

QUÍMICA ORGÂNICA AVANÇADA A

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Sala 201A (bloco E - 43122)



biolab

3ª Parte - Ementa

- Processos de enolização.
- Modelo de Ireland.
- Modelos de adição ao grupo carbonila.
- Estados de transição Zimmerman-Traxler em compostos carbonílicos.
- **Modelos de adição ao grupo carbonila (auxiliares quirais)**

Auxiliares Quirais

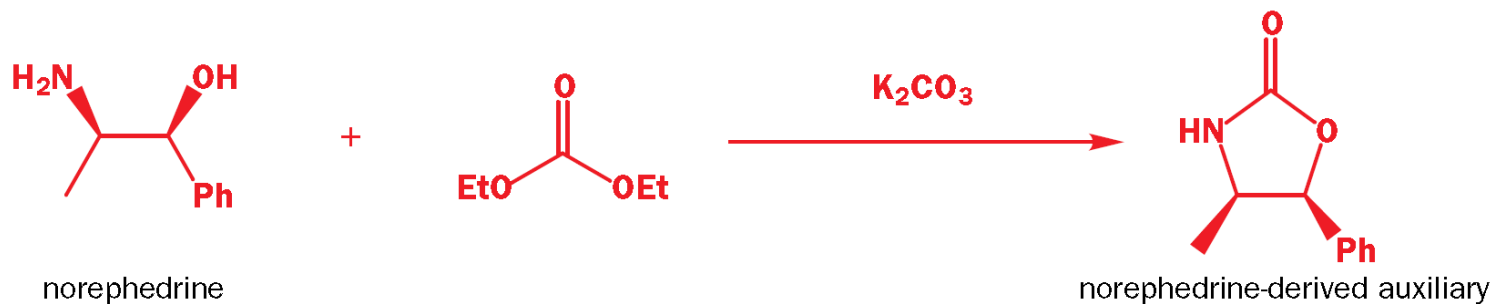
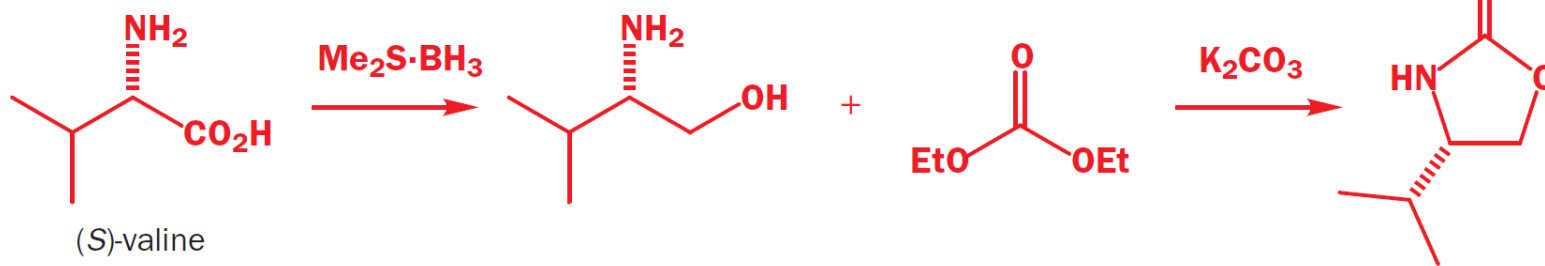
● This is what we mean by a chiral auxiliary strategy

1. An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material.
2. A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product.
3. The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer. The best chiral auxiliaries (of which the example above is one) can be recycled, so although stoichiometric quantities are needed, there is no waste.

