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1,1-DICHLORO-2,2,2-TRIFLUOROETHYL ZINC AND LITHIUM COMPOUNDS IN ASYMMETRIC SYNTHESIS

A. SOLLADIE-CAVALLO and S. QUAZZOTTI
Laboratoire de Stéréochimie Organométallique (UA du CNRS 466), EHICS,
1 rue B. Pascal, 67008 Strasbourg (France)

SUMMARY

Addition of 1,1-dichloro-2,2,2-trifluoroethyl zinc chloride 2 complexed with optically pure ligands leads to zero percentage of asymmetric induction due to too large a distance between the chiral centers involved. However, addition of 2 and of the corresponding lithium derivative 3 on a chiral aldehyde leads respectively to 20% and 80% of asymmetric induction. Therefore lithium derivative 3 provides a good route to optically pure alcohols of type Ar-CH(OH)-CCl_2-CF_3.

INTRODUCTION

Being very lipophilic, the CF_3 group when present on a bioactive compound could influence its rates of absorption and transport, therefore, stereo and/or enantioselective introductions of this group on chiral molecules are important targets.

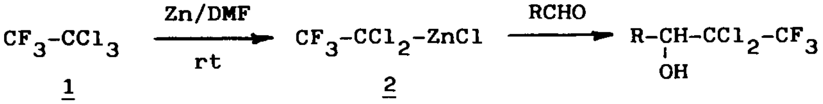
During our work on enantioselective synthesis of polyfluoro alcohols having CF_3 groups [1], we became interested in the use of 1,1,1-trichloro-2,2,2-trifluoroethane 1, which provides the possibility of building up the 1,1,1-trifluoroethyl group (CF_3-CH_2) [2].

We want to report here our preliminary results concerning the use of 1,1-dichloro-2,2,2-trifluoroethyl zinc chloride and 1,1-dichloro-2,2,2-trifluoroethyl lithium in asymmetric synthesis of chiral alcohols.

RESULTS AND DISCUSSION

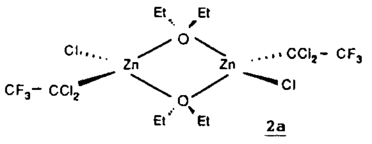
I 1,1-dichloro-2,2,2-trifluoroethyl zinc chloride 2

Known since 1972 [3] 1,1-dichloro-2,2,2-trifluoroethyl zinc chloride 2 has been recently studied and used by Lang et al. [4] for the synthesis of fluoro-containing building blocks.

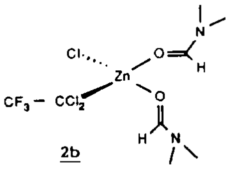


$$\underset{1}{CF_3\text{-}CCl_3} \xrightarrow[rt]{Zn/DMF} \underset{2}{CF_3\text{-}CCl_2\text{-}ZnCl} \xrightarrow{RCHO} R\text{-}\underset{OH}{CH}\text{-}CCl_2\text{-}CF_3$$

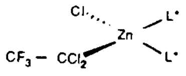
Compound 2 in DMF reacts with a wide variety of substituted aliphatic and aromatic aldehydes [4a] and it has been shown [4b, 5] that the key intermediate and the reacting species in this one-pot synthesis is the DMF complex of 2:2b. Therefore chiral and optically pure "analogs of DMF" such as c,d and e could be used in the place of DMF to induce chirality during the reaction.



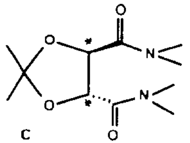
2a



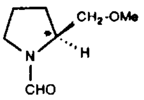
2b



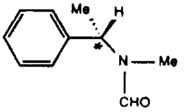
2c L* = c
2d L* = d
2e L* = e



c



d



e

Like complex 2b [4b, 5], complexes 2c-e are obtained by a ligand exchange reaction from the ether complex 2a, which is synthesized in the usual way [3]

$$2a \quad + \quad \mathrm{DMF\ or\ L^*} \longrightarrow \quad 2b \quad \mathrm{or} \quad 2c\text{–}e \qquad [4b]$$

The results are given in Table 1.

