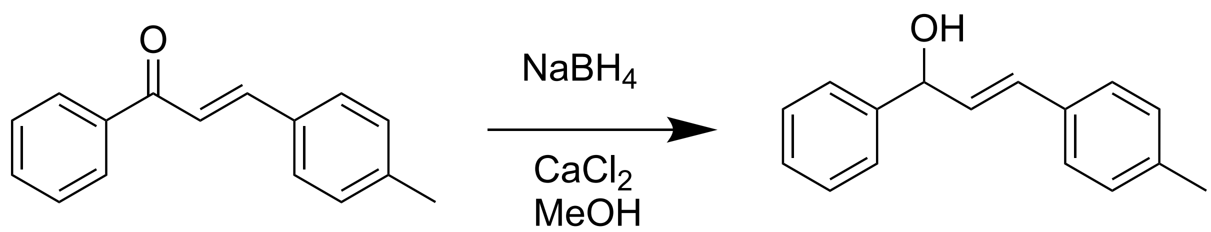
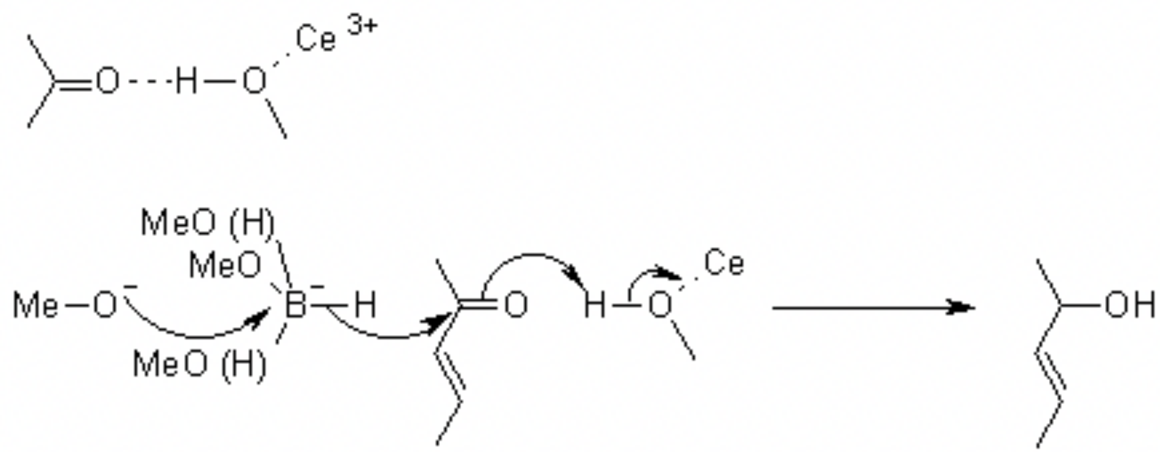
Esperienza 1: Riduzione del benzofenone

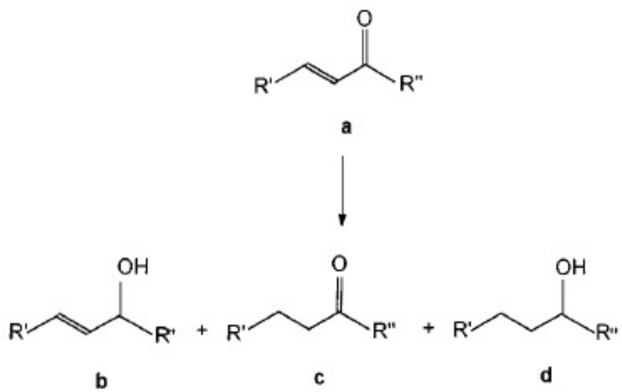




Riduzione di Luche - Il $CeCl_3$ è un catalizzatore acido di Lewis selettivo per la metanolisi di $NaBH_4$. I vari metossiboroidruro di sodio risultanti sono agenti riducenti più duri (secondo i principi HSAB) e quindi effettuano una riduzione 1,2 con maggiore selettività.

