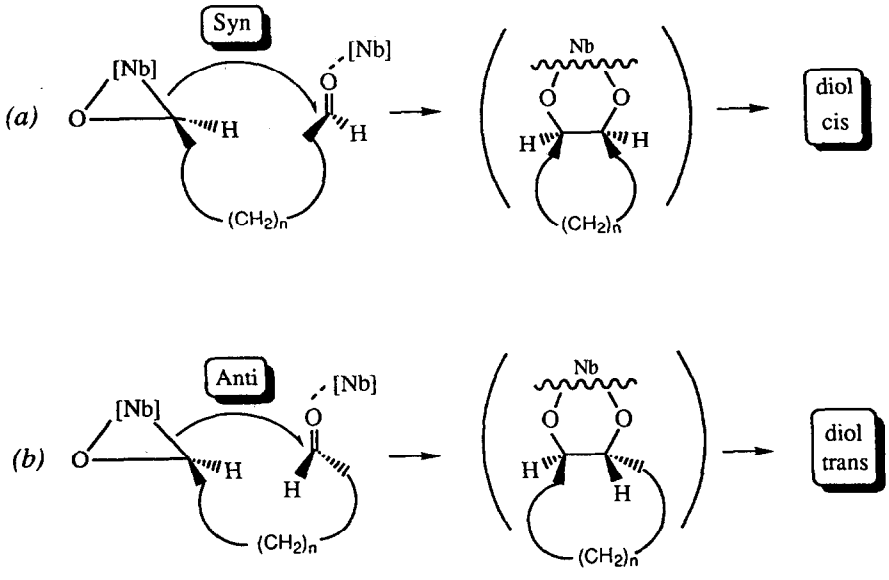
In order to reach supplementary insight into the Nb(III) mediated carbonyl coupling we tried to perform the intramolecular pinacol reaction using $NbCl_3$(DME). Two α, ω - dialdehydes **1f, g** (Scheme 2) were employed as model compounds. The reactions were carried out at -10°C in THF and the high-dilution technique (see experimental section) used in order to avoid intermolecular polymerization.

We noticed that the cyclic pinacol products, i.e. 1, 2-cyclohexanediol (**2f**) and 1, 2-cyclooctanediol (**2g**), could be obtained by this procedure with moderate yields. However, in

(1) Intermolecular Reaction



(2) Intramolecular Reaction



Scheme 3

contrast to the predominant cis stereochemistry characterizing the Ti(0) induced cyclization as well as to the high threo (dl) stereoselectivity observed for the Nb(III) induced intermolecular coupling, the reductive cyclization of dialdehydes **1f, g** gave rise to the quasi equimolar mixture of the isomeric cis and trans diols **2f, g**.

The cis stereochemistry of the diol observed in the Ti(0) mediated reductive cyclization is that expected for the dimerization of anion radicals on the common surface of the metal. In contrast to that, two competitive pathways (Scheme 3, entries 2a and b) could be assumed to rationalize the lack of stereoselectivity revealed in the Nb(III) mediated intramolecular coupling. Indeed, the *syn* orientation (entry 2a) appears to be geometrically favored for the cyclic series provided that the small or medium carbon cycles are considered. Nevertheless, assuming the mechanism proposed, the generally privileged thermodynamic *anti* orientation (entry 2b) should also take place.

In conclusion, the high stereoselectivity observed in the Nb(III) mediated intermolecular pinacol coupling is a promising feature. The enantioselective intermolecular pinacolization is under investigation.

Experimental Section

Methods and Materials. All manipulations were carried out under argon using vaccum line techniques. The solvents used were distilled under argon from sodium benzophenone ketyl. Dialdehydes **1f, g** were prepared shortly before use by oxidative cleavage (KIO_4 in H_2O / Et_2O)[12] of the corresponding diols. All aldehydes were distilled under argon prior to use. $NbCl_3$ (DME) was prepared by a reported procedure.[13] ^1H and ^{13}C NMR spectra were recorded at 400 and 100.53 MHz, respectively. Mass spectra were obtained by positive ion FAB MS technique employing thioglycerol as the matrix solvent.

General Procedure for Pinacol Coupling - Acetalization of Aldehydes 1a -e. To a stirred suspension of $NbCl_3$ (DME) (1.02 g, 3.53 mmol) in 20 mL of THF at -10°C was added via syringe a solution of hexanal (**1b**) (0. 71 g, 7. 10 mmol) in 5mL of THF. After stirring at -10°C for 30 min, the temperature was allowed to rise to 20°C over a 1.5 h period and then the reaction was continued for 5 h. The reaction mixture was poured into a separatory funnel, treated with saturated K_2CO_3 solution (30 mL) and extracted with ether / ethyl acetate = 1 / 1 (3 x 70 mL). The combined organics were washed with saturated NaCl solution, dried ($MgSO_4$) and the solvent was removed in vacuo. Separation by flash chromatography (silica gel, 230-400 mesh, light petroleum / diethyl ether = 95 / 5 followed by ether alone) gave 0.18 g (25% based on starting **1b**) of 6, 7-dodecanediol (**2b**) as white crystals: mp 134-135°C[14,15] , dl / meso = 9 / 1.[14,16] Moreover, diastereomeric acetals, namely 2,4,5-tri-(n-pentyl)-1,3-dioxolanes (**3b**) were isolated in two fractions, as a meso + meso' (mo+ mo') mixture (0.027 g) and dl isomer (0.36 g) (dl / mo+mo' = 93 / 7), overall yield 59%; the meso / meso' ratio as determined by ^1H NMR was of about 7:1.