The optical purity of the alcohols is readily determined from the tertiary proton ($R\text{-}C\underline{H}(OH)\text{-}CCl_2\text{-}CF_3$) using $Eu(hfc)_3$ (Tris[3-(heptafluoropropylhydroxymethylene) (+) camphorato] europium III).

The zero yield obtained with ligand c could be due either to the fact that the corresponding complex 2c is not formed or to the fact that this complex is too stable and does not react. Therefore complex 2c ,which is easily obtained by the usual exchange reaction [6], was isolated and allowed to react with the same aldehyde in a 1/1 mixture of DMF and THF. As no reaction was observed one can conclude that complex 2c is too stable to react and even to exchange with DMF.

In the case of ligand e, the zero yield is due to the fact that complex 2e is insoluble in the reaction mixture (a precipitate appears rapidly when 2a is dissolved in a 1/1 mixture of e/THF). With ligand d the yield is satisfactory but the asymmetric induction is nil; we think that the chiral center of ligand d is too far remote from the asymmetric carbon created (Fig. 1).

The same situation has been already found during asymmetric alkylation of olefins complexed with palladium [7]. We thus decided to change our approach and to add complex 2b on a chiral substrate (entry 11, Table 1).

The zinc complex 2b adds smoothly to chiral complex 7 in very good yield, however the asymmetric induction is small (20%), and disappointing but consistent with our previous results on addition of perfluoro zinc iodide to the same complex 7 [1a].

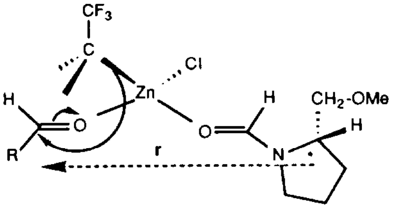
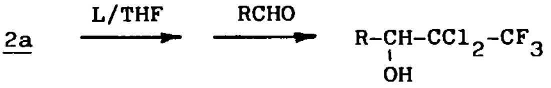


Fig. 1. Schematic representation of ligand positions.

TABLE 1

Reaction conditions and yields for :



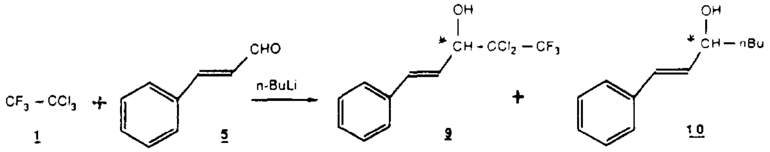
$$\underline{2a} \xrightarrow{L/THF} \xrightarrow{RCHO} \underset{\displaystyle OH}{R\text{-}\overset{}{C}H}\text{-}CCl_2\text{-}CF_3$$

En-try	Lig. L	L/THF	T °C	Time days	RCHO[‡]	Yields[a] %	e.e.[b] %
1[c]	THF	THF	65°	1	4	0	-
2	DMF	8/2	rt	4	5	65	-
3	"	5/5	"	"	5	50	-
4	"	"	"	2	4	100	-
5	"	"	"	"	6	70	-
6	c[d]	THF	60°	5	5	0	-
7	d	5/5	rt	2	5	50	0
8	d	"	"	"	6	50	0
9	e	"	"	"	5	0	-
10	e	"	"	"	6	0	-
11	DMF	5/5	rt	0.8	7	100	20

[a] Yields are obtained from 200MHz spectra of crude products and referred to the aldehyde.
[b] Enantiomeric excess measured by NMR. [c] see ref. 5 . [d] c (solid) is dissolved in THF and then reacted with 2a . [‡] 4 : Ph-CHO ; 5 : Ph-CH = CH-CHO ; 6 : iPr-CHO ; 7 :((CO)$_3$Cr)-CH$_3$-C$_6$H$_4$-CHO ,see Table 3 .