Introduction

Since the discovery of the reducing properties of borohydride, sodium borohydride has received considerable attention as a selective and mild reducing agent; it is particularly attractive for general use thanks to its ease of handling. However, reduction of conjugated aldehydes and ketones is generally complicated by competing 1,2 and 1,4 processes, (Scheme 1) and the clean reduction of α,β-unsaturated aldehydes and ketones by hydride reagents has offered considerable difficulty: $NaBH_4$ predominantly reduces the C=O bond of conjugated systems in most cases, but substantial amounts of fully saturated alcohols have been found in general,[1,2] and the selectivity depends on several factors such as steric hindrance of the double bond, as well as the ring size in cyclic systems, and the solvent used.[1]



Scheme 1. Possible products from reductions of α,β-unsaturated ketones

The selective reduction of α,β-unsaturated aldehydes and ketones is of interest as this problem is often encountered in synthetic schemes. For the selective reduction of the carbonyl function considerable progress has been made in the development of reducing agents derived from $NaBH_4$: good selectivity has been achieved by addition of lanthanide ions[3] or $CaCl_2$,[4] by use of $Zn(BH_4)_2$[5] or $NaBH_4$ in carboxylic acid as reaction medium.[6] The selective reduction of the C=C bonds has been achieved by addition of $CoCl_2$ or $NiCl_2$ to solutions of $NaBH_4$, with formation of solid borides and of H_2, which acts as the reducing agent.[7] This kind of reaction is usually carried out in MeOH, but since $NaBH_4$ reacts with MeOH at a rapid rate, and metal borides further accelerate this breakdown,[8] and since $NaBH_4$ is considerably more stable in water than in MeOH,[9] the use of water as solvent was explored. Ganem et al.[10] have already explored the use of aqueous tetrahydrofuran, but only to carry out the reduction of nitriles to amines by $NaBH_4$ in the presence of $CoCl_2$: they found that the presence of water provides advantages in terms of reactivity with respect to methanol. Moreover, the use of water as solvent is particularly attractive for developing mild, cheap, and environmentally benign reaction conditions, and there is considerable interest in water as a reaction medium.[11]

Furthermore, aqueous association colloids are alternatives to the use of organic solvents in that they provide reaction media distinct from bulk water in terms of polarity, and they can also compartmentalize reagents so that they can provide chemo-, regio-, or stereoselectivity.[12] Attention has also been devoted to the selective reduction of enones in surfactant-rich media with $NaBH_4$ where it seems that they affect regioselectivity.

An improvement in the selectivity for products of 1,4 reduction with cationic micelles of CTABr or CTA(BH_4) for several enones was reported by Sukeninik:[13a] only the totally reduced products **d** or the 1,2 reduction product **b** were produced, and only for one of them was the selectivity in product **d** up to 70%; no attempts to rationalize the results based on substrate structure or to improve conditions for the other substrates have followed these preliminary studies. The use of hydrotopes[13b] in heterogeneous conditions has been shown to lead to totally reduced products **d** with high selectivity (90%), but only one substrate, isophorone, has been investigated.

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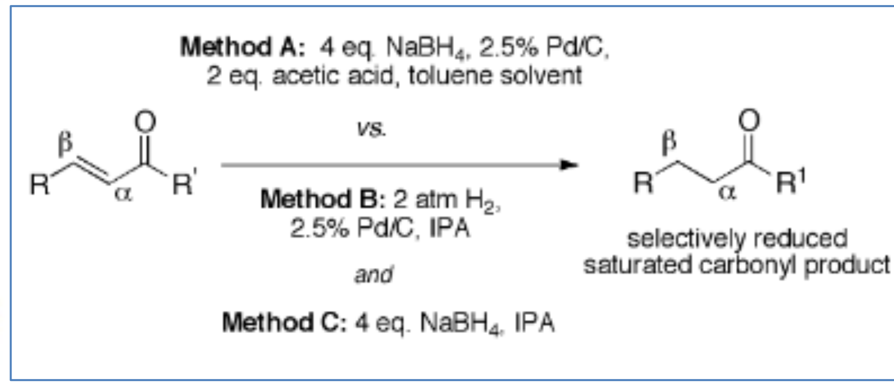
Although alkali metal borohydrides have received much attention in organic synthesis, the studies on the use of alkaline earth metals are limited. For example, α,β-unsaturated ketones more readily converted to allylic alcohols selectively using $NaBH_4$ in the presence of $CaCl_2$ (Eq. (58)) [65]. Among the alkaline earth metal chlorides examined, $CaCl_2$ gives the best combination of good yields and selectivities in the $NaBH_4$ reduction of 2-cyclohexen-1-one. Further, this method provides a simple, inexpensive alternative procedure for the selective 1,2-reduction of α,β-unsaturated ketones.