3b(dl) : IR (neat) ν 1464, 1377, 1259, 1143, 1110, 1075, 1026 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 4.93 (t, J = 4.9 Hz, 1H), 3.54 (dt, J = 7.2 and 5.2 Hz, 2H), 1.60-1.20 (m, 24H), 0.91 (m, 9H); ^{13}C {^1H} NMR ($CDCl_3$) δ 103.8, 82.8, 81.6, 35.1, 33.8, 32.6, 32.4, 26.3, 24.3, 23.1, 14.6; MS m/z 284 (M^+, 10), 213 (35), 197 (20), 185 (50), 147 (100). **3b**(mo / mo' = 7 / 1) : ^1H NMR ($CDCl_3$) δ 5.09 (t, J = 5.0 Hz, 1H-mo'), 4.86 (t, J = 5.0 Hz, 1H-mo), 3.91 (t, J = 5.8 Hz, 2H-mo'), 3.82 (t, J = 5.8 Hz, 2H-mo), 1.50-1.32 (m, 24H), 0.89 (m, 9H); ^{13}C {^1H} NMR ($CDCl_3$) δ 104.1 (mo'), 103.8 (mo), 79.2 (mo), 78.9 (mo'), 35.9 (mo'), 35.5 (mo), 32.5, 30.5, 26.6, 26.2, 24.2, 23.1, 14.6. **3a** : ^1H NMR ($CDCl_3$) δ 5.10 (t, J = 5.3 Hz, 1H-mo), 4.98 (t, J =

5.0 Hz, 1H-dl), 4.89 (t, J = 5.4 Hz, 1H-mo'), 3.80 (br t, 2H-mo), 3.66 (br t, 2H-mo'), 3.50-3.37 (m, 2H-dl), 1.55-1.39(m, 6H), 1.07-0.90 (m, 9H); MS (FAB) m/z 158 (M^+, 10), 129 (40), 101 (45), 83 (100). **3c** : IR (neat) ν 1462, 1370, 1110, 1092, 1070, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (d, J = 5.4 Hz, 1H-mo), 4.66 (d, J = 4.8 Hz, 1H-dl), 4.41 (d, J = 5.7 Hz, 1H-mo'), 3.66 (d, J = 5.3 Hz, 2H-mo), 3.58 (d, J = 6.2 Hz, 2H-mo'), 3.52 (dd, J = 5.4 and 6.4 Hz, 1H-dl), 3.42 (dd, J = 5.3 and 6.4 Hz, 1H-dl), 1.80-1.59 (m, 3H), 1.05-0.92 (m, 18H); MS (FAB) 201 (MH^+, 15), 157 (90), 129 (45), 111 (100). **3d** : ^1H NMR ($CDCl_3$) δ 4.88 (br d, J = 5.4 Hz, 1H-mo), 4.70 (br d, J = 5.0 Hz, 1H-dl), 4.45 (br d, J = 5.6 Hz, 1H-mo'), 3.75-3.48 (m, 2H), 1.70-1.15 (m, 15H), 0.98-0.92 (m, 18H); MS (FAB) m/z 284 (M^+, 10), 283 (40), 267 (15), 221 (45), 213 (55), 185 (15), 147 (100).
The yields and dl / meso ratio of diols (**2a-e**) and acetals (**3a-d**) obtained are compiled in Table 1.

Procedure for Intramolecular Coupling of Dialdehydes 1f, g. The suspension of $NbCl_3$ (DME) (0.95 g, 3.30 mmol) in THF (10 mL) was stirred for 15 min at -10°C. A solution of dialdehyde (2.20 mmol) in 7 mL of THF was then added at -10°C over a period of 6 h, using a syringe pump. After stirring at -10°C for 1h, the temperature was allowed to rise to 20°C over a 1.5 h period. Saturated K_2CO_3 solution (25 mL) was added, the mixture vigorously stirred for additional 0.5 h and extracted with ether / ethyl acetate = 1 / 1 (3 x 50 mL). The combined organics were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Separation by flash chromatography (n-hexane / EtOAc = 9 / 1) afforded pure cycloalkane diols : **2f** (overall yield 48%, cis / trans = 9 / 11) or **2g** (overall yield 43%, cis / trans = 1 / 1).[15,16]

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15. All known compounds have physical and spectral characteristics in agreement with the literature data.

16. The diastereomeric ratio of diols was established by means of comparison of the peak heights of the methine PMR resonances, according to the literature configurational assignments.

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