TABLE 2

Reaction conditions and yields for ;

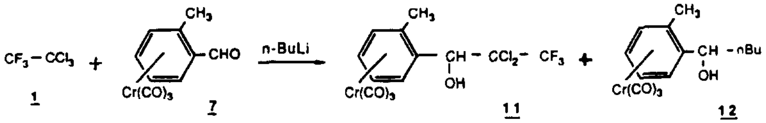


En try	1 eq.	BuLi eq.	5 eq.	Solvant	T °C	Time mn	Yields%[a] 9	10	5
1	1	1	1	Et_2O	-78°	150	0	90	10
2	1	1	1	Pent/Et_2O 85/15	-95°	30	60	6	34
3	1	1	1	"	-120°	60	58	9	33
4	2	1	1	"	-95°	30	55	2	43
5	2	1	0.5	"	-95°	30	66	6	28
6	2	1.3	1	Et_2O	-95°	30	92	3	5

[a] Yields are obtained from 200MHz spectra of crude products and referred to the aldehyde.

TABLE 3

Reaction conditions and yields for :



En-try	1 eq.	BuLi eq.	7 eq.	Solv.	T °C	Time mn	Yields% (A.I.%)[a] 11	12	7	13
1	4	2	1	Et_2O	-95°	100	47(80)	38	15	
2	2	1.3	1	"	-78°	300	55(80)	37	9	
3	4	1	1	"	-40°	30	60(80)	8	32	
4[b]	3	2	1	"	-40°	20				
	3	2		"		20	50(76)	0	15	35(96)

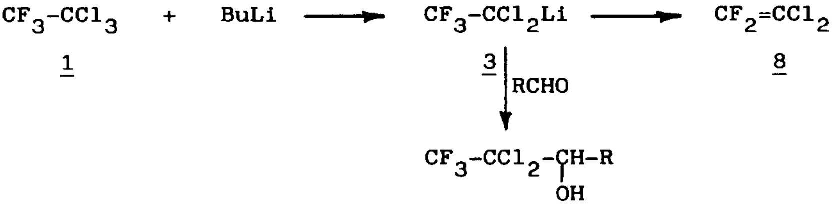
[a] Yields are obtained from 200Mhz NMR spectra of the crude compounds and referred to the aldehyde;A.I.is the asymmetric induction.

[b] After the first addition of 2 eq.of BuLi, the reaction is stirred for 20 mn,then 3 more eq. of 1 are added,followed by 2 more eq. of BuLi to force the reaction to completion.

II 1,1-dichloro-2,2,2-trifluoroethyl lithium 3.

Polyhaloorganolithium compounds are very useful reagents in organic synthesis however they undergo rapid decomposition. 1,1-Dichloro-2,2,2-trifluoroethyl lithium 3 needs very low temperature and special solvent-mixtures to react correctly on a substrate [8].

To avoid these difficulties the lithium derivative 3 is generated in situ (in the presence of the substrate) from compound 1 and BuLi in ether at low temperature.



$$\underset{\underline{1}}{CF_3-CCl_3} + BuLi \longrightarrow \underset{\underline{3}}{CF_3-CCl_2Li} \longrightarrow \underset{\underline{8}}{CF_2{=}CCl_2}$$

$$\underset{\underline{3}}{CF_3-CCl_2Li} \xrightarrow{RCHO} CF_3-CCl_2-\underset{OH}{\underset{|}{C}}H-R$$

Lithium sodium (1%) alloy which had been used successfully with perfluoroiodides (1c) does not react

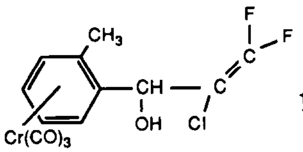
The reaction-conditions are optimized on the inexpensive aldehyde 5 and the results are given in Table 2.

At -95°C, and lower, addition of BuLi to aldehyde 5 is minimal. The best reaction-conditions correspond to entry 6; Et_2O is the solvent, -95°C the temperature and the ratio CF_3-CCl_3/ BuLi/ 5 is 2/1.3/1.

Compared with the reaction-conditions proposed in the literature[8], this method ,with generation of the anion in situ, allows the use of classical solvent and higher temperatures.