Additive	Yield(%)	Ratio of 1,2:1,4
None	-	51:49
$MgCl_2$	85	95:05
$CaCl_2$	92	97:03
$SrCl_2$	91	81:19
$BaCl_2$	86	93:07

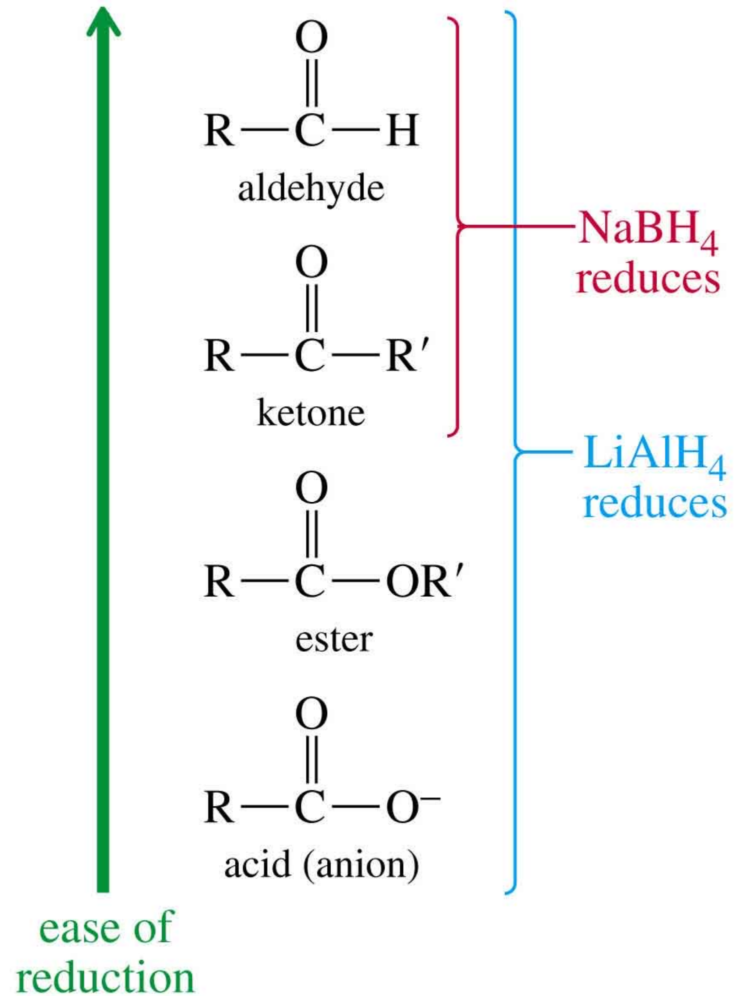
(58)



’’ Methods of enhancement of reactivity and selectivity of sodium borohydride for applications in organic synthesis’’ Journal of Organometallic Chemistry 609 (2000) 137–151

