BENZOTRIAZOLE-STABILISED CARBANIONS: GENERATION, REACTIVITY AND SYNTHETIC UTILITY

1. **General**
2. **General reactivity**
3. **Bis(benzotriazol-1-yl)-(*p*-tolyl)methyl anion as an arylacyl anion equivalent**
4. **Tris(benzotriazol-1-yl)-methyl anion as a $^{-}$COOH equivalent**
5. **(Benzotriazol-1-yl)-methoxymethyl as a 1,1-dipole and methylal [$^{-}$CH(OMe)$_2$] synthon**
6. **(Benzotriazol-1-yl)-phenylthiomethane as 1,1-dipole equivalent in aromatic annulation**
7. **Synthesis of nitrogen containing heterocycles involving 1-(cyanomethyl)-1*H*-benzotriazole**
    - **7.1. Synthesis of the adduct**
    - **7.2. Synthesis of 5-polysubstituted tetrazoles**
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    - **7.4. Synthesis of 2,4-polysubstituted thiazoles: C-C heterocoupling with furan and thiophene**
8. **Synthesis based on benzotriazole-aldehyde-amine adducts**
    - **8.1. Synthesis of amines**
    - **8.2. Synthesis of substituted tetrahydroquinolines**

References:

Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Aldrichimica Acta*, **1994**, 27(2), 31 – 38
Katritzky, A. R.; Belyakov, S. A. *Aldrichimica Acta*, **1998**, 31(2), 35 – 44

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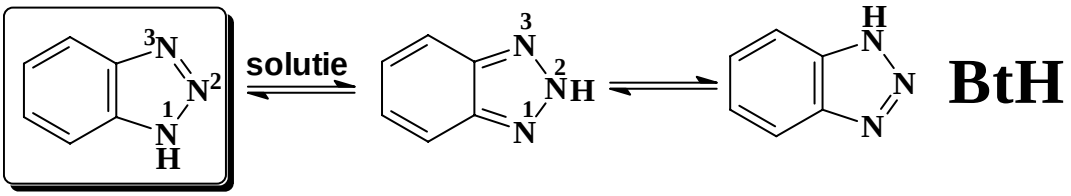
BENZOTRIAZOL – CARBANIONI STABILIZATI: GENERARE, REACTIVITATE, VALOARE PREPARATIVA

1. Generalitati:

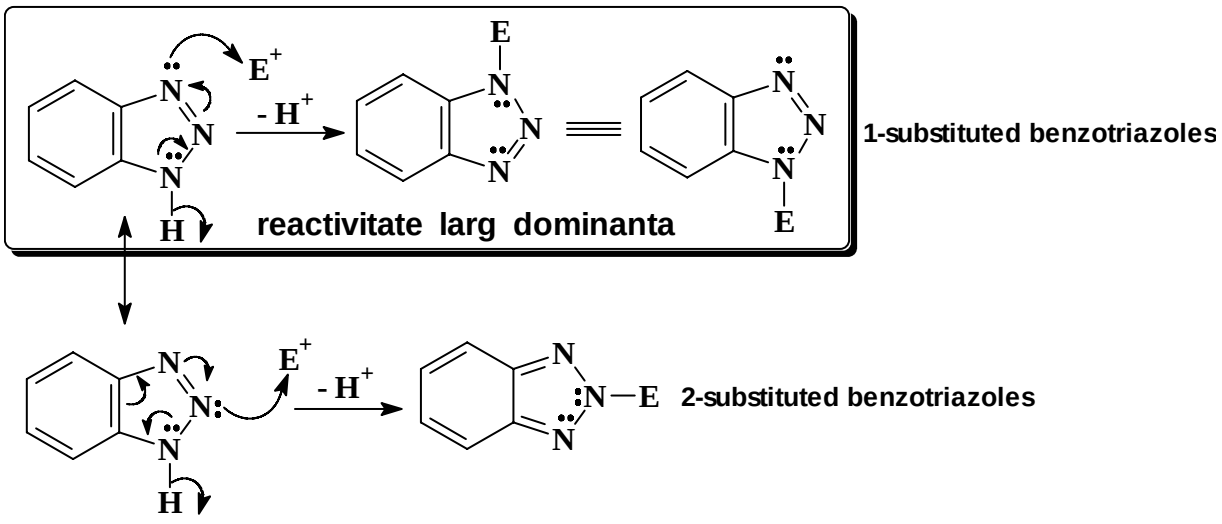


1*H*-benzotriazole stare solida **2*H*-benzotriazole**

- pulbere alba, microcristalina, cu p.t. = 100^{o}C
- insolubil in apa
- netoxic
- ieftin
- in **stare solida**, i se atribuie structura tautomerului **1*H***; in **solutie** se stabileste un echilibru rapid intre tautomeri (^{1}H – RMN: doar **doua tipuri** de protoni aromatici **ddd + ddd**) nediferentiabili.
- Acid slab: este deprotonabil (chiar cu baze uzuale alcaline) si solubil in solutii bazice.

2. Reactivitatea generala

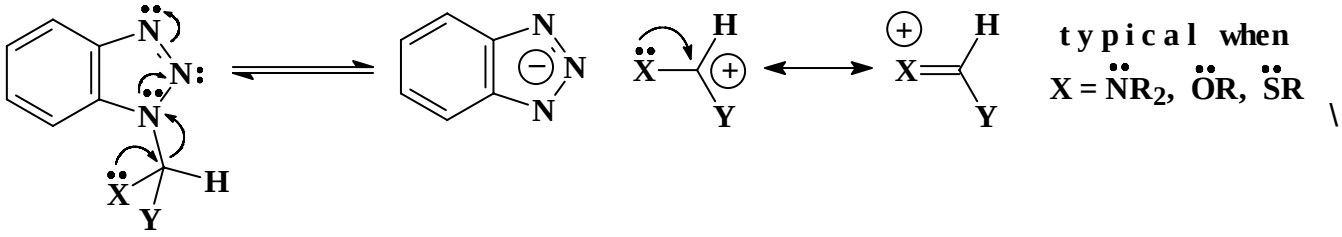
- este reactiv fata de electrofili la ***N* – piridinic**, exact ca orice triazol; **derivatii monosubstituiti pot genera regioizomerie, regiozimerul dominant fiind 1*H*.**



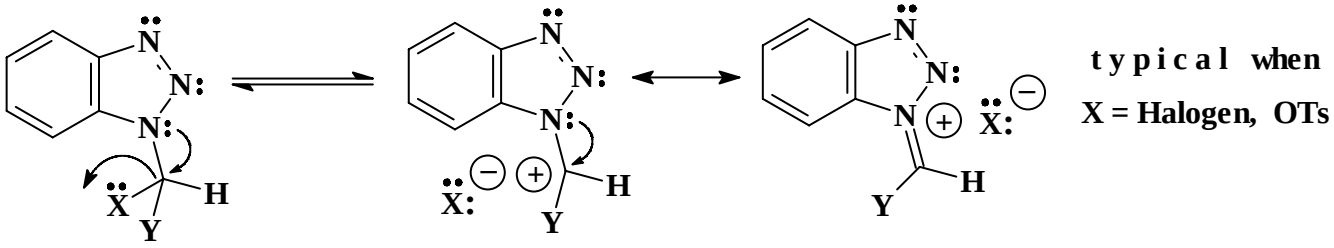
- reactivitatea fata de electrofili in **partea aromatica** este **neglijabila** in context
- reactivitatea in directia formarii **benzotriazolilor *N* - 2 substituiti** este **neglijabila** in context

Why is it challenging ?

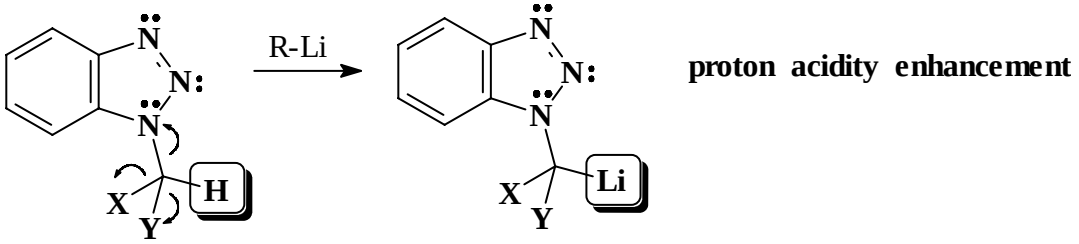
1. Excellent *L*eaving *G*roup as stabilized anion: WITHDRAWING G R O U P



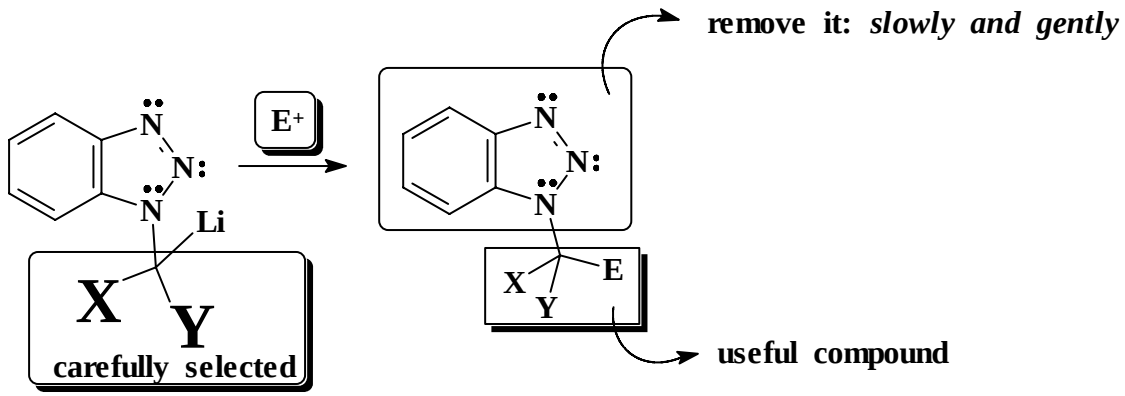
2. Excellent cation stabilizer: DONOR G R O U P



3. Proton acidity enhancement (α - position *vs.* heteroatom)



4. So what ?…



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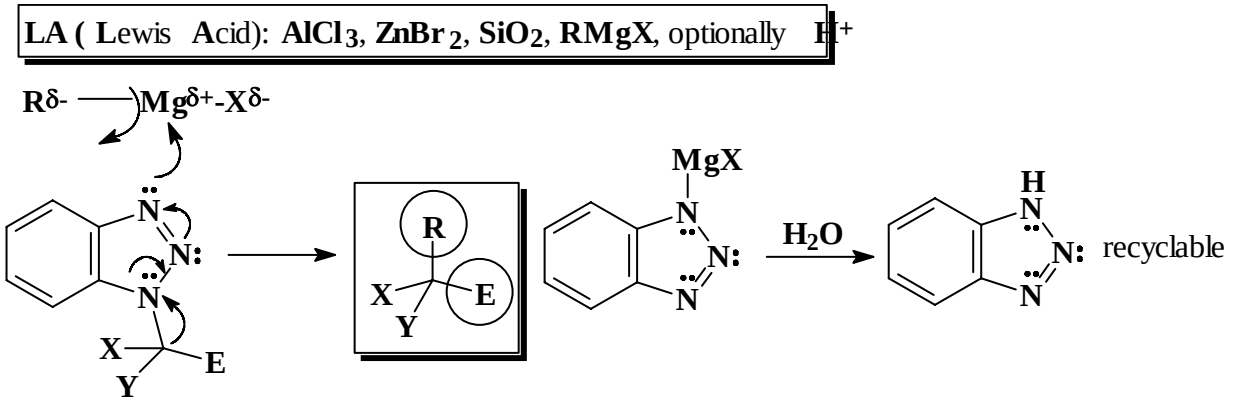
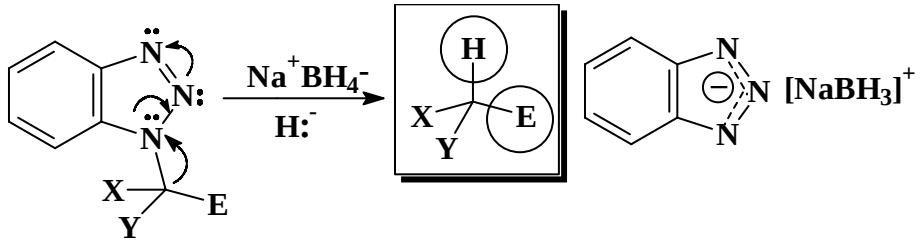
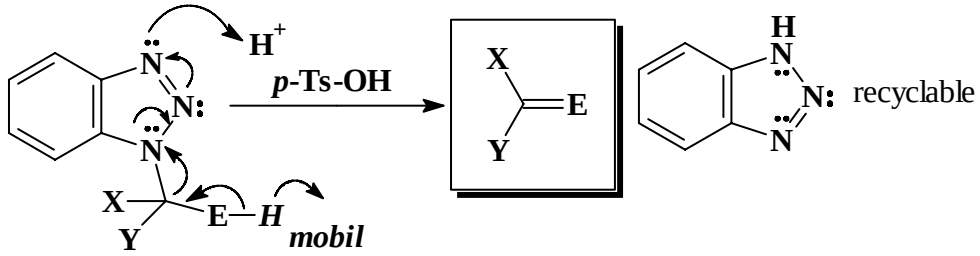