The optimized reaction-conditions found above have been used with chiral complexed aldehyde 7 ,Table 3. Under those conditions (entry 1, Table 3) the reactivities of BuLi toward aldehyde 7 and compound 1 are similar (47 and 38% of 12). But at -40°C the percentage of addition of BuLi on aldehyde 7 is reduced to 8%. The asymmetric induction is readily obtained from the diastereomer ratio measured by 200MHz NMR on the CH,OH and CH_3 signals in complexed alcohol 11. The percentage of asymmetric induction is high enough (80%) to provide an efficient synthesis of optically pure alcohol A.

However,in an attempt to force the reaction to completion (by adding more 1 and BuLi after 20mn reaction) formation of a new alcohol 13 is observed .



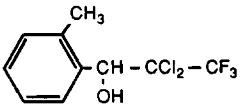
13

Proton NMR of compound 13 is similar to the one of compound 11 except for the tertiary proton which is a broad multiplet at 5.6ppm in 13 (due to long-range coupling constants with the fluorine atoms through the double bond), and a doublet ($^3J_{OH}$=4Hz) at 5.2ppm in 11.
Fluorine NMR corroborates structure 13 with two doublets for the two non-equivalent fluorine ($^2J_{FF}$=34Hz).A singlet is observed for the CF_3 group in compound 11.
Observation of alcohol 13 in the last experiment (Table 3,entry 4 suggests that olefin 8 formed during the first 20min of the reaction (after the first addition of BuLi on the mixture 1 +7) reacts with BuLi faster than compound 1 and adds to aldehyde 7.

CONCLUSION

Addition of the lithium derivative 3 of compound 1 leads to satisfactory percentage of asymmetric induction (80%), and after purification optically pure alcohols of type A can be obtained .

The zinc derivative 2b gives better yield (~100%) but poor asymmetric induction.



A

EXPERIMENTAL

1,1,1-Trichloro-2,2,2-trifluoroethane 1 was supplied by Ciba-Geigy and used without further purification The solvents were dried before use (THF and Et_2O are refluxed over $LiAlH_4$, DMF and pentane are stored over activated molecular sieves 4A). Zinc powder (from Prolabo) was activated according to Fieser and Fieser [10]. BuLi is titrated before use. Aliphatic and aromatic aldehydes were obtained from Aldrich and used without further purification except for benzaldehyde which was purified in the usual way [11]. Complex 7 was synthesized, purified and identified according to our method [12]. All the reactions were run under Argon. ^1H NMR spectra were recovered on a Bruker WP 200 SY (in $CDCl_3$/TMS) and the ^{19}F NMR spectrum on a Bruker AM 360 (^{19}F frequency= 338.8MHz).

Reaction of complex 2a with aldehydes

Complex 2a (1.5mmols) is dissolved in DMF (2ml) or in the desired chiral ligand ; after 15min. stirring, THF (2ml) and the aldehyde (2mmols) are added successively. After 2 days stirring at room temperature the usual work-up is done and the crude products analyzed by 200MHz NMR.

Addition of 3 to aldehydes

Compound 1 and the aldehydes (5 or 7) are dissolved in the solvent (about 1mmol of 5 in 20ml of solvent) and cooled under stirring to the desired temperature (15min). Then BuLi in hexane is added dropwise [9] using a precooled syringe. After stirring at low temperature for the desired amount of time, the temperature is allowed to reach 0°C and 10% HCl added. After the usual extraction, crude products are analyzed by 200MHz NMR.

The alcohols obtained from aliphatic and aromatic aldehydes 4,5, and 6 have already been described by Lang [4a], our compounds have the same physical and spectral characteristics.

Alcohol 11: 2,2-dichloro-1,1,1-trifluoro-3-o-methylphenyl chromiumtricarbonyl-propan-3-ol.