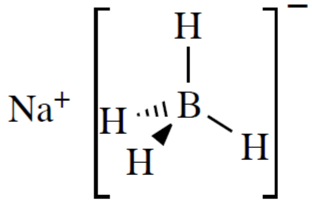
Esperienza 4: Riduzione del benzofenone

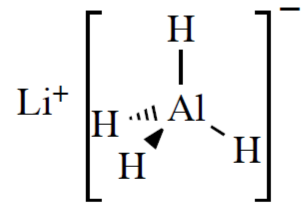
- Use of $NaBH_4$ vs $LiAlH_4$



- Reduction of a carbonyl group
- Use of $NaBH_4$ vs $LiAlH_4$

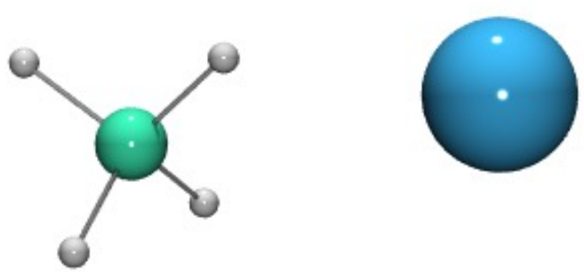
Different reactivity

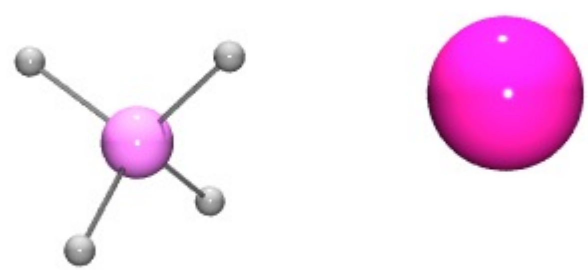




$NaBH_4$ - Sodium Borohydride $LiAlH_4$ - Lithium Aluminum Hydride or LAH

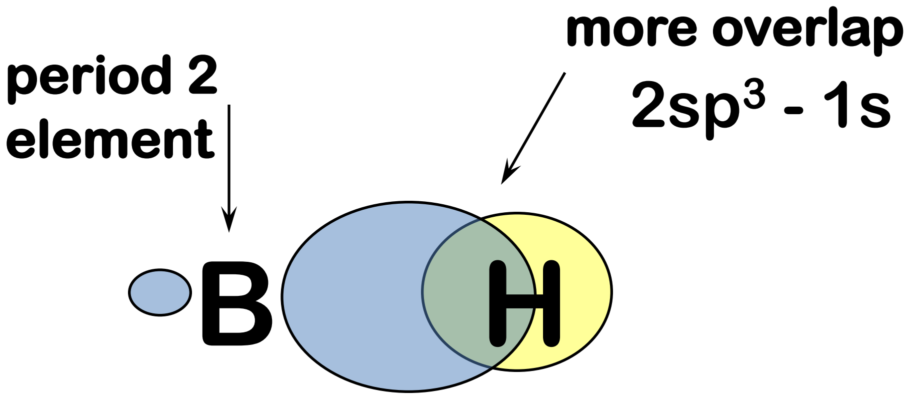
LAH is a more powerful hydride reducing agent (greater ΔEN). It will reduce some functional groups that $NaBH_4$ cannot.





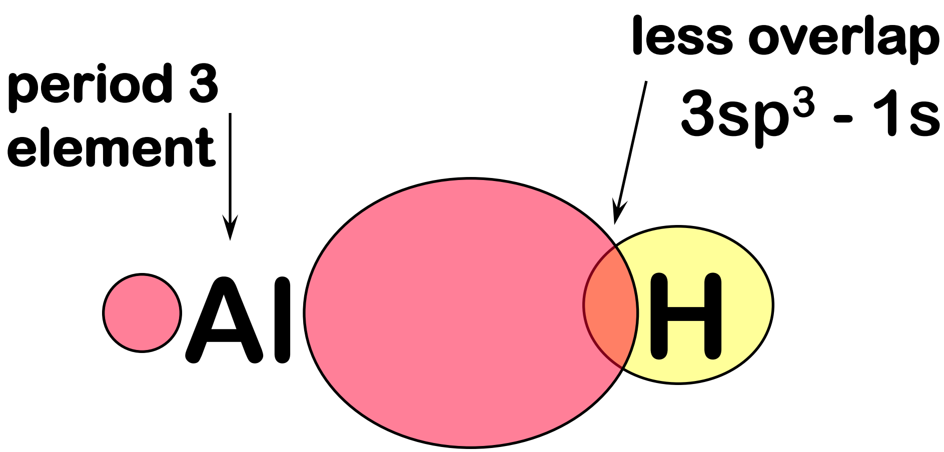
- CATION
- Atom bearing the hydride

Different reactivity



$NaBH_4$

meno reattivo



$LiAlH_4$

più reattivo

Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride $NaBH_4$	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1º-alcohols ketones to 2º-alcohols inert to most other functions	**1)** simple neutralization **2)** extraction of product
Lithium Aluminum Hydride $LiAlH_4$	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1º-alcohols ketones to 2º-alcohols carboxylic acids to 1º-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functions react	**1)** careful addition of water **2)** remove aluminum salts **3)** extraction of product

$LiAlH_4$ reagisce violentemente e si incendia

$LiAlH_4 + 4\,H_2O \longrightarrow$

$LiOH + Al(OH)_3 + 4\,H_2 +$ heat

Solventi usati: etere etilico, THF anidro.

$NaBH_4$ reagisce con H_2O o alcoli molto lentamente

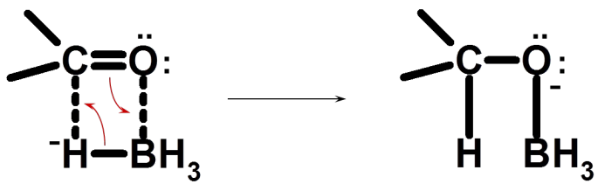
$NaBH_4 + 4\,H_2O \longrightarrow$

$NaOH + B(OH)_3 + H_2$

H_2O o alcoli possono essere usati come solvente

Esperienza 1: Riduzione del benzofenone

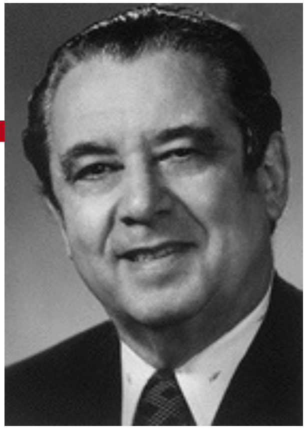
Meccanismo



✓formazione di un intermedio organoborano per addizione SIN, concertata

✓Il sodio boro idruro reagisce con <u>4 equivalenti</u> di substrato

✓**Studi posteriori hanno dimostrato che non si tratta di un meccanismo concertato**