Double synthetic option: *E* and *R*

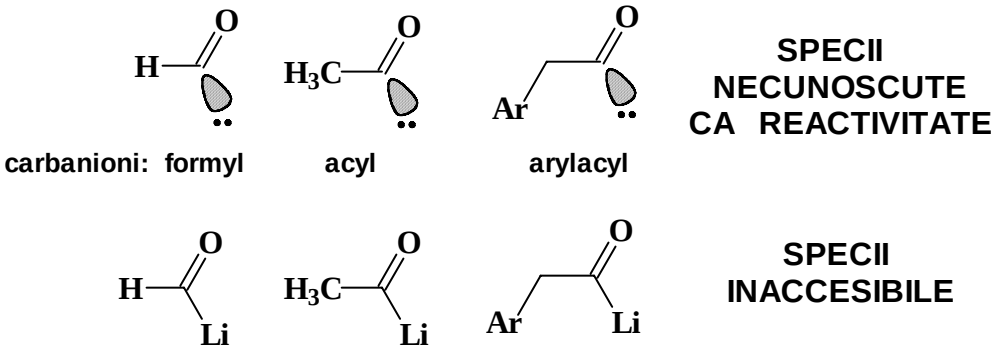




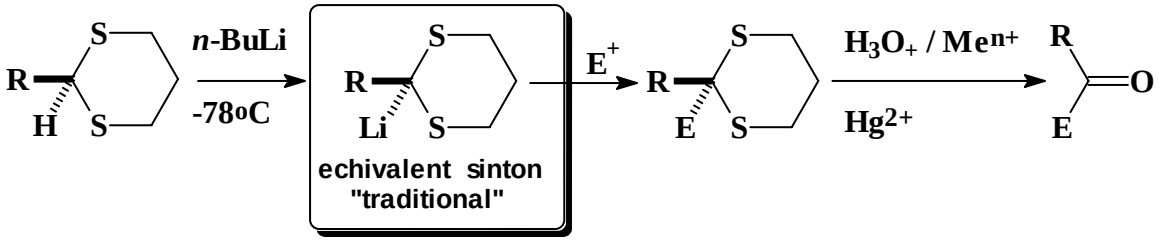
3. Carbanionul Bis(benzotriazol-1-il)-(*p*-tolil)metil ca echivalent sintetic al carbanionului arilacil

Generalitati:

i) **problema:** carbanionii exemplificati mai jos **sunt imposibil** de obtinut prin **metalare directa (deprotonare)**

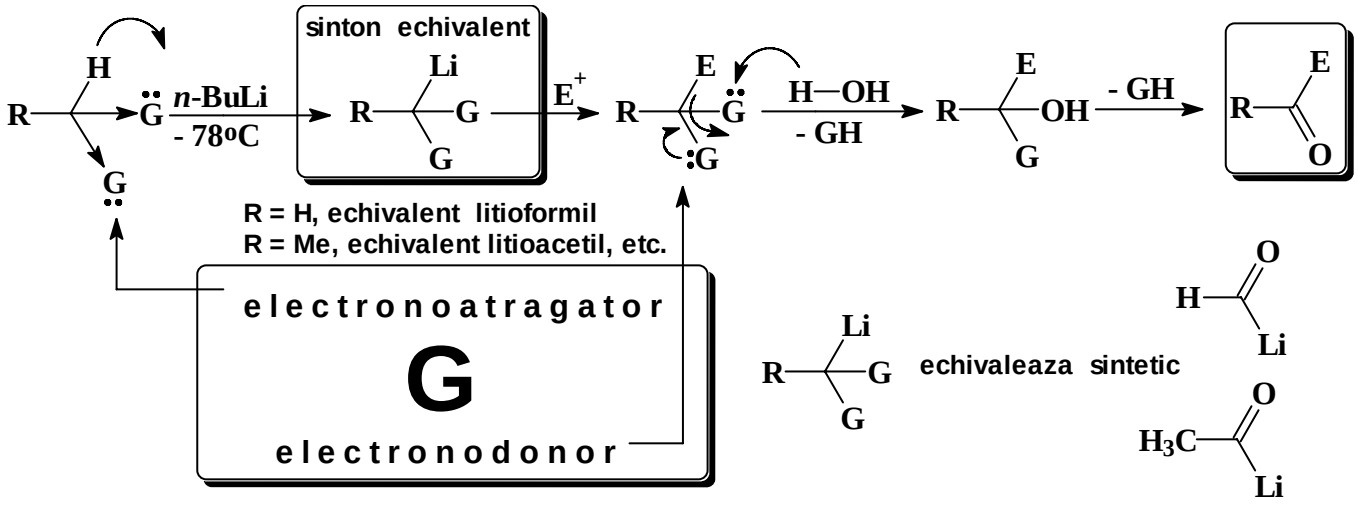


ii) **rezolvarea traditionala:** utilizarea **sulfului** ca **stabilizant de carbanioni**



Nota: in afara caracterului **foarte toxic**, conditiile de indepartare a restului ditianic sunt, comparativ, energice

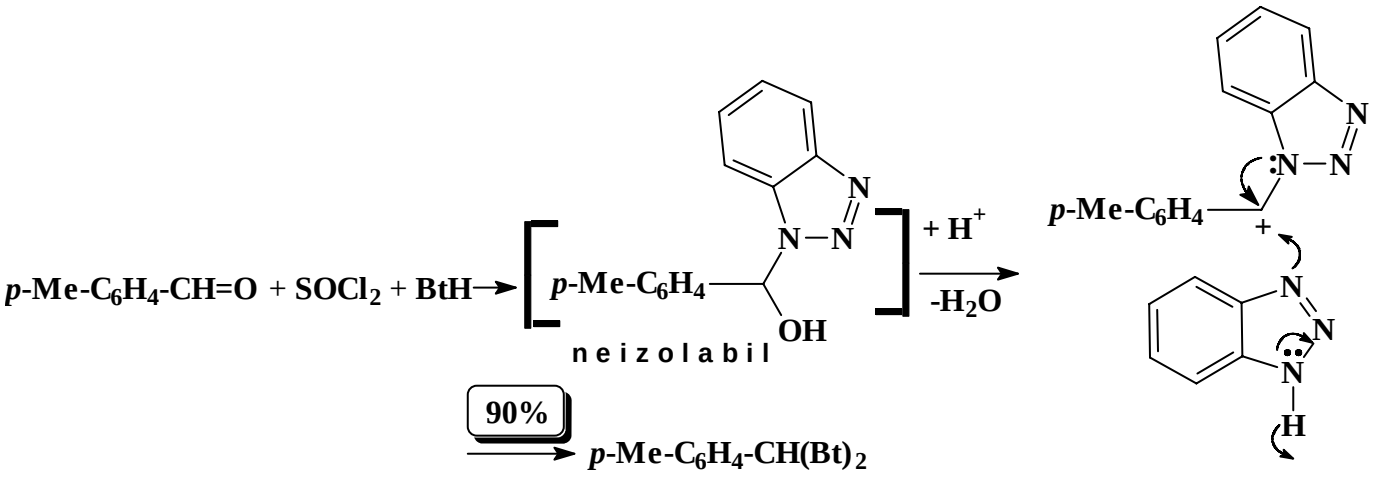
iii) **metodologia Benzotriazolului:** heterociclu **stabilizant atat de carbanioni** cat si **carbocationi (exemplul general, ca grupa –G:)**



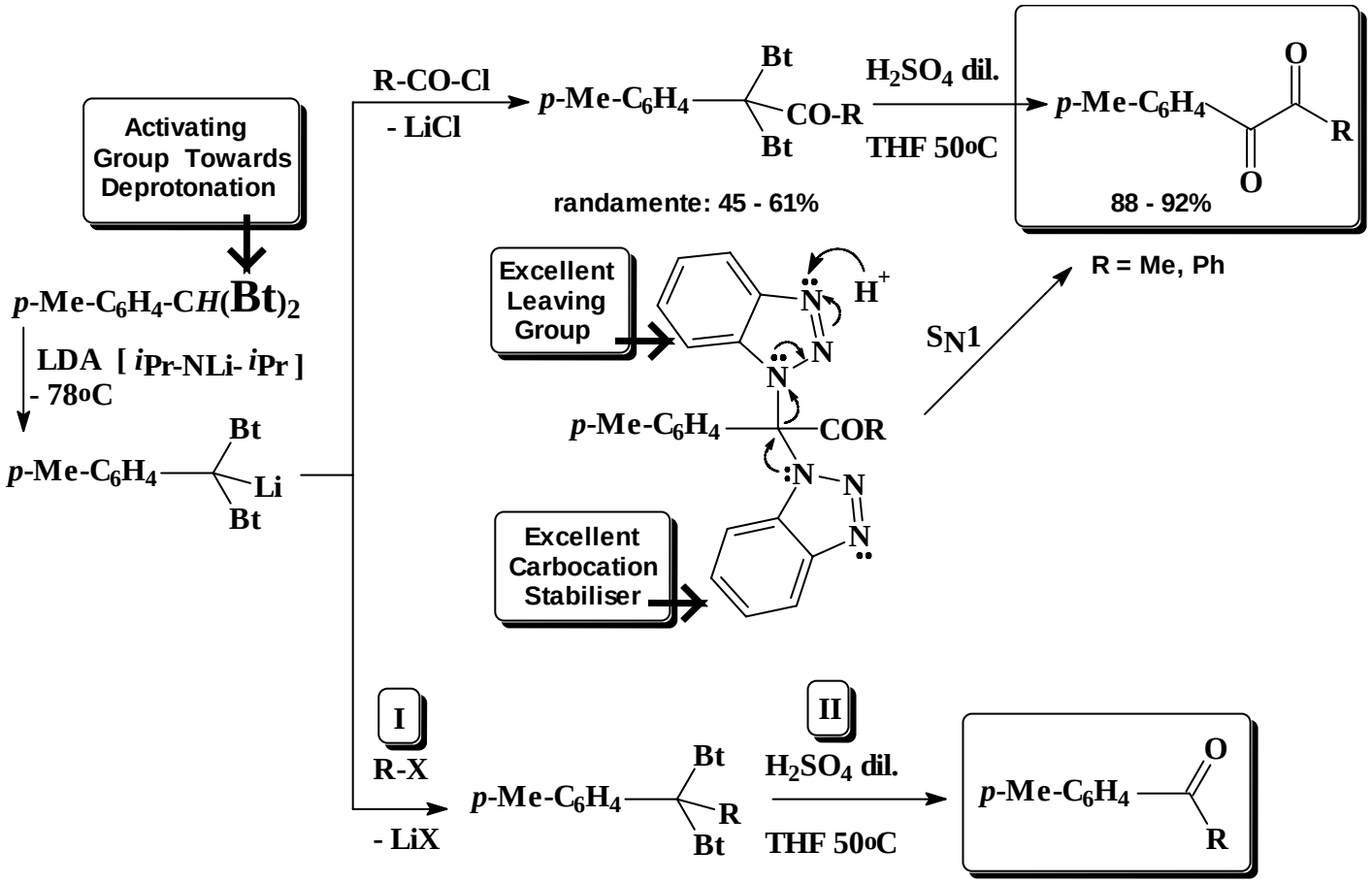
Avantaje: netoxic, conditii de reactie foarte blande, randamente mult mai mari, recuperarea mediatorului, spectru mult mai larg de electrofili.