This alcohol has been obtained as a mixture of diastereomers from the zinc derivative 2b (20% asymmetric induction) and from the lithium derivative 3 (76-80% asymmetric induction). The diastereomers were separated by flash chromatography (Merck Silica gel 60, 230-400 mesh; Et_2O/Hexane 20/80)

Diastereomer I : minor compound, rf = 0.20;
IR ($CHCl_3$) (OH)=3585(free),3300(bounded)cm^{-1}, (CO)=1980, 1900cm^{-1} ;
H-1NMR : 2.56(3H,s,CH_3),3.01(1H,d,OH,^3J=6Hz),4.95(1H,d,CH, ^3J=6Hz),5.11(1H,d, aromatic H),5.14(1H,t,aromatic H),5.53(1H,t, aromatic H), 5.56 (1H,d,aromatic H).

Diastereomer II: major compound, rf = 0.39 ;
H-1 NMR : 2.34(3H,d,CH_3),2.71(1H,d,OH,^3J=4Hz),5.06 (1H,d.d, aromatic H, ^3J=6.5Hz, ^4J=1Hz),5.20(1H,d,CH,^3J=4Hz), 5.26 (1H,t.d,aromatic H,^3J=6.5Hz, ^4J=1Hz),5.56(1H,t.d,aromatic H, ^3J=6.5Hz,^4J=1Hz), 6.10(1H,d.d, aromatic H,^3J=6.5Hz,^4J=1Hz) ;
F-19 NMR ($CDCl_3$, ext. ref. C_6F_6), 86.63(3F,s, CF_3).

Alcohol 13: major compound;

H-1 NMR : 2.16(3H,s,CH_3),2.4(1H,b,OH)5.15(1H,d.d,aromatic H,^3J=6.5Hz, ^4J=1Hz),5.29(1H,t.d,aromatic H, ^3J=6.5Hz, ^4J=1Hz),5.45 (1H, t.d,aromatic H,^3J=6.5Hz,^4J=1Hz), 5.61 (1H,bm,CH),5.93(1H,d.d, aromatic H,^3J=6.5Hz,^4J=1Hz); F-19 NMR ($CDCl_3$,ref ext C_6F_6), 77.01(1F,d,^2J=34Hz),73.80 (1F,d,^2J=34Hz).

A minor diastereomer is detected with two doublets: 75.40(1F,d, ^2J=34Hz), 72.20(1F,d,^2J=34Hz). The ratio 13 minor/13 major is 2/98 .

ACKNOWLEDGMENT

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REFERENCES

1 a-A. Solladié-Cavallo, D. Farkhani,S. Fritz,T. Lazrak and J. Suffert; Tetrahedron Lett.,25 (1984) 4117

b-A. Solladié-Cavallo, J. Suffert and D. Farkhani; Ann. Chim.Fr.,9 (1984) 683

c-A. Solladié-Cavallo and J. Suffert; Synthesis, (1985) 659

2 A. Posta, O. Paleta and J. Hemer; Coll. Czech. Chem. Comm. 32 (1967) 2301.

3 A. Posta and O. Paleta; Coll. Czech. Chem. Comm., 37 (1972) 3946

4 a- R.W. Lang; Helv. Chim. Acta, 69 (1986) 881.

b- D. Bellus, B. Klingert, R.W. Lang and G. Rihs; J. Organometall. Chem., 339 (1988) 17.

c- R.W. Lang;Helv. Chim. Acta, 71 (1988) 369.

5 R.W. Lang and B. Schaub (Ciba-Geigy), private communication.

6 2a (1eq) and c (2eq) are dissolved in THF, a precipitate appears, after addition of pentane and cooling the precipitate (2c) is filtered.

7 A. Solladié-Cavallo and J.L. Haesslein; Helv. Chim. Acta 56, (1983) 1760.

8 D. Seyfert, D.C. Mueller and F.M. Armbrecht; Organometall. Chem. Syn., 1, (1970) 3.

9 Addition of BuLi must be very slow (0.3ml in 7mn).

10 L.F. Fieser and M. Fieser; Reagents for Organic Synthesis, J. Wiley & Sons; NY;1967, p.1276.

11 D.D. Perrin,W.L.F. Armarego and D.R. Perrin;Purification of Laboratory Chemicals; Pergamon Press, 2d ed.,1980

12 A. Solladié-Cavallo, G. Solladié and E. Tsamo; J. Org. Chem., 44 (1979) 4189.