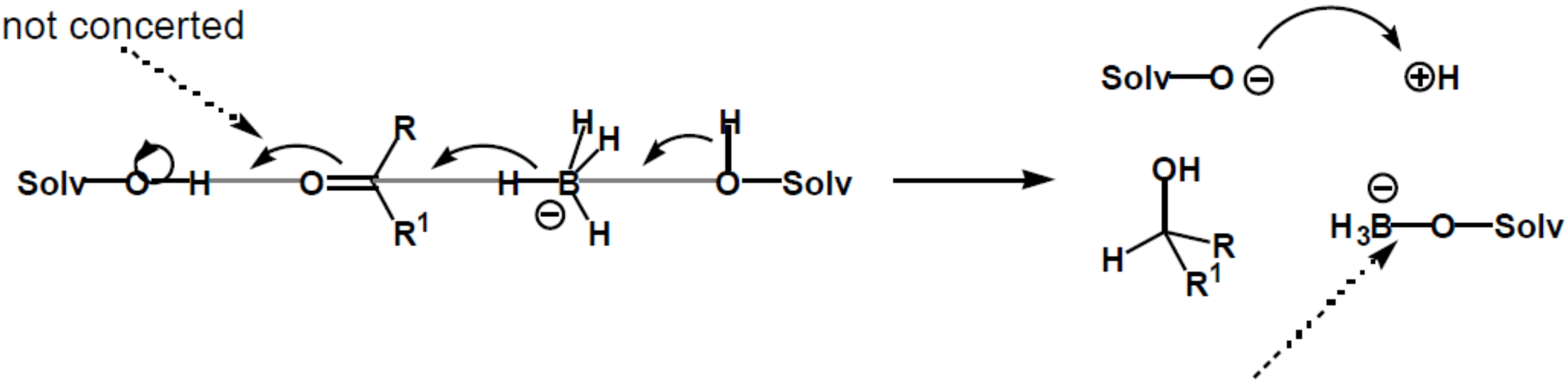
H. C. Brown

the Nobel Prize in Chemistry in 1979

Meccanismo

• In $NaBH_4$ reactions cation is not important but ***solvent*** can be

• not concerted

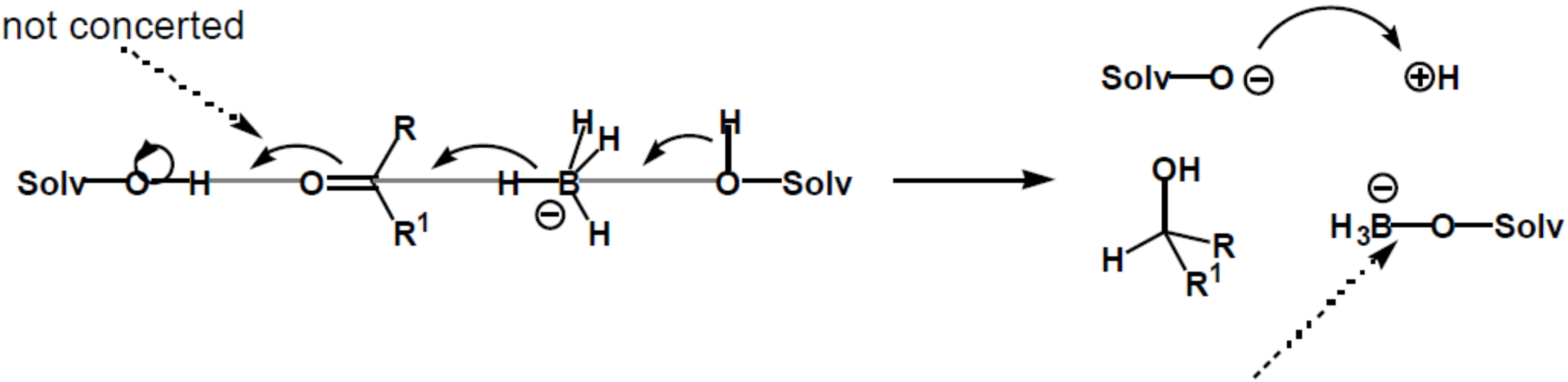


• multiple reductions occur
• alkoxide makes hydride less reactive

Meccanismo

• In $NaBH_4$ reactions cation is not important but ***solvent*** can be

• not concerted



iple reductions occur
nakes hydride less reactive

Deuterium Isotopic Labeling

Isotopic Labeling with Deuterated Reagents

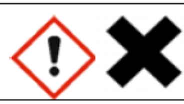
$NaBH_4$ then H_3O^+ ⟶ R_2C**H**-O**H**
$NaBD_4$ then H_3O^+ ⟶ R_2C**D**-O**H**
$NaBD_4$ then D_3O^+ ⟶ R_2C**D**-O**D**
$NaBH_4$ then D_3O^+ ⟶ R_2C**H**-O**D**

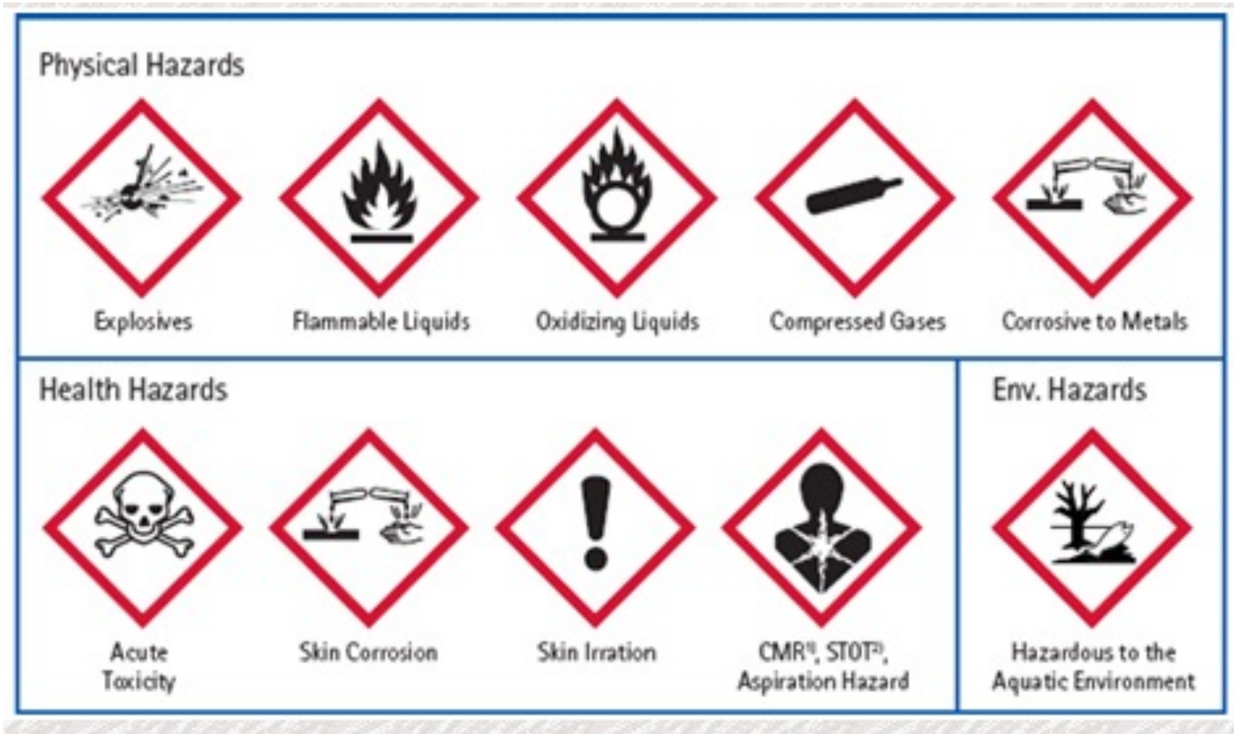
^1H = H normal hydrogen
^2H = D deuterium
^3H = T tritium

from hydride reagent

from acidic work-up

Esperienza 1: Riduzione del benzofenone

Cloruro di metilene		Nocivo se ingerito o inalato, anche al contatto con la pelle. Provoca irritazioni nella pelle e occhi. Possibilità di effetti cancerogeni
Benzofenone		Provoca irritazione cutanea, grave irritazione oculare, può irritare le vie respiratorie. Nocivo per gli organismi acquatici
Sodio boroidruro		Tossico a contatto con la pelle e per ingestione. Provoca ustioni cutanee e gravi lesioni oculari. A contatto con l'acqua libera gas estremamente infiammabili (idrogeno). È incompatibile anche con sostanze ossidanti, acidi o metalli chimicamente attivi come palladio o rutenio.
Metanolo		Tossico a contatto con la pelle, per ingestione e per inalazione. Provoca danni al cuore e fegato, può provocare cecità. Altamente infiammabile. Provoca danni agli organi
Acido cloridrico		L'acido cloridrico commerciale (37%) provoca gravi ustioni e gravi lesioni oculari. Le soluzioni diluite sono meno pericolose ma comunque provocano ancora irritazioni cutanee e oculari. Irrita le vie respiratorie.
Benzidrolo		Irritante per gli occhi, le vie respiratorie e la pelle