Exemplu:

i) prepararea "aductului": Bis(benzotriazol-1-il)-*p*-tolilmetan



ii) utilizarea "aductului" la prepararea unor cetone si α - dicetone:

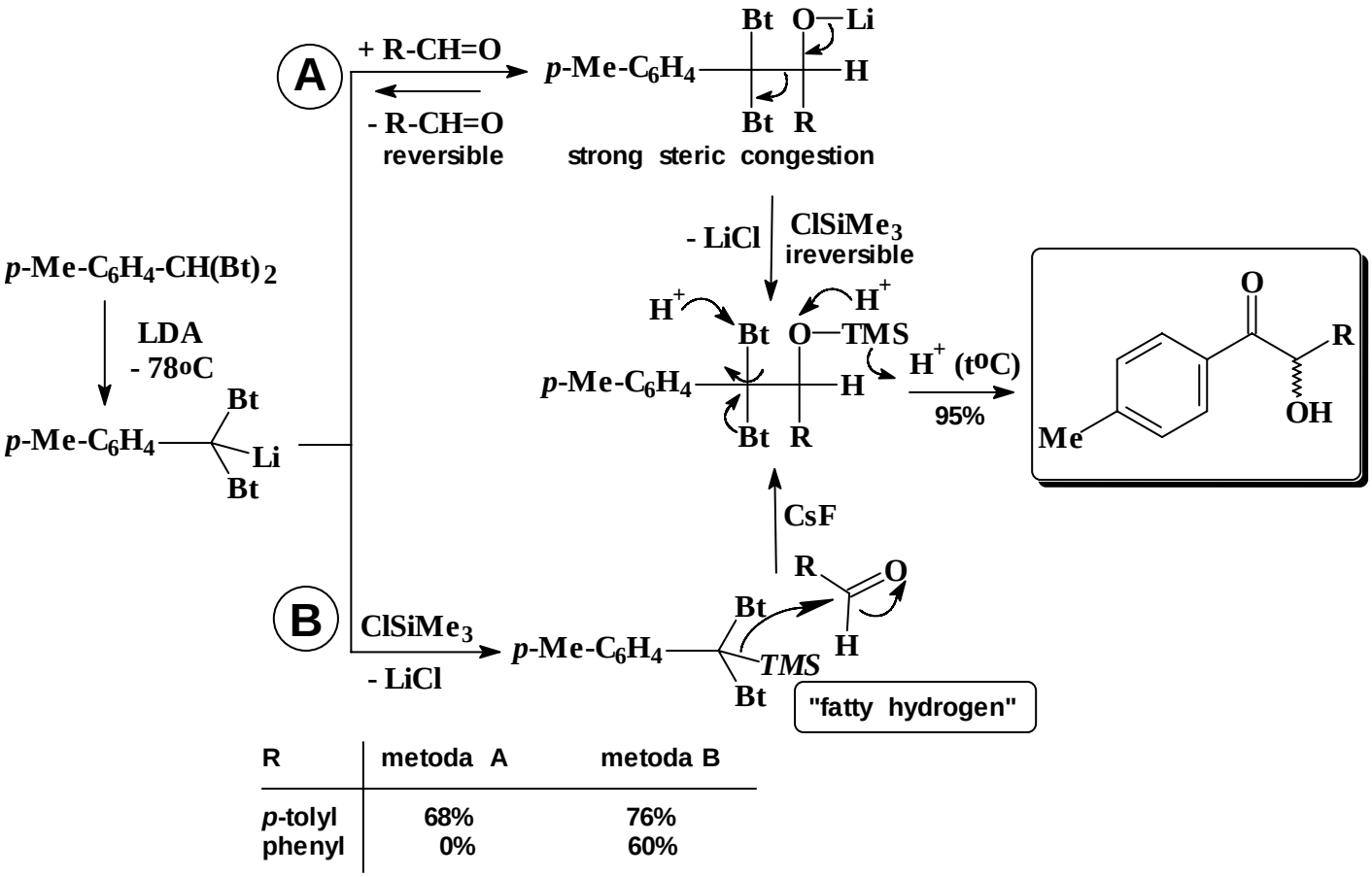


RX	*sec*-BuBr	*i*-Pr	hexyl(I)	*n*-BuBr	hexyl(Br)	AllylBr	MeI	BnBr
Randament I (%)	8	52	52	78	83	84	92	95
Randament II (%)	91	84	96	95	93	80	95	93

Nota 1: sinteza "aductului" trebuie sa fie **T R I V I A L A** si cu **randament maxim**
Nota 2: la **prepararea cetonelor** apare **controlul steric** pe care metodologia **nu-l poate evita**

Exemplu:

- prepararea unor α - hidroxicetone:



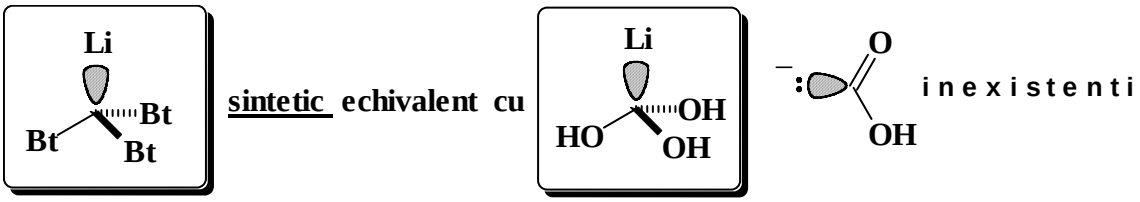
R	metoda A	metoda B
p-tolyl	68%	76%
phenyl	0%	60%

Nota 1: reversibilitatea aditiei organo litioderivatilor la aldehide este un fapt **frecvent**
Nota 2: TMS^+ este o **LG superioroara H^+**

4. Carbanionul Tris(benzotriazol-1-il)-metil ca echivalent sintetic al carbanionului $^{-}$COOH

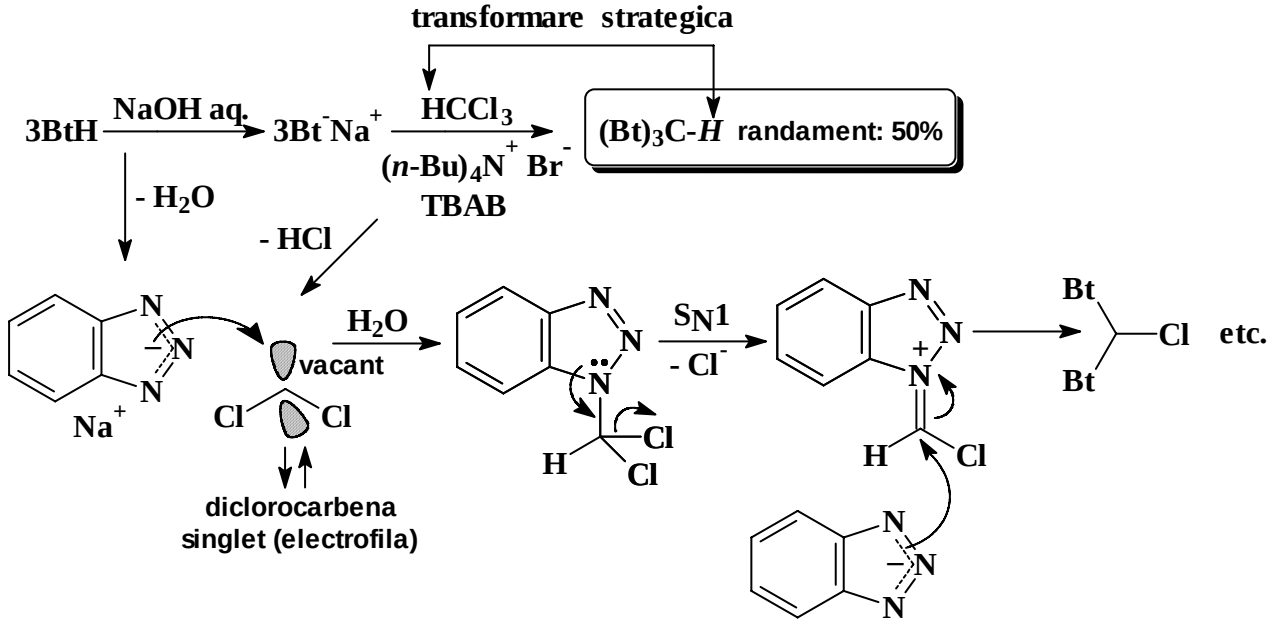
Generalitati:

i) **problema:** carbanionii exemplificati mai jos **sunt imposibil** de obtinut prin **metalare directa (deprotonare)**



Nota 1: solutii alternative: nu se cunosc
Nota 2: obiectivele consta in **prepararea unor acizi carboxilici (**inclusiv α **- functionalizati)**

ii) prepararea "aductului":



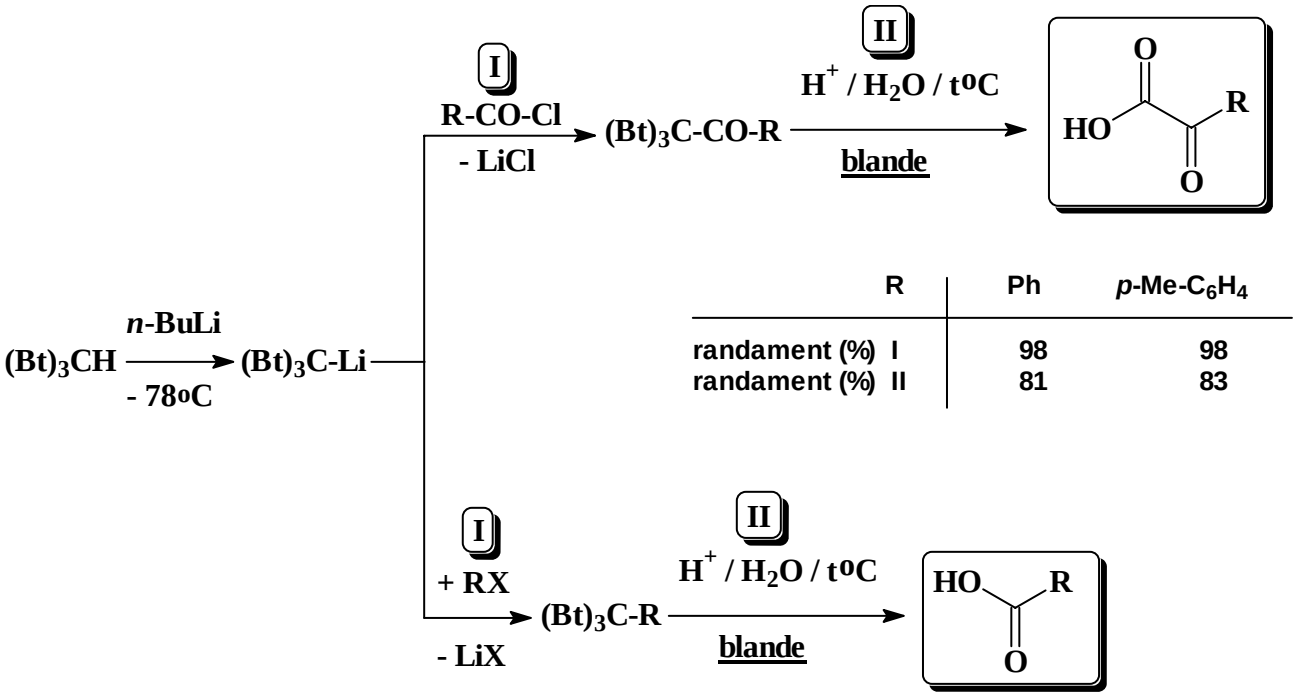
Nota 1: randamentul **modest** pledeaza in favoarea regioizomerului **1*H* - Bt** si **nu 2*H* - Bt (mai degajat steric)**