Auxiliares Quirais

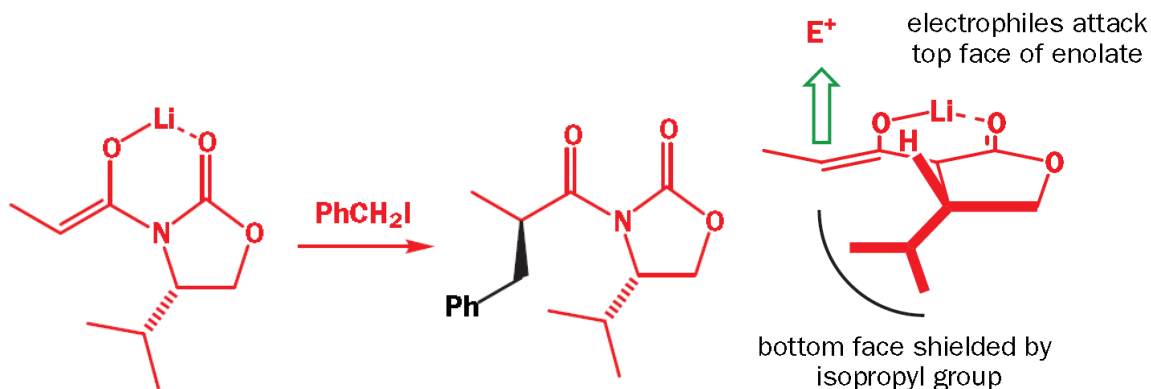
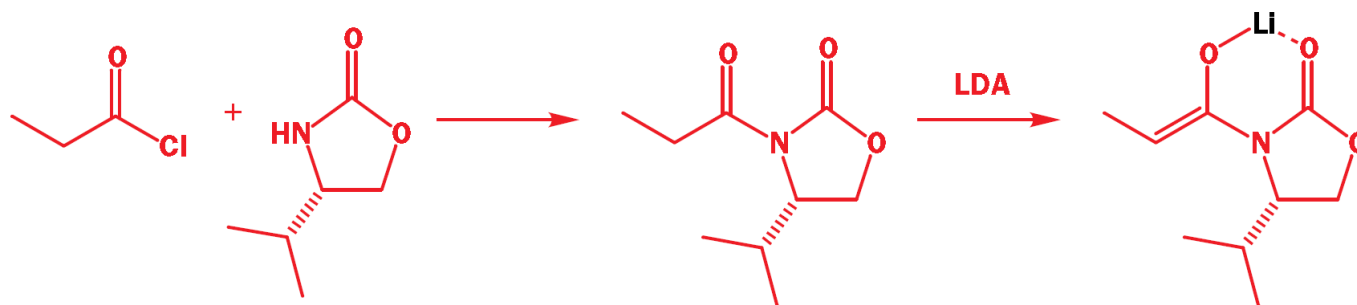
(Oxazolidinonas de Evans)

synthesis of Evans's oxazolidinone chiral auxiliary from (S)-valine



Alquilação de enolatos

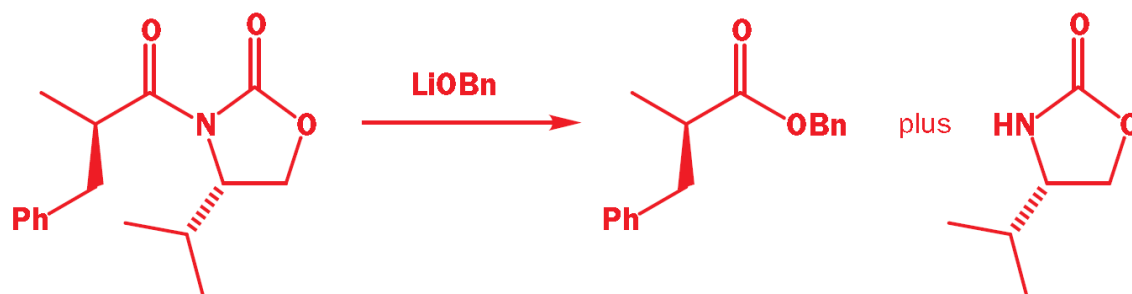
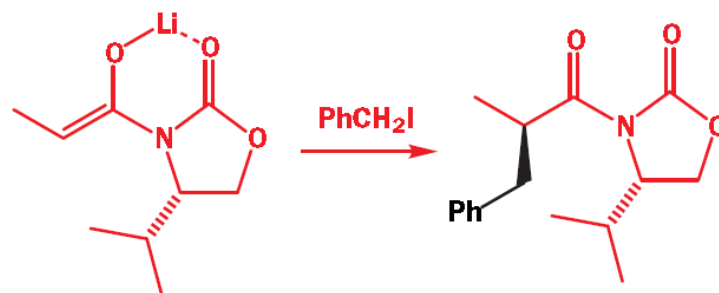
(Oxazolidinonas de Evans)



Electrophile	Ratio of diastereoisomers
PhCH_2I	>99:1
allyl bromide	98:2
EtI	94:6

Alquilação de enolatos

(Oxazolidinonas de Evans)

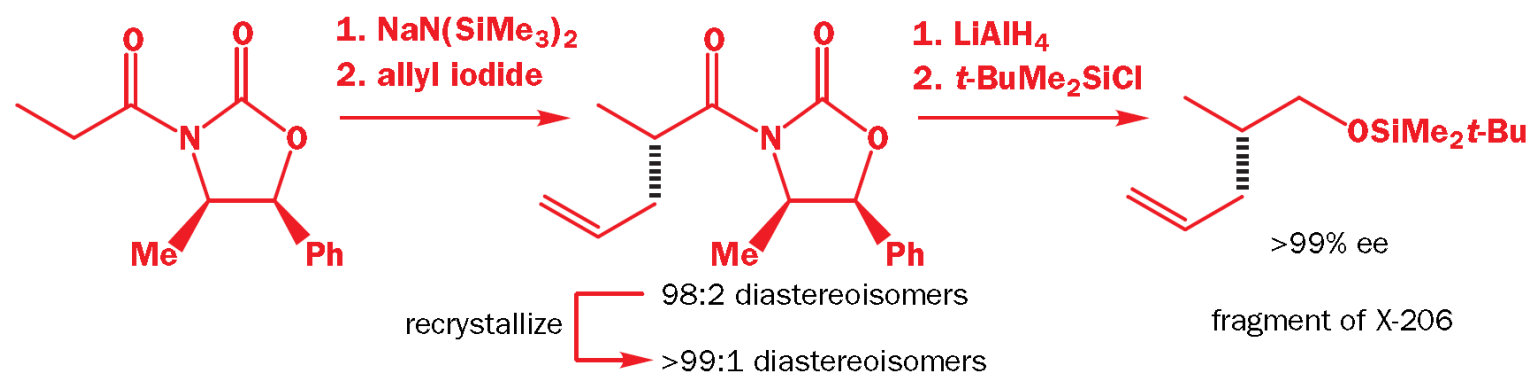


98:2 mixture of diastereoisomers

98:2 mixture of enantiomers
96% enantiomeric excess

Recristalização

(Aumento da pureza ótica)



Method

chiral auxiliary

Advantages

often excellent ees; can recrystallize to purify to high ee

Disadvantages

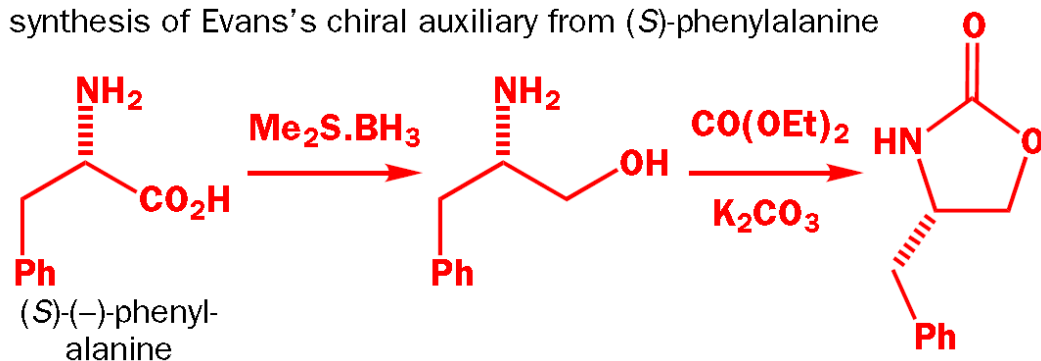
extra steps to introduce and remove auxiliary

E ainda, precisam ser utilizados em quantidades estequiométricas na reação.

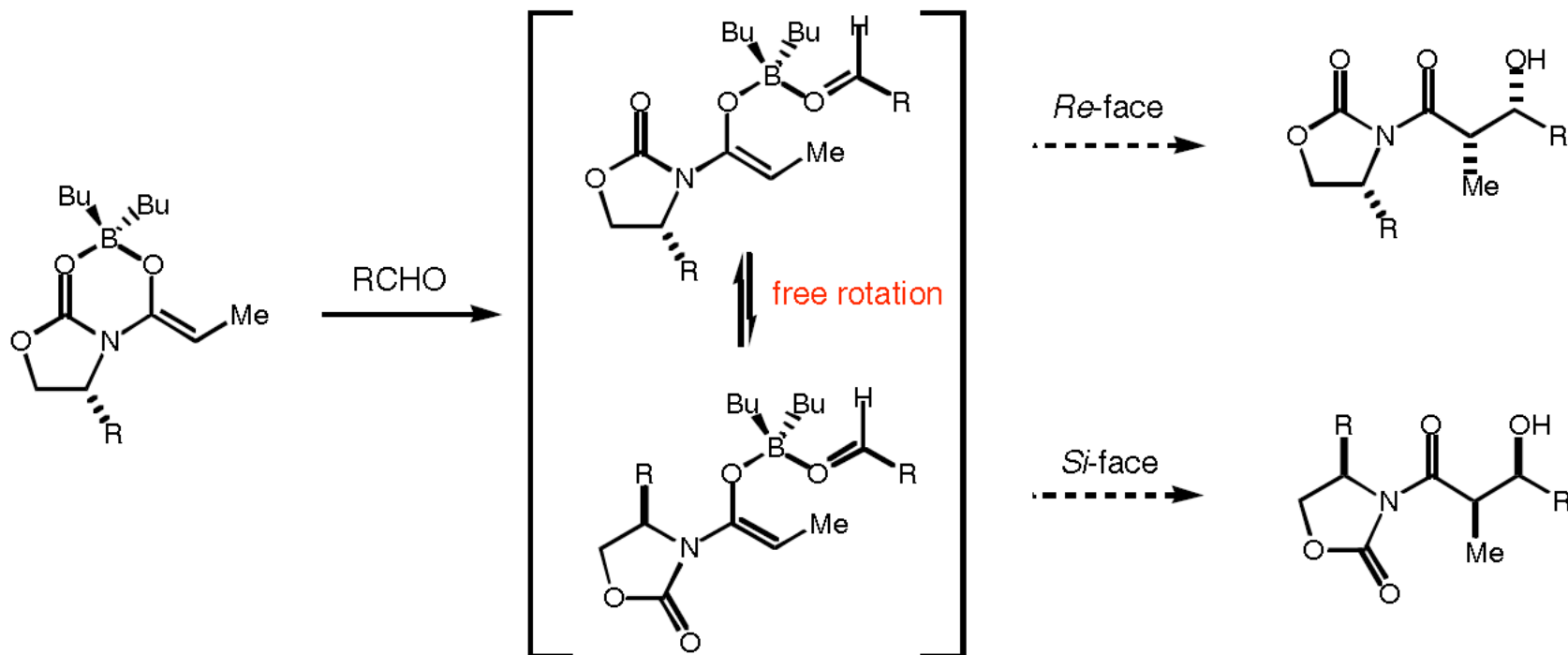
Exercício:

An alternative to the Evans chiral auxiliary described in the chapter is this oxazolidinone, made from natural (*S*)-(-)-phenylalanine. What strategy is used for this synthesis and why are the conditions and mechanism of the reactions important?

synthesis of Evans's chiral auxiliary from (*S*)-phenylalanine

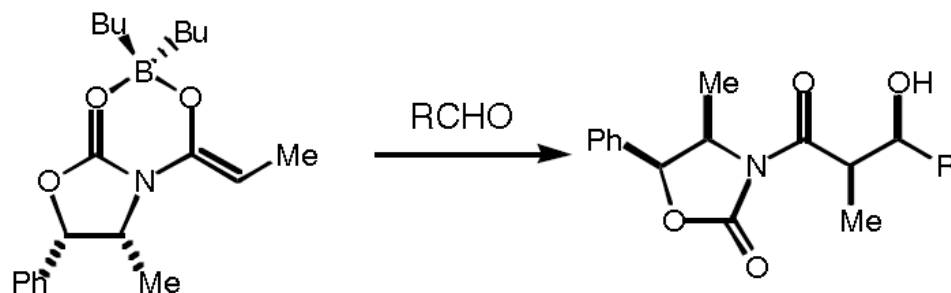
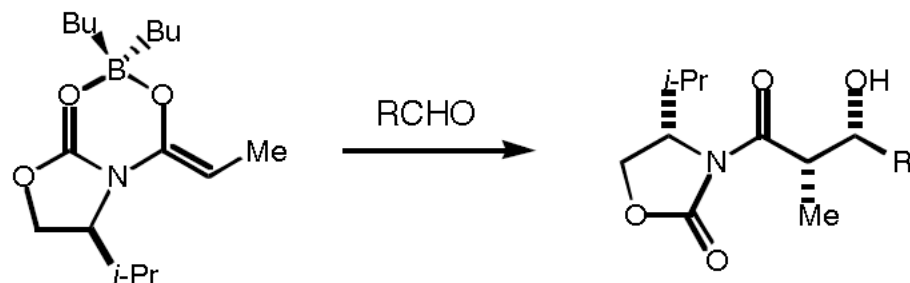


Evans - Aldol



Essa reação apresentará controle pelo efeito de quelação?

Evans - Aldol

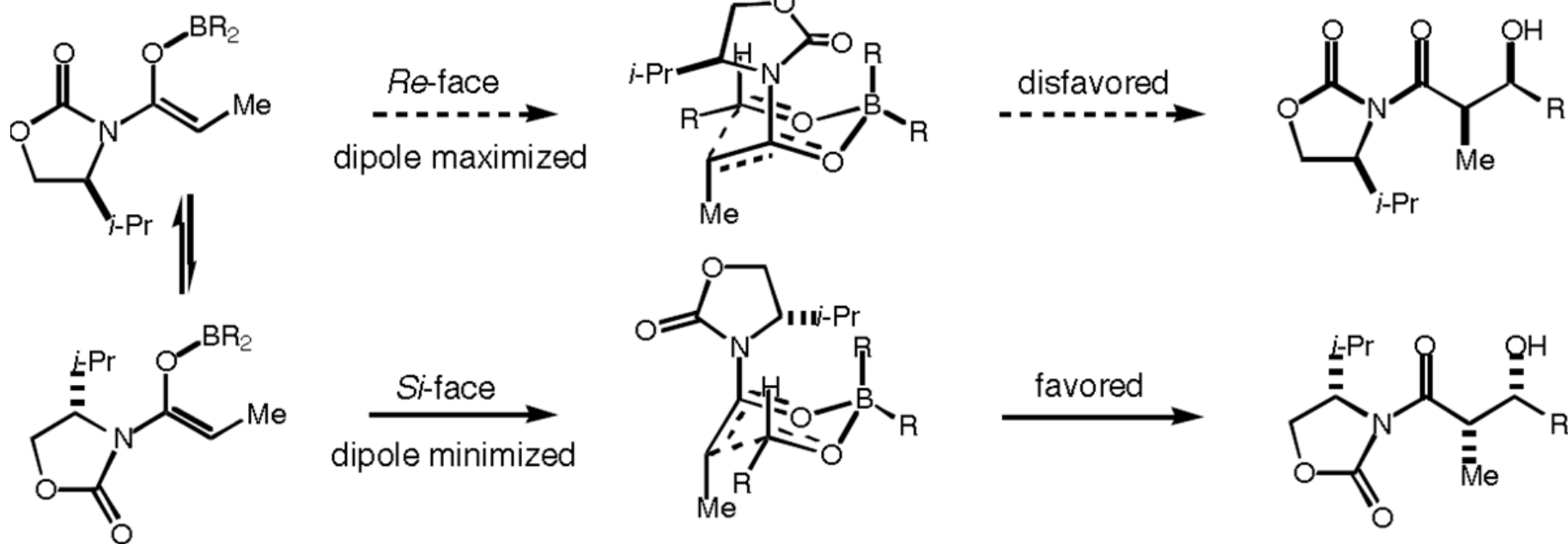


Evans, D. A.; Bartroli, J.; Shih, T. L.
J. Am. Chem. Soc. **1981**, *103*, 2127

- ◆ Reação altamente diastereosseletiva (141:1 a >500:1).
- ◆ Grande quantidade de aldeídos (R = alquil, aril...)
- ◆ Uma das reações mais previsíveis sinteticamente – aplicação industrial

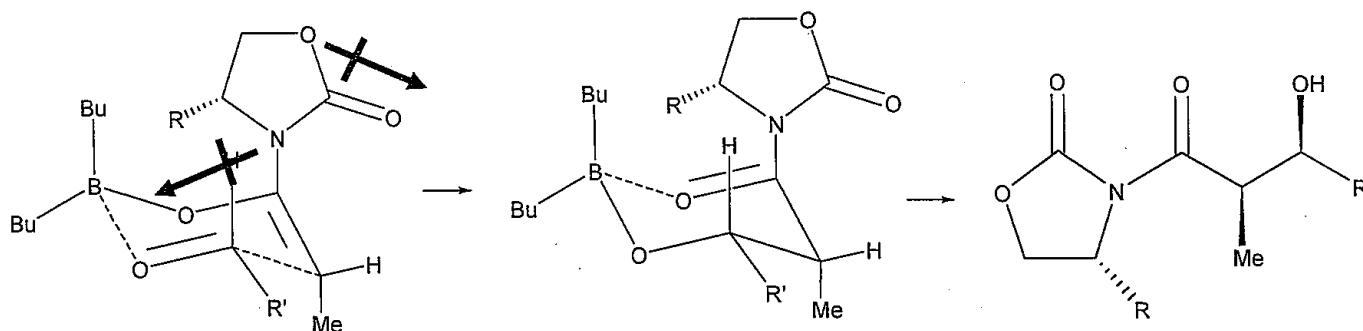
Evans - Aldol

Modelos possíveis para indução assimétrica:

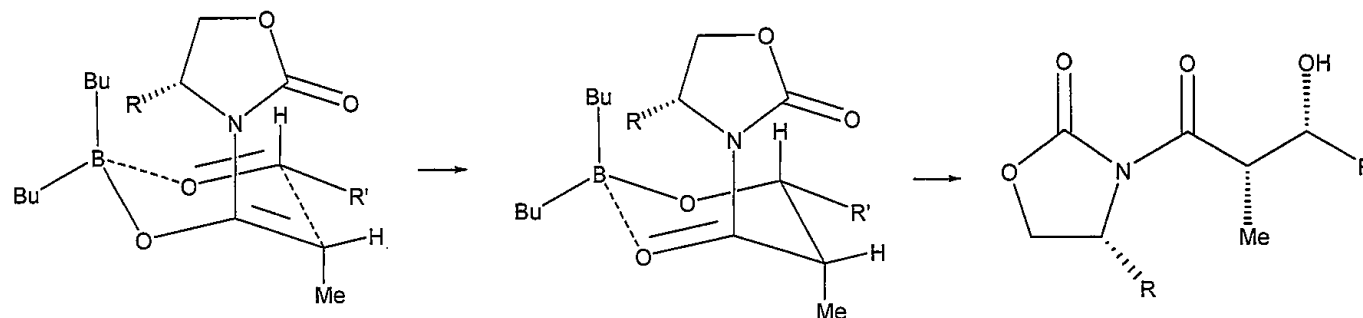


Evans - Aldol

1st: aldehyde in front, enolate on the back



2nd: enolate in front, aldehyde on the back



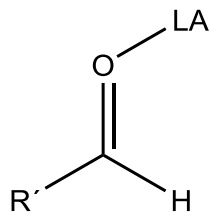
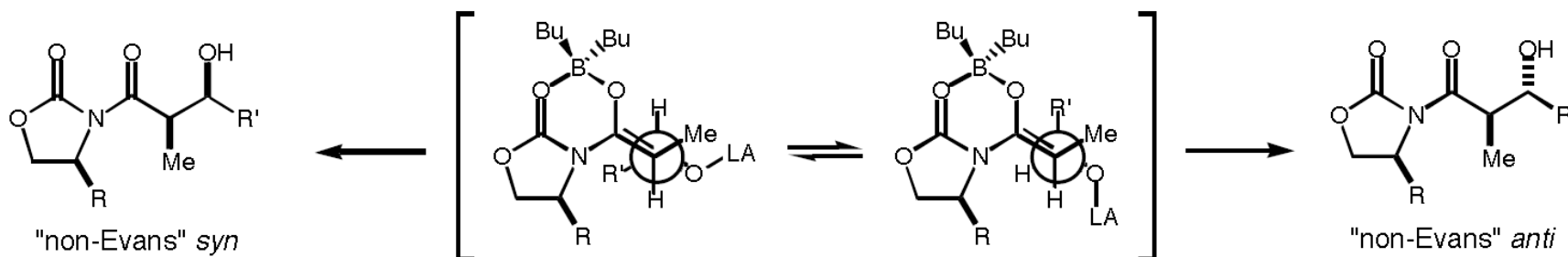
Produto Evans

O primeiro intermediário será favorecido devido ao menor impedimento estérico e pela oposição dos vetores das carbonilas.

Evans – Aldol - Heathcock

(ácido de Lewis – LA)

No modelo de Heathcock, a quelação com o aldeído é dificultada pela presença do LA. Desta forma, o ET ZT permanece entre o enolato e a oxazolidinona. A face do aldeído a ser atacada depende do tamanho do LA e não dos grupos R no auxiliar e R' no aldeído.

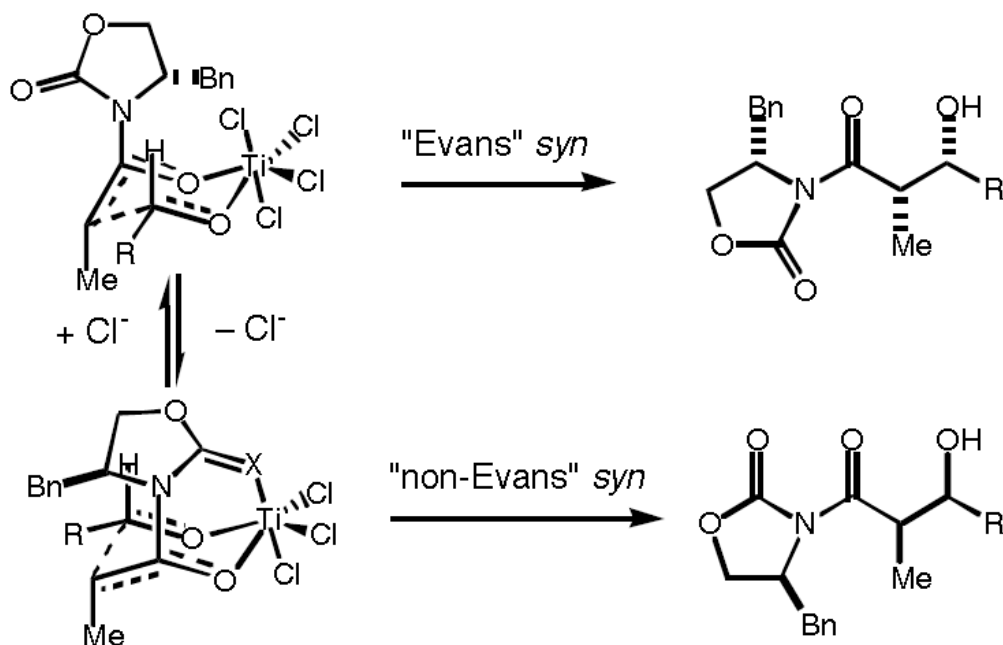


<u>R</u>	<u>R'</u>	<u>Lewis Acid</u>	<u>equiv.</u>	<u>syn: anti</u>
<i>t</i> -Bu	<i>i</i> -Pr	TiCl ₄	2.0	94 : 6
<i>t</i> -Bu	<i>i</i> -Pr	SnCl ₄	2.0	93 : 7
<i>i</i> -Pr	<i>i</i> -Pr	Et ₂ AlCl	3.0	5 : 95

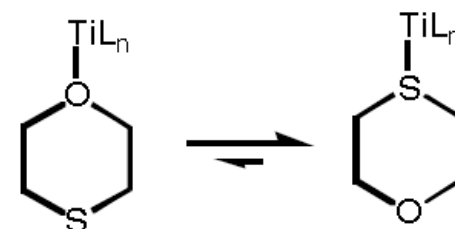
Tamanho do LA afeta a diastereoseletividade.

Evans – Aldol - Crimmins

Titânio favore a complexação com a carbonila da oxazolidinona invertendo a face do enolato que ataca o aldeído. Utilização da tiozolidinona favore ainda mais a complexação com o Ti levando ao produto non-Evans.



Ti possui maior afinidade por S que O

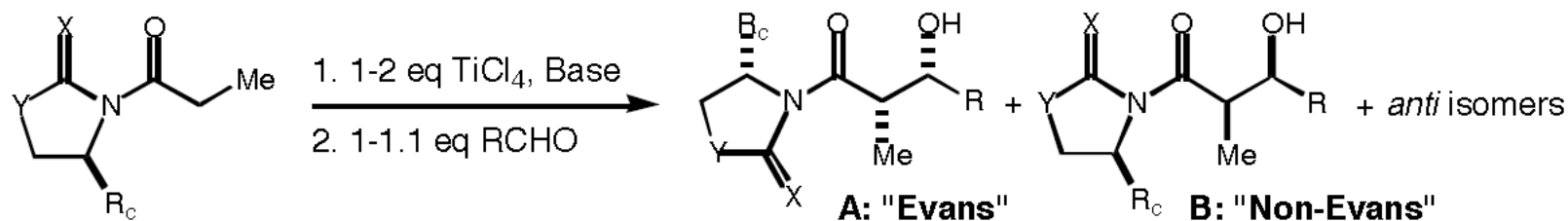


Fowles, et al. *J. Chem. Soc.* **1971**, 1920.

Quando X=S a complexação com Ti é favorecida.

Evans – Aldol

Efeito de bases e Ti:



X, Y = O; R_C = Bn

X, Y = S; R_C = *i*-Bu (X = S, Y = O, R_C = Bn gave similar)

T (°C)	R	yield	A : B : anti
0	Et	84	99 : 1 : 0
0	MeCH=CH	89	97 : 3 : 0
0	<i>i</i> -Pr	89	98 : 2 : 0
0	<i>t</i> -Bu	87	97 : 3 : 0
-78	<i>i</i> -Pr	98	98 : 2 : 0

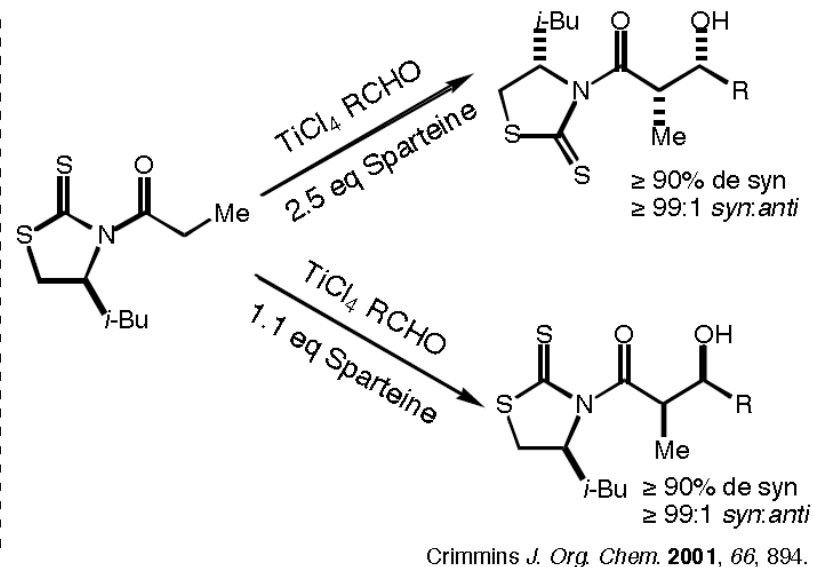