Physical Hazards
Explosives
Flammable Liquids
Oxidizing Liquids
Compressed Gases
Corrosive to Metals
Health Hazards
Acute Toxicity
Skin Corrosion
Skin Irration
CMR[1], STOT[2], Aspiration Hazard
Env. Hazards
Hazardous to the Aquatic Environment

Esperienza 1: Riduzione del benzofenone

	Esperienza n. 1 Riduzione del benzofenone
25	Il sodio boro idruro deve essere aggiunto a freddo perché 1) La resa della reazione diminuisce con l'aumentare della temperatura 2) A caldo si sviluppa H_2 che è tossico 3) Si sviluppa H_2 che, a caldo, può incendiarsi
26	Durante l'aggiunta di $NaBH_4$ cosa non si deve assolutamente fare: 1) Agitare la miscela di reazione 2) Tenere la cappa accesa al massimo della sua portata 3) Lasciare vicino alla beuta di reazione un mantello riscaldante acceso

TECNICHE UTILIZZATE

- reazione condotta a 0°C

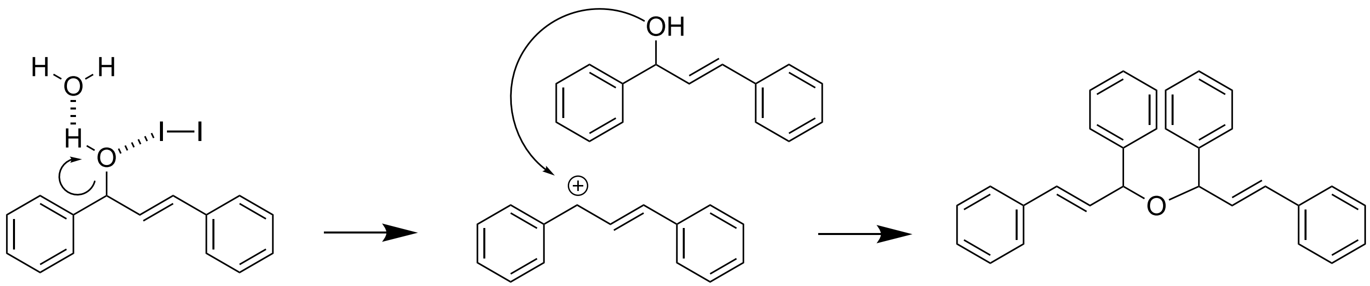
- il sodio boro idruro è un reagente potenzialmente infiammabile
ATTENZIONE LA REAZIONE DEVE ESSERE MANTENUTA IN BAGNO DI GHIACCIO E CONDOTTA SOTTO CAPPA

- WORK-UP con acido cloridrico al 10% produce H_2
- Filtrazione sotto vuoto del prodotto
- anidrificare il campione per analisi

Tubo a cloruro di calcio

Caratterizzazione: TLC, NMR, IR, GC-MS

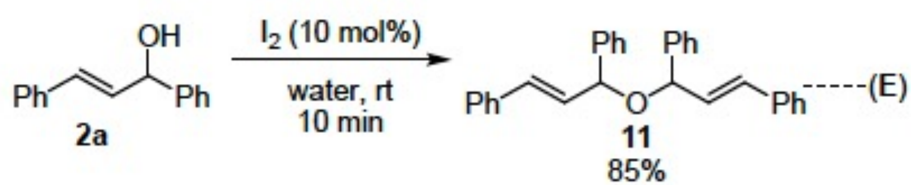
^{1}H-NMR con D_2O: cosa succede?