Nota 2: se regaseste, inca in **etapa sintetica incipienta,** capacitatea **Bt** de a **stabiliza carbocationi de tip benzil**

Nota 3: importanta preparativa a "aductului" ca atare **depaseste importanta randamentului**

Exemplu:

- prepararea unor acizi (α - ceto)carboxilici:

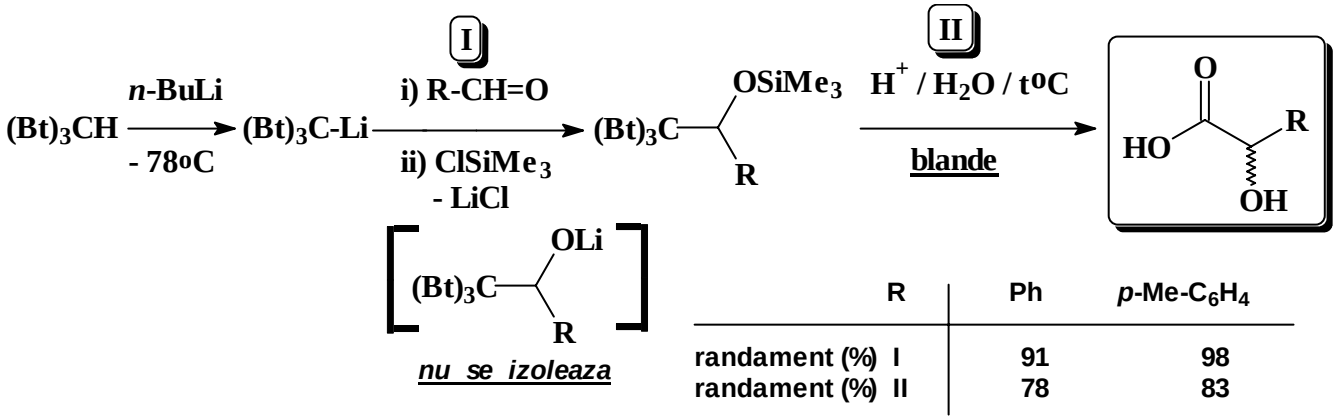


R	Ph	*p*-Me-C_6H_4
randament (%) I	98	98
randament (%) II	81	83

R	Ph-CH=CH-Br	*n*-BuI	$PhCH_2Br$
randament (%) I	84	86	92
randament (%) II	73	79	92

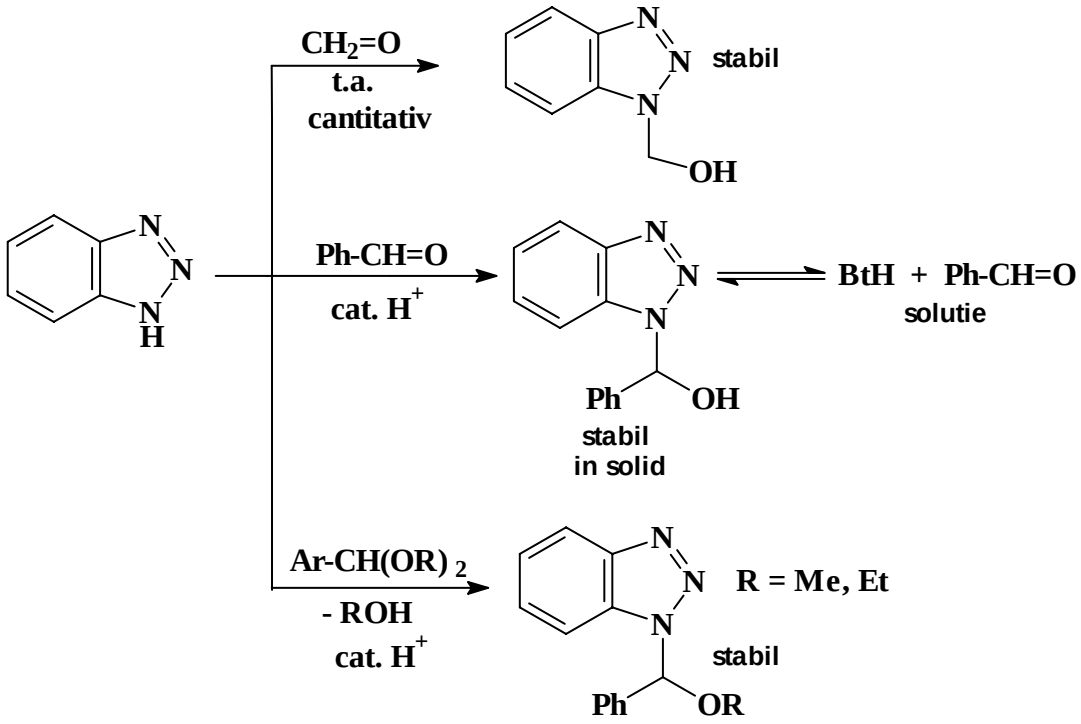
Exemplu:

- prepararea unor α - hidroxiacizi:



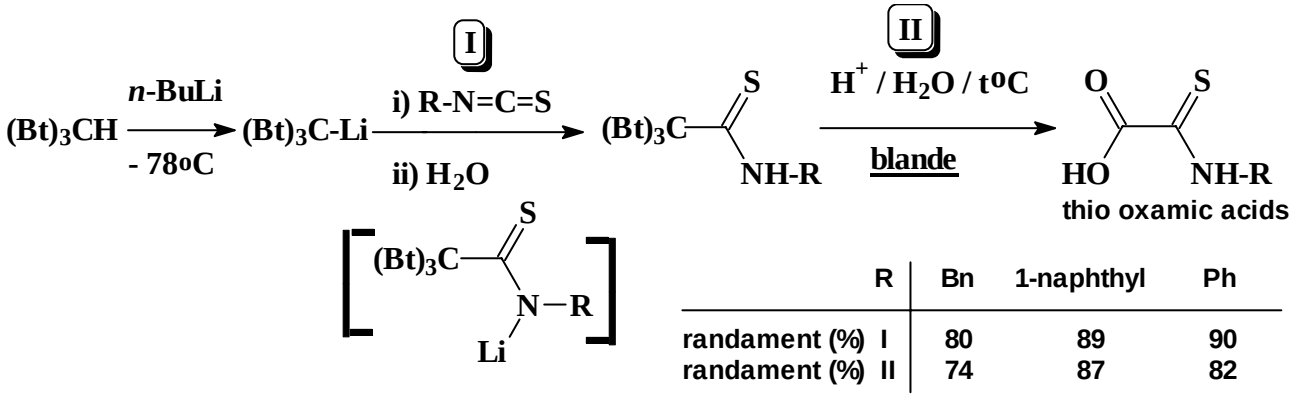
R	Ph	*p*-Me-C_6H_4
randament (%) I	91	98
randament (%) II	78	83

Nota: reversibilitatea reactiei **BtH** cu aldehide se manifesta astfel:



Exemplu:

- prepararea unor acizi tio oxamici:



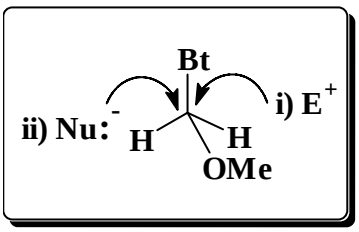
R	Bn	1-naphthyl	Ph
randament (%) I	80	89	90
randament (%) II	74	87	82

Nota: **solutii alternative competitive nu se cunosc**

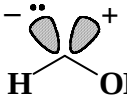
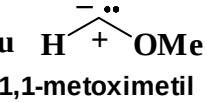
5. Carbanionul Benzotriazol-1-il-metoximetil ca echivalent sintetic 1,1-dipolar, respectiv metilal:

Generalitati:

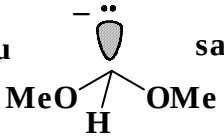
i) problema: speciile reactive de mai jos sunt **necunoscute:**



foarte accesibil

sintetic echivalent cu  sau 

1,1-metoximetil dipol

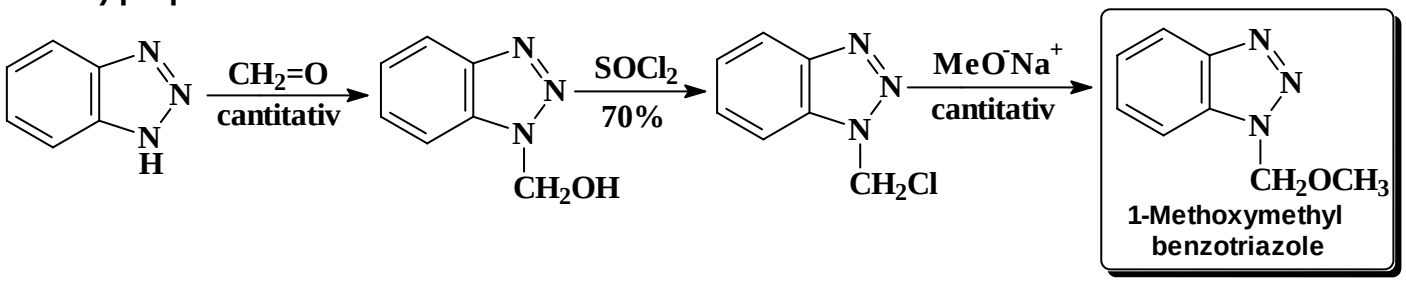
sintetic echivalent cu  sau $^-$:CH(OMe)$_2$

carbanion metilal (dimetoximetil)

Nota 1: 1,1-dipolul este **necunoscut (*a nu se confunda cu o carbena !!*)**

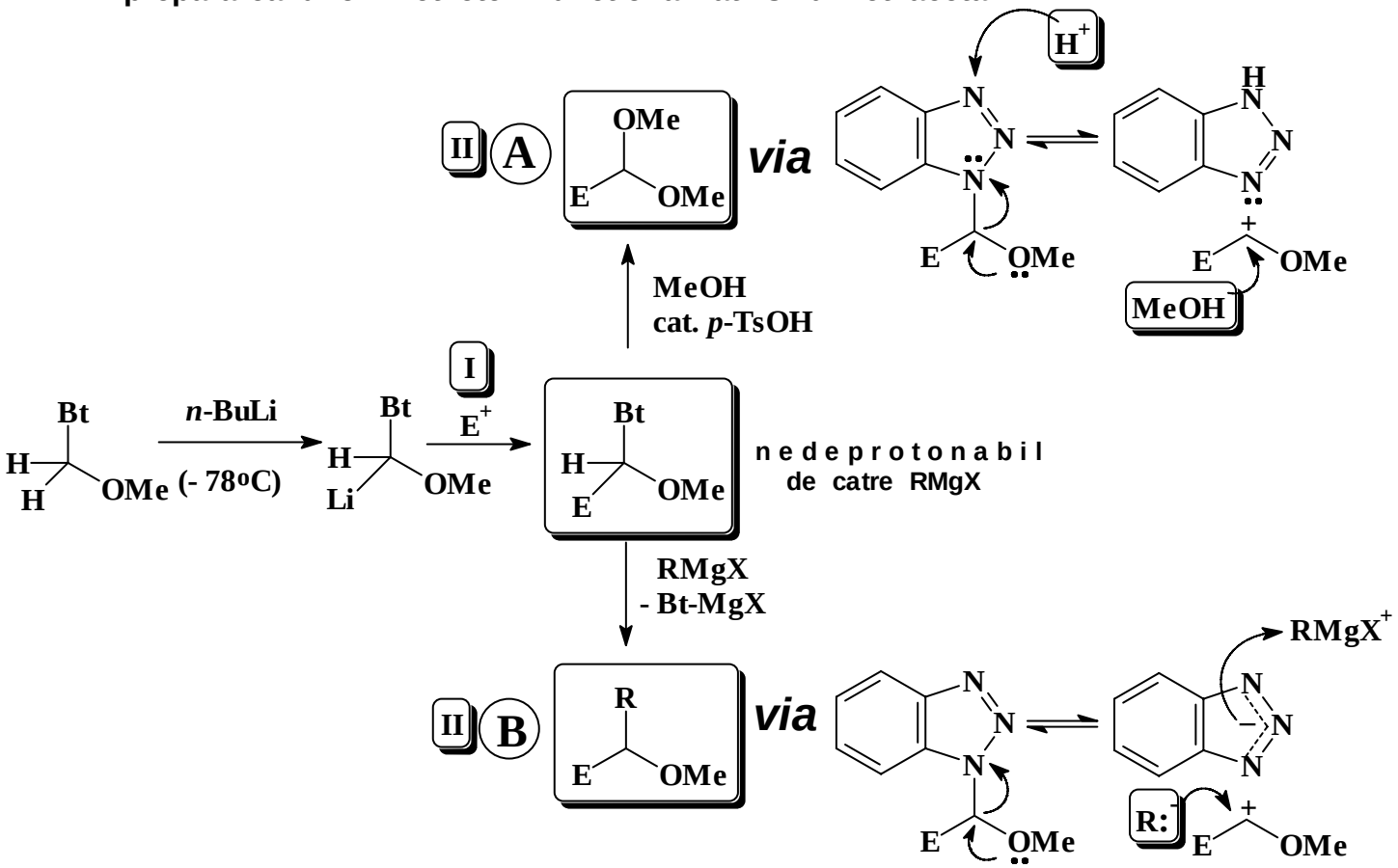
Nota 2: carbanionul metilal si **analogii** de tip **RO-(CH:$^-$)-OR** nu sunt cunoscuti a avea **vreo valoare preparativa**

ii) prepararea "aductului":



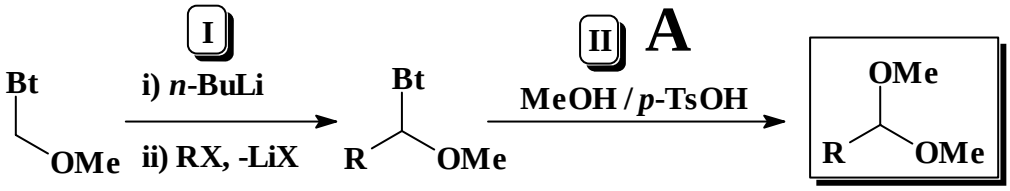
Exemplu:

- prepararea unor metileteri functionalizati si dimetilacetali:



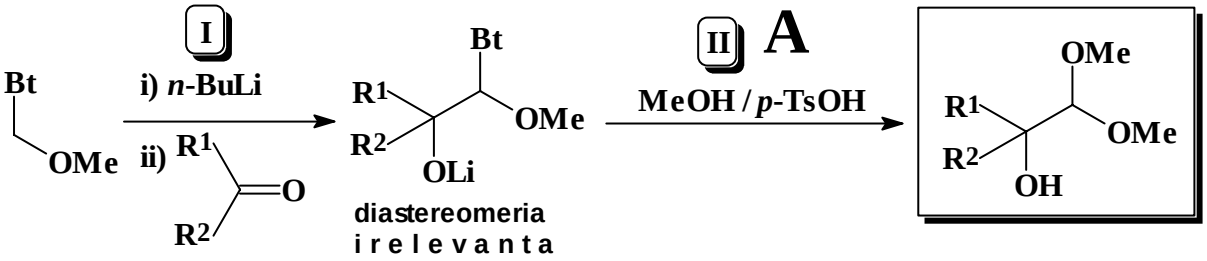
valoarea preparativa:

- prepararea unor dimetilacetali simpli:



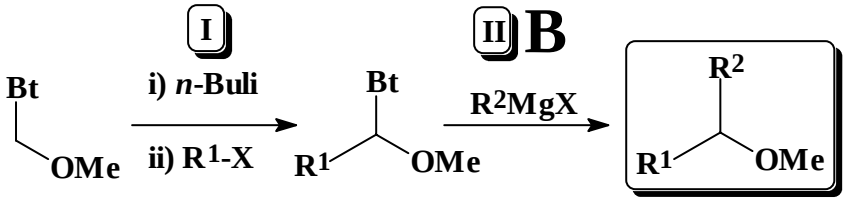
RX	Me_3SiCl	*n*-BuBr	MeI	$CH_3(CH_2)_9Br$	$CH_3(CH_2)_7Br$	$Ph(CH_2)_3Br$	BnBr
Randament I (%)	75	80	85	87	89	91	94
Randament II (%)	-	-	-	94	83	91	88

- prepararea unor α - hidroxidimetilacetali (chirali):

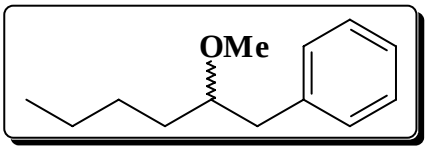


R^1 / R^2	Ph / H	Me / H	4-Me-C_6H_4 / H	Ph / Ph
Randament I (%)	53	80	82	84
Randament II (%)	-	-	78	54

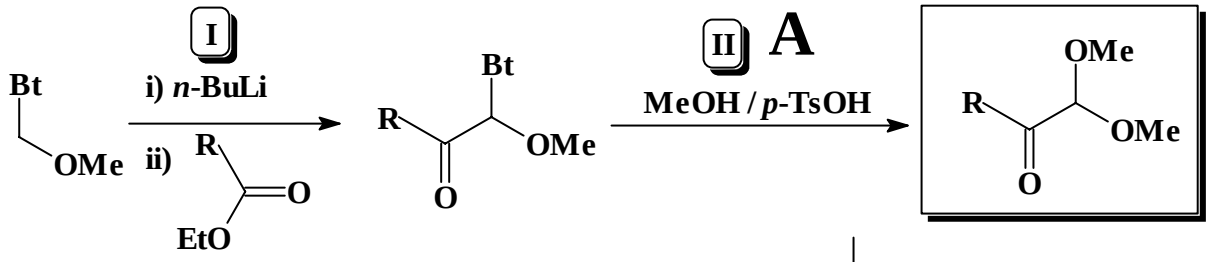
- **prepararea unor eteri ai alcoolilor secundari chirali:**



R^1-X / R^2MgX	*n*-BuBr / $CH_3(CH_2)_7MgI$	$CH_3(CH_2)_9Br$ / *n*-BuMgI	$CH_3(CH_2)_9Br$ / BnMgBr	$CH_3(CH_2)_7Br$ / *n*-BuMgI	BnBr / *n*-BuMgI
Randament I(%)	80	87	87	89	94
Randament II(%)	60	64	50	57	68



- **prepararea unor α - oxodimetil acetali:**

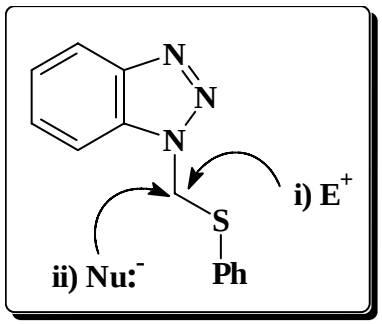


R	Ph	4-Me- C_6H_4
Randament I (%)	91	92
Randament II (%)	86	88

6. Carbanionul Benzotriazol-1-il-feniltiometan ca echivalent sintetic 1,1 - dipolar, in anelari aromatice:

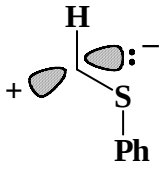
Generalitati:

i) problema: 1,1 – dipolul de mai jos este **necunoscut**



1-Phenylthiomethyl-1*H*-benzotriazole

sintetic echivalent cu

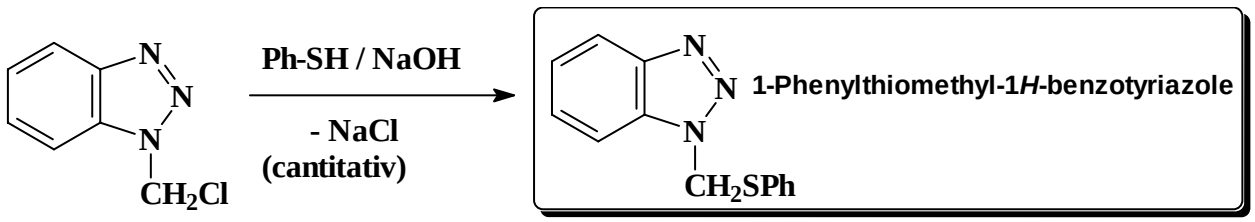


necunoscut

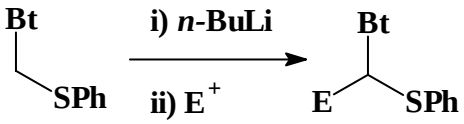
1,1-Phenylthiomethyldipole

Nota: 1,1-dipolul **nu trebuie confundat** cu o carbena !!

ii) prepararea "aductului":

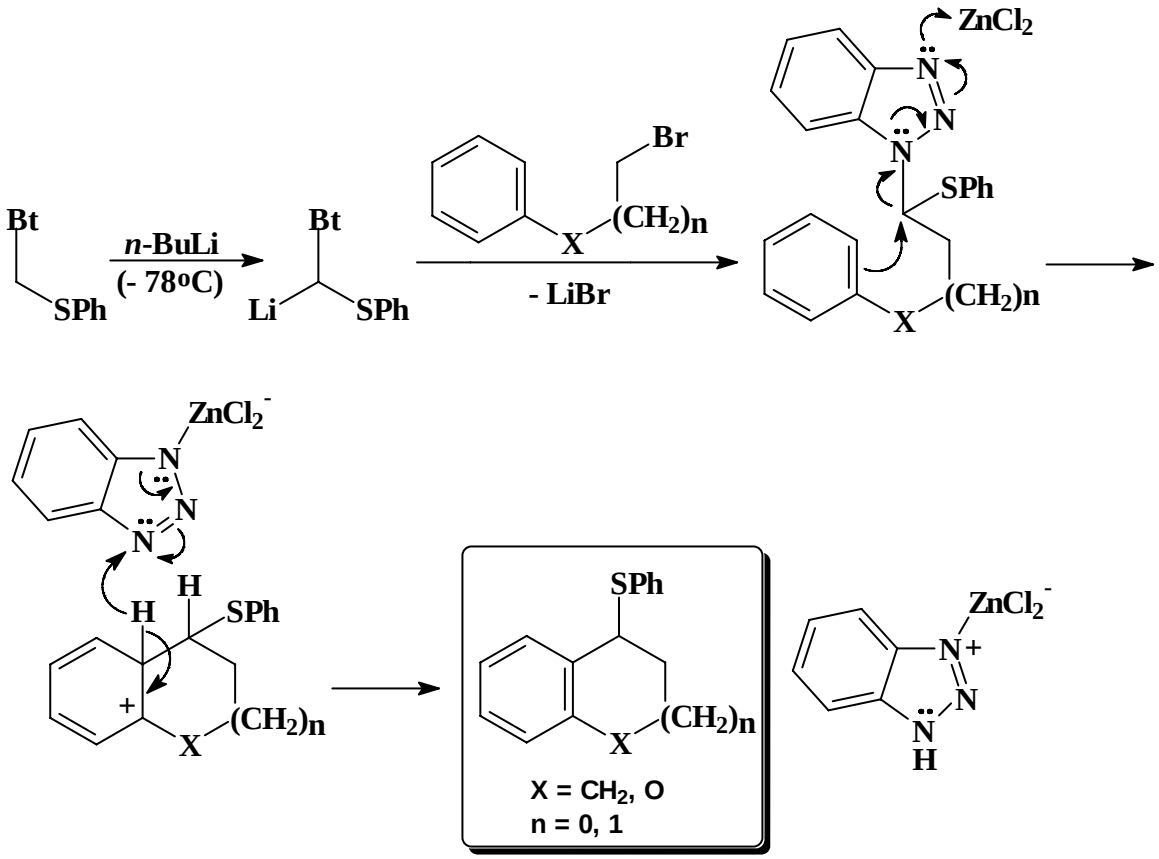


iii) testarea reactivitatii aductului fata de electrofili:

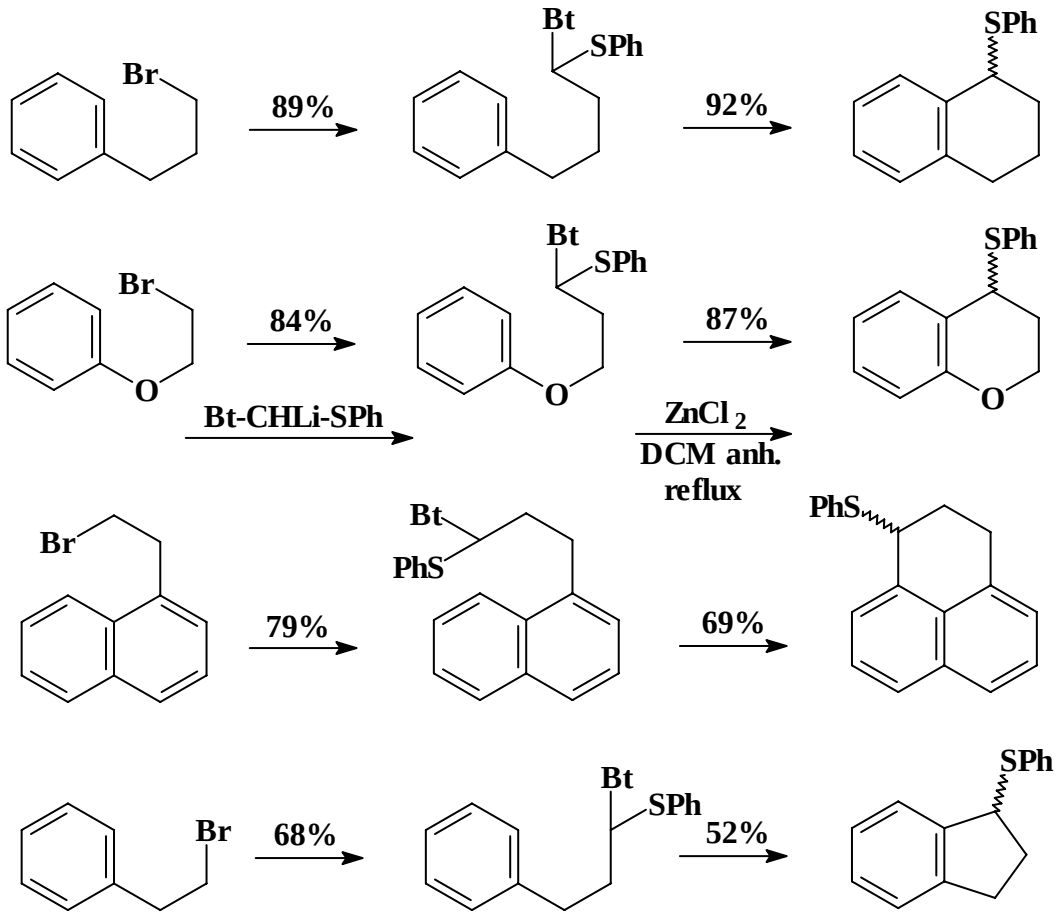


(Purtator de) Eletrofil E	MeI Me	BnCl Bn	CH_2=CH-CH_2Br CH_2=CH-CH_2	*p*-Me-C_6H_4-CH=O *p*-Me-C_6H_4-CH(OH)	Ph_2CO Ph_2CH(OH)	PhCN PhC(=NH)
Randament (%)	49	68	46	44	76	71

- **Utilizarea aductului in anelari aromatice:**



Exemple concrete de aplicare: **toti bromoderivatii** de prornire sunt **produse comerciale disponibile**



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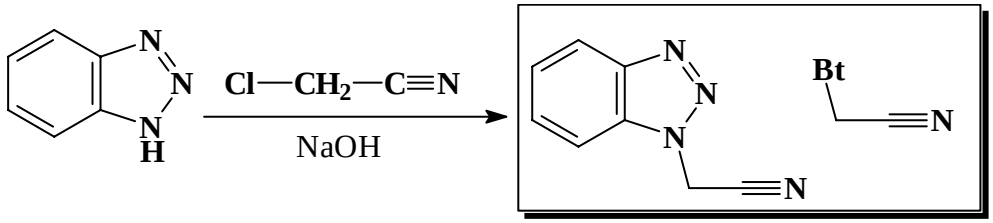
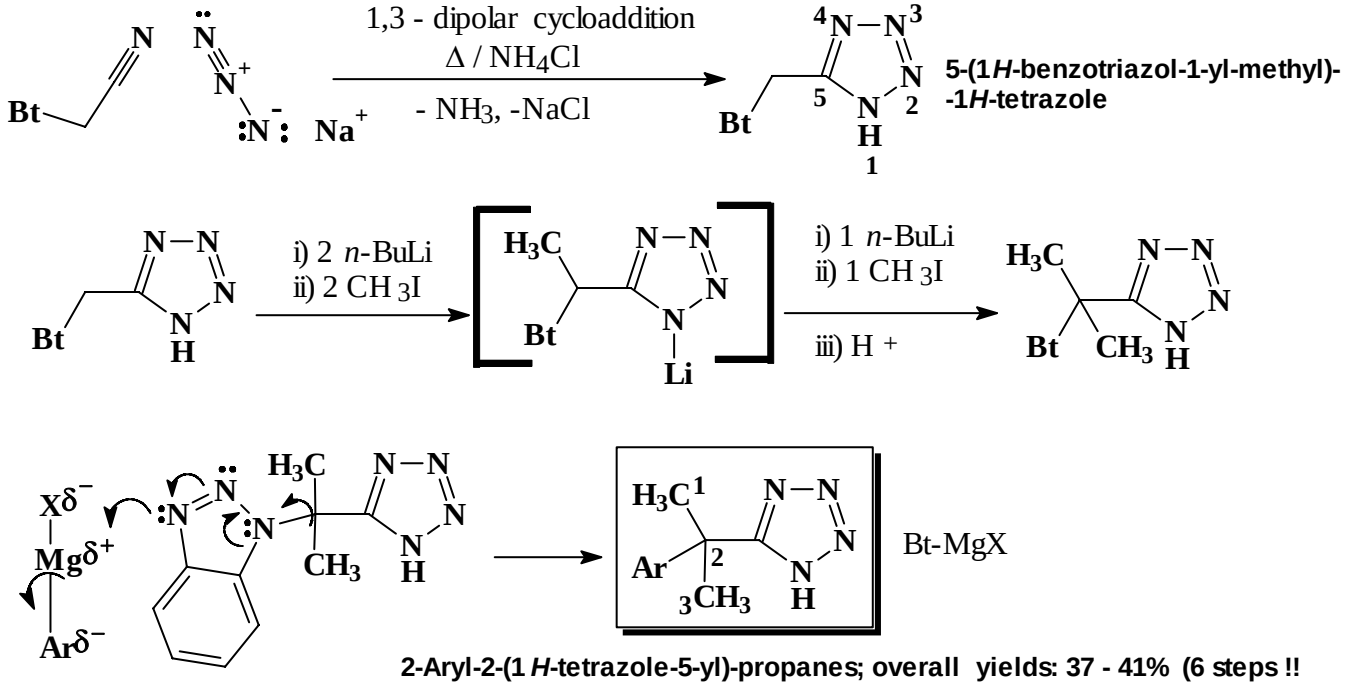
7. Synthesis of nitrogen containing heterocycles involving 1-(Cyanomethyl)-1*H*-benzotriazole

1. Synthesis of the adduct:

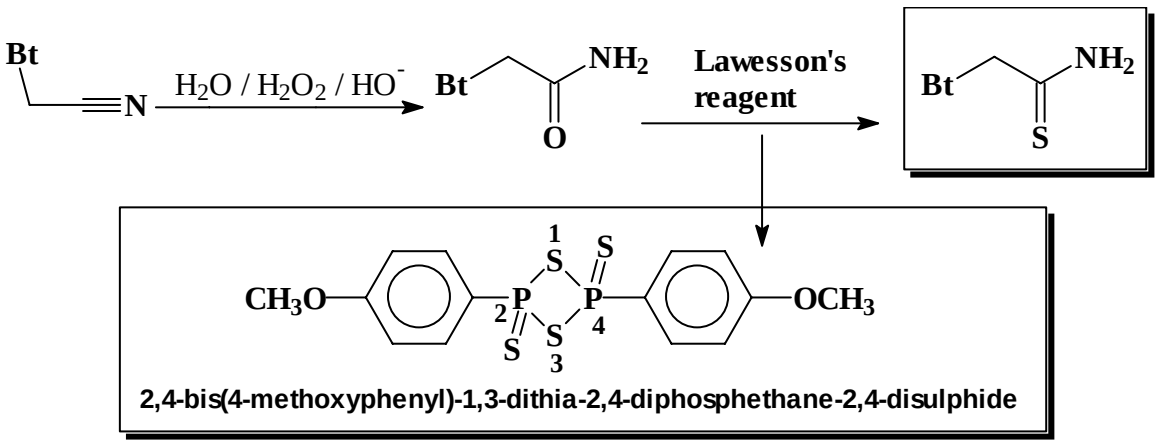


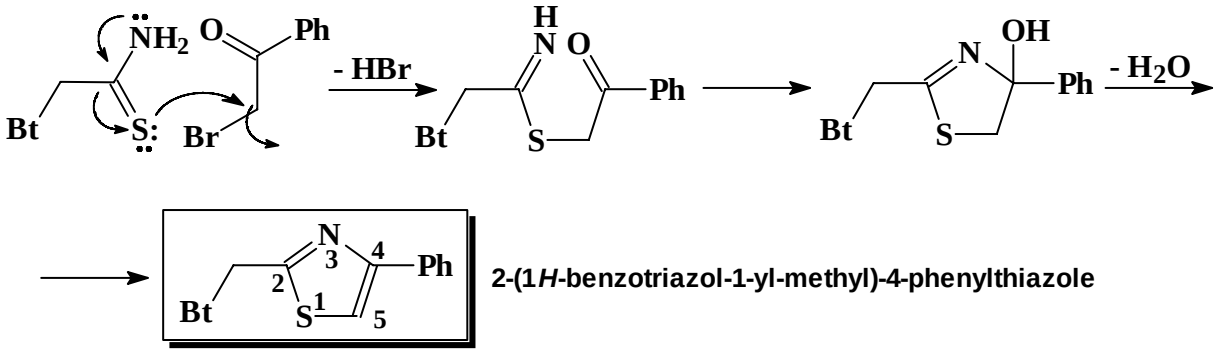
2. Synthesis of 5-polysubstituted tetrazoles:



2-Aryl-2-(1 *H*-tetrazole-5-yl)-propanes; overall yields: 37 - 41% (6 steps !!

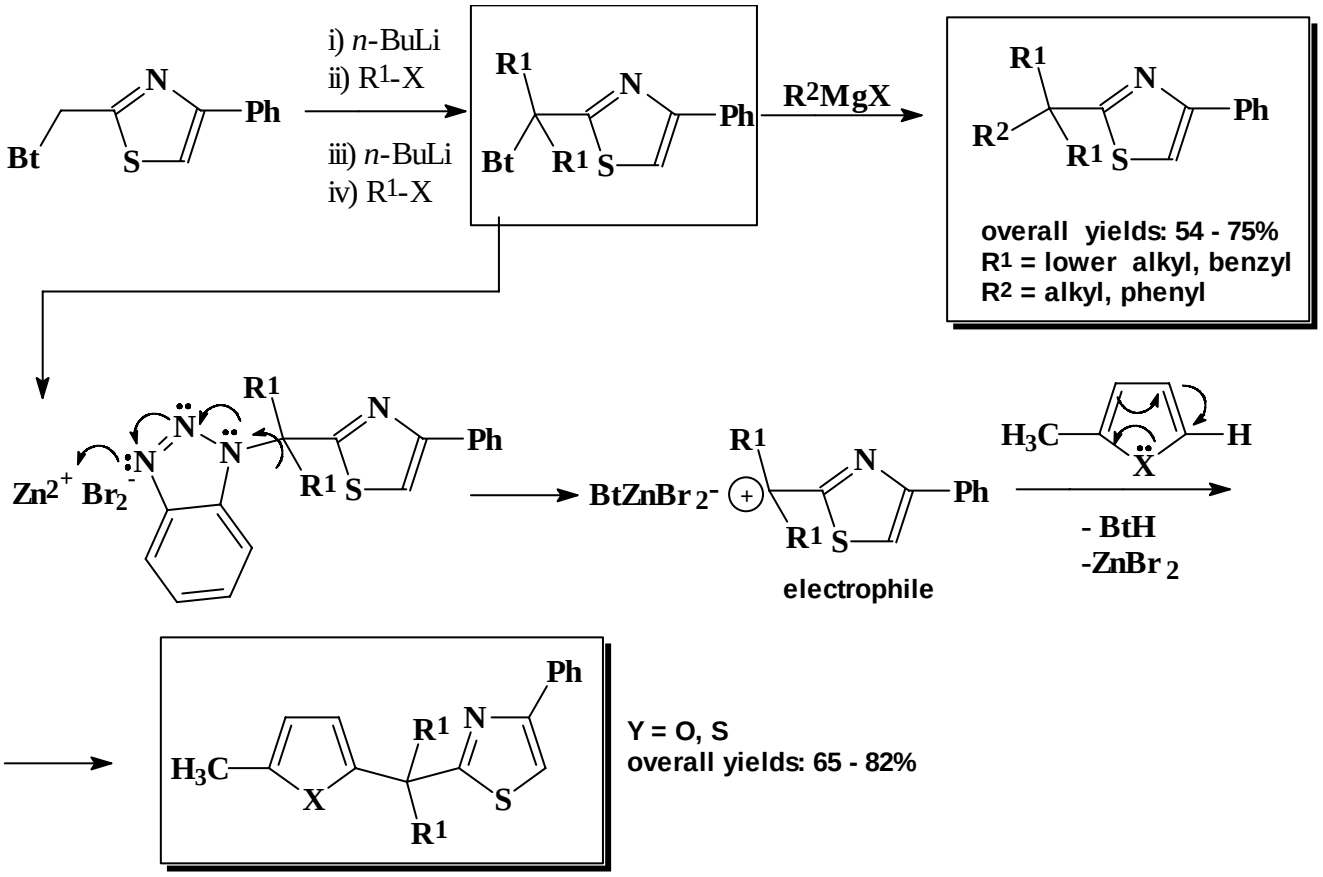
3. Synthesis of 2,4-disubstituted thiazoles





2-(1*H*-benzotriazol-1-yl-methyl)-4-phenylthiazole

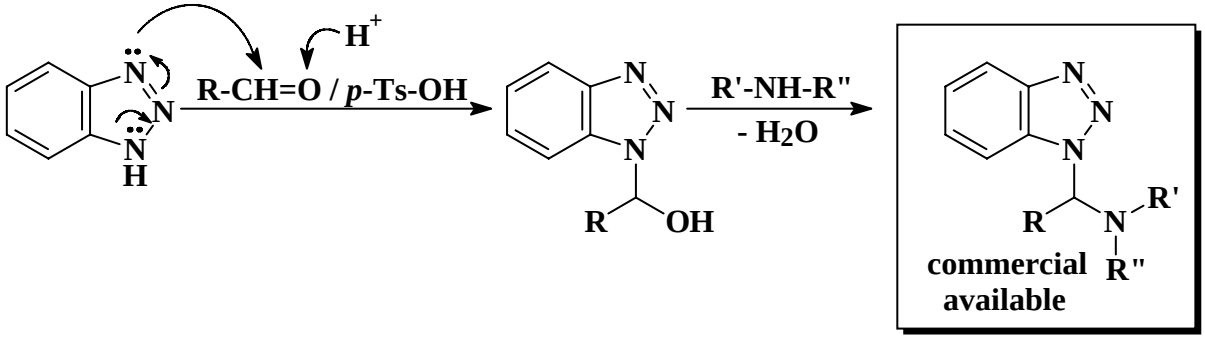
4. Synthesis of 2,4-polysubstituted thiazoles; C-C heterocoupling with furan ant thiophene



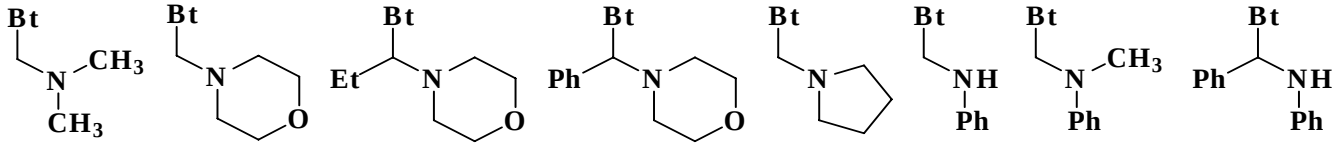
8. Synthesis based on benzotriazole-aldehyde-amine adducts

8.1. Synthesis of amines:

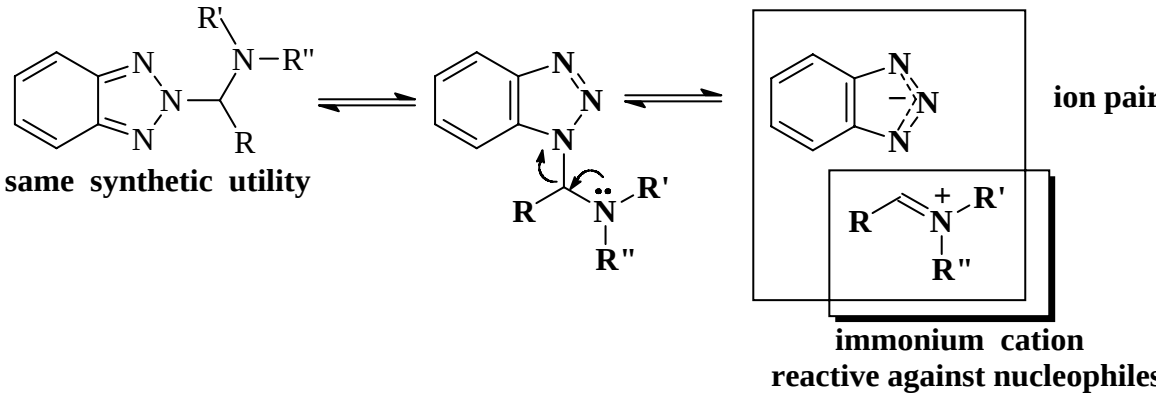
-synthesis of the adducts:



Examples:



Synthetic utility:

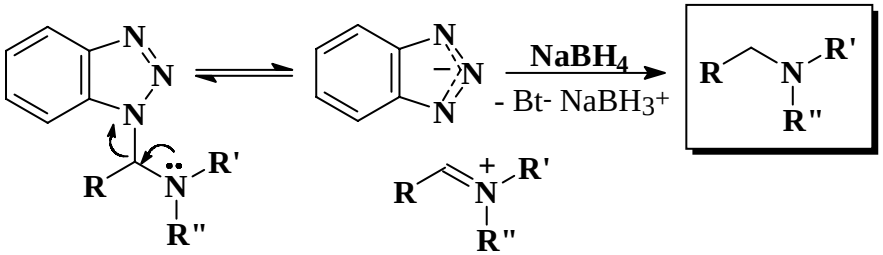


- shifting of the equilibria towards **the immonium cation:**

a) in polar solvents

b) by heating

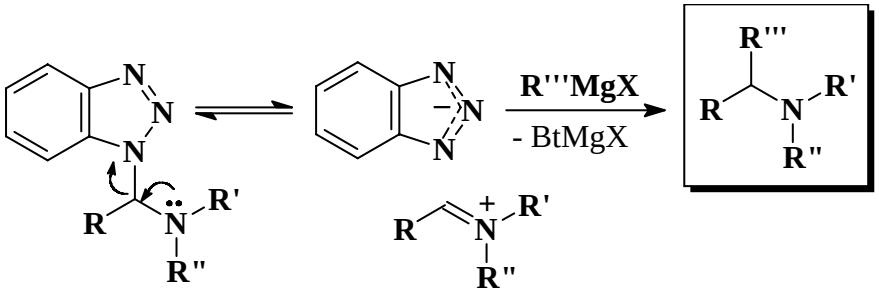
Preparation of secondary and tertiary amines: nucleophilic displacement of Bt by hydride anion:



Yields: 68 - 98 %; R" = H ; R, R' = aryl, hetaryl

50 - 95 %; R, R', R" = alkyl, cycloalkyl, aryl, aralkyl, hetaryl

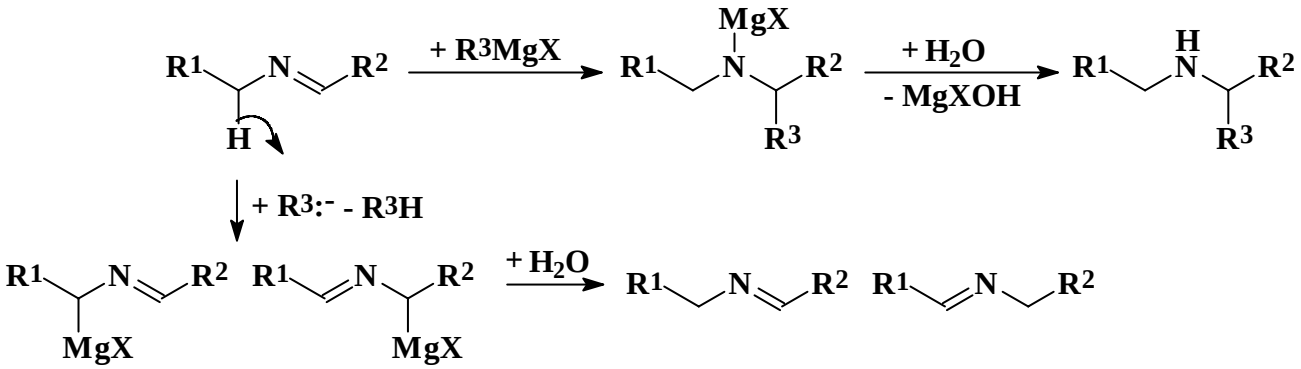
Preparation of secondary and tertiary amines: nucleophilic displacement of Bt by Grignard Reagents:



Yields: 62 - 95 %; R" = H ; R, R', R''' = alkyl, cycloalkyl, aryl, aralkyl, hetaryl
20 - 99 %; R, R', R", R''' = alkyl, cycloalkyl, aryl, aralkyl, hetaryl, alkyny

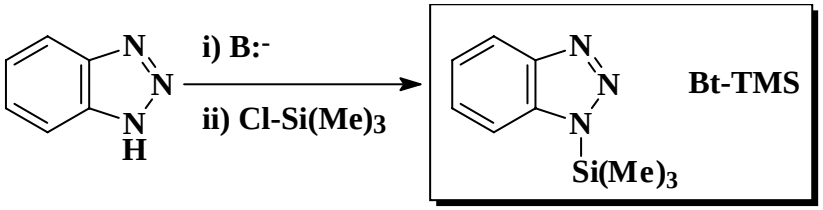
Preparation of unsymmetrical secondary amines from imino derivatives:

- classical methodologies are inappropriate in some cases, due to side reactions: isommerisations, reversed regioselectivities, etc.

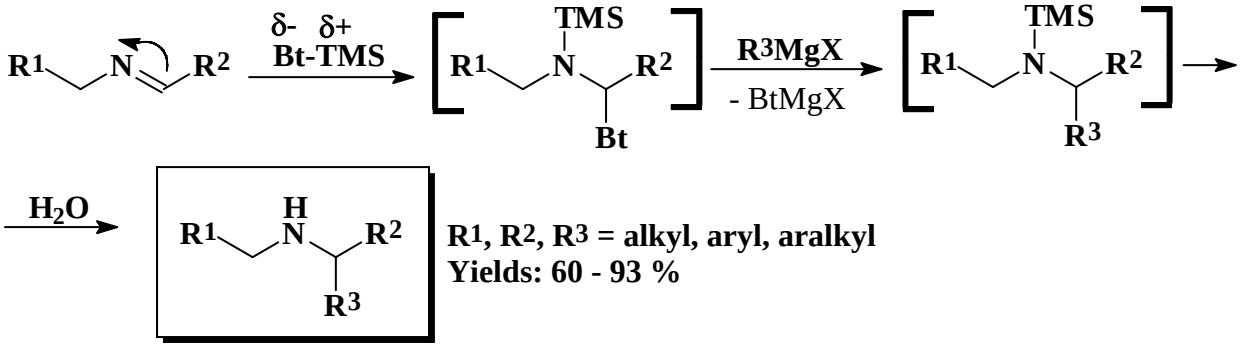


Benzotriazole methodology:

Preparation of the adduct

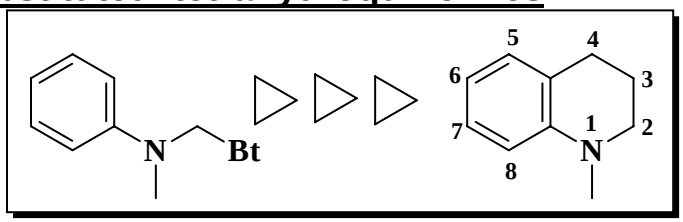


The adduct use:

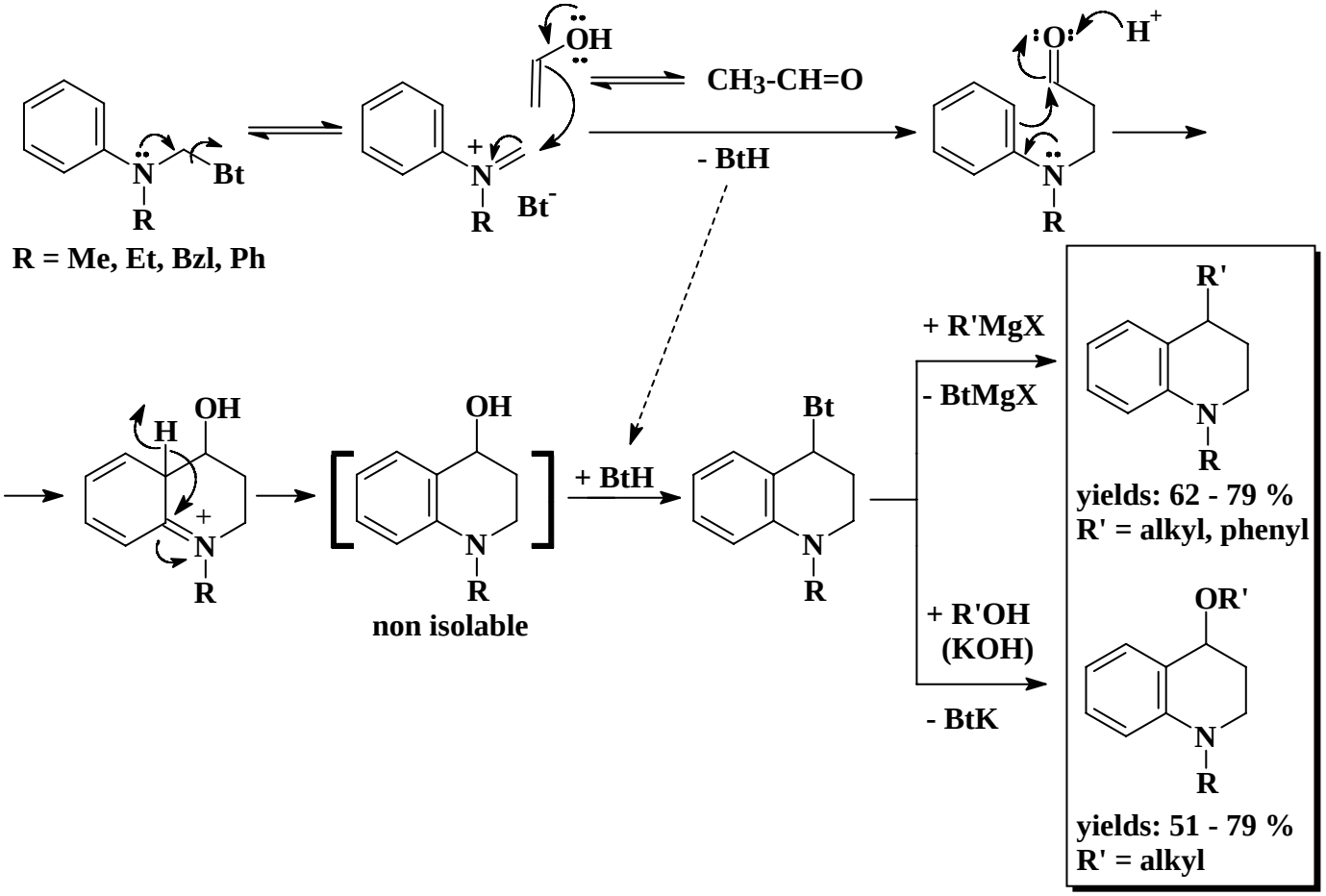


R1, R2, R3 = alkyl, aryl, aralkyl
Yields: 60 - 93 %

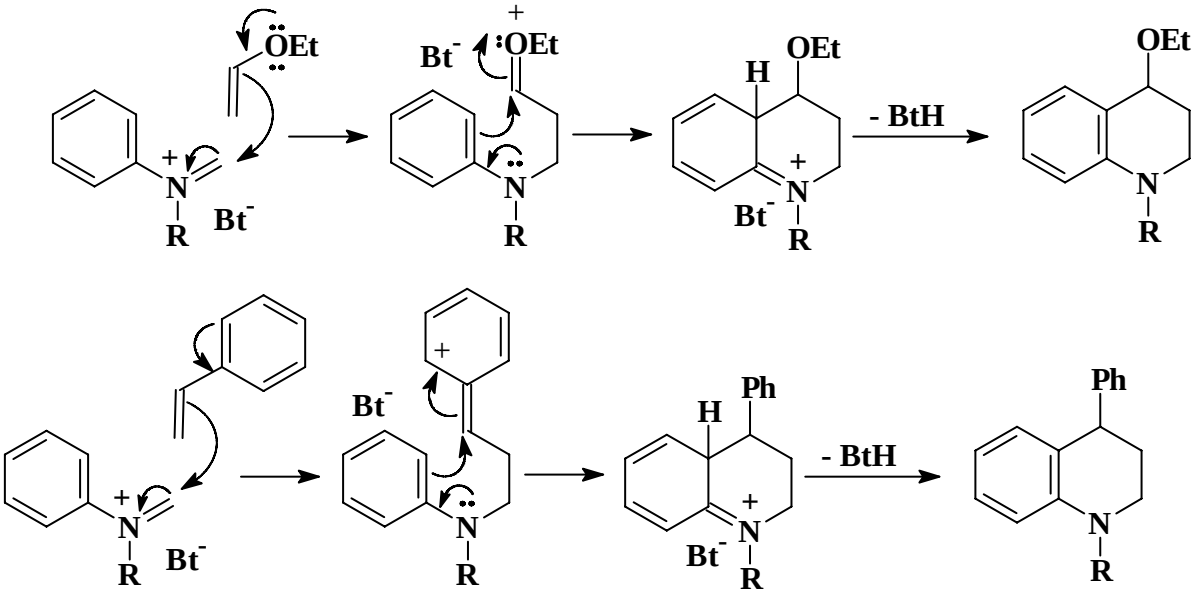
8.2. Synthesis of substituted tetrahydroquinolines



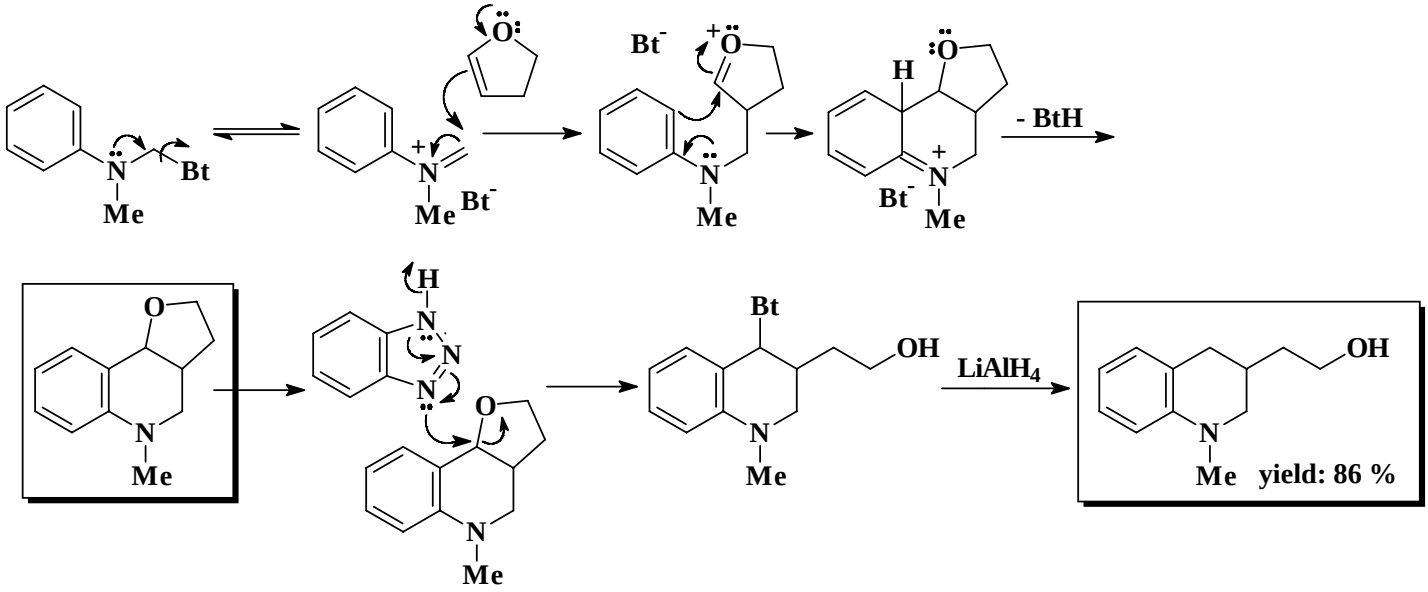
-some benzotriazole-aldehyde-amine adducts allow ***N*-phenylimmonium cations** to be generated **under mild conditions**; subsequent addition to **functionalised olefins** in accordance with Markovnikov's rule **in regioselective reactions** leads to the preparation of several types of ***2-unsubstituted*-1,2,3,4-tetrahydroquinolines:**



- special situations:



- **fused tetrahydroquinolines and remote functionalisation:**



- **diastereoselective synthesis:**