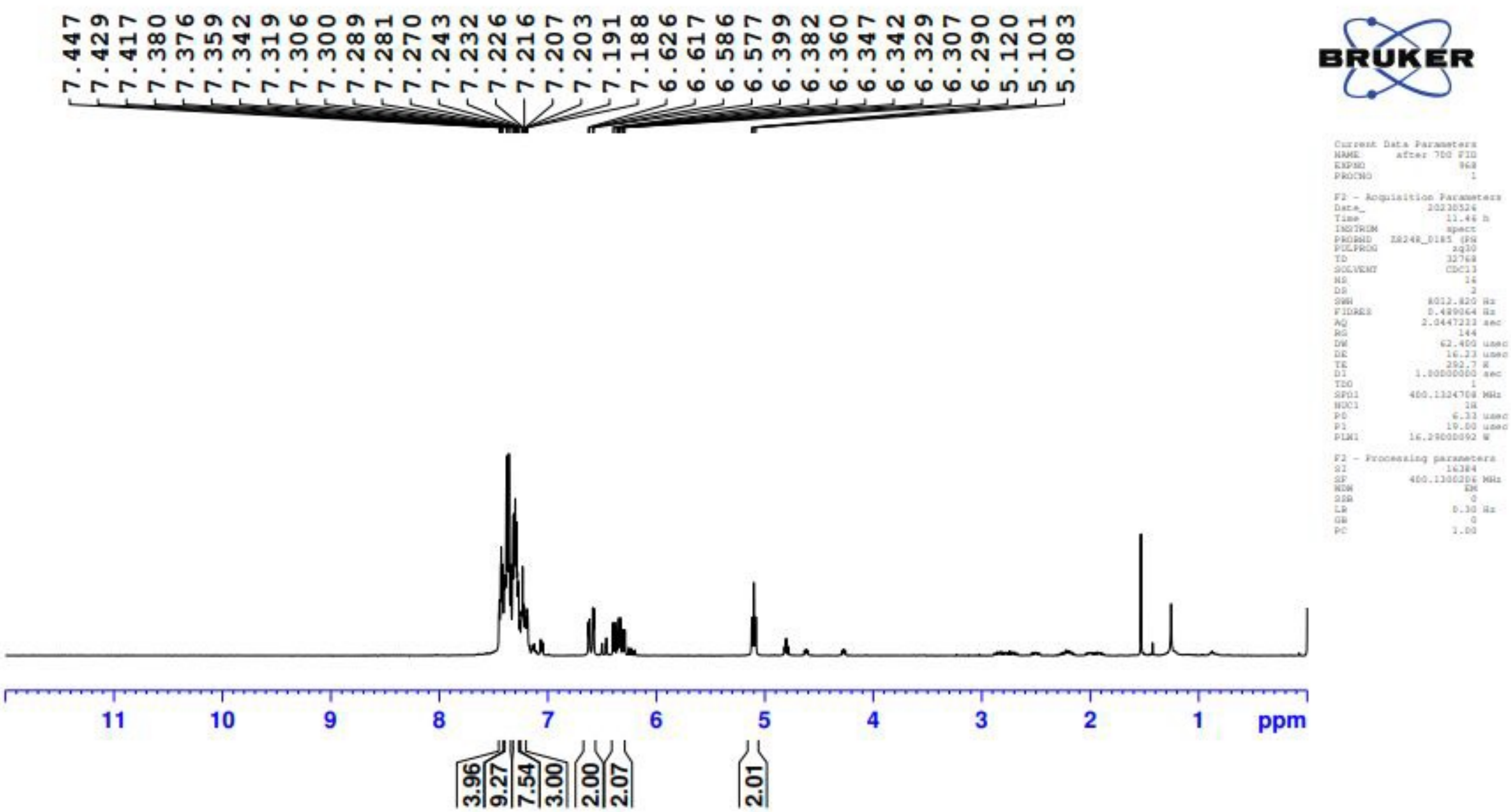
Al posto di I2 si può usare un acido che favorisca l'elimminazione di H_2O e la formazione del carbocatione

Eq. E: In an oven dried reaction tube (*E*)-1,3-diphenylprop-2-en-1-ol (**2a**, 0.3 mmol, 0.063 g), and I_2 (10 mol%, 0.008 g) were taken and 1.5 ml water was added. Then the reaction mixture was stirred at room temperature for 10 min. After the completion of the reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane-water and organic part was dried over anhydrous Na_2SO_4. Finally, dichloromethane was evaporated to obtain crude product and it was purified by column chromatography with 60-120 mesh silica gel using a mixture of ethyl

acetate/hexane as an eluent to obtain the ((1*E*,1'*E*)-oxybis(prop-1-ene-3,1,3-triyl))tetrabenzene (**11**).



AKB-SP-Allyl-ether-I 26.05.2023



^{1}H NMR (500MHz, $CDCl_3$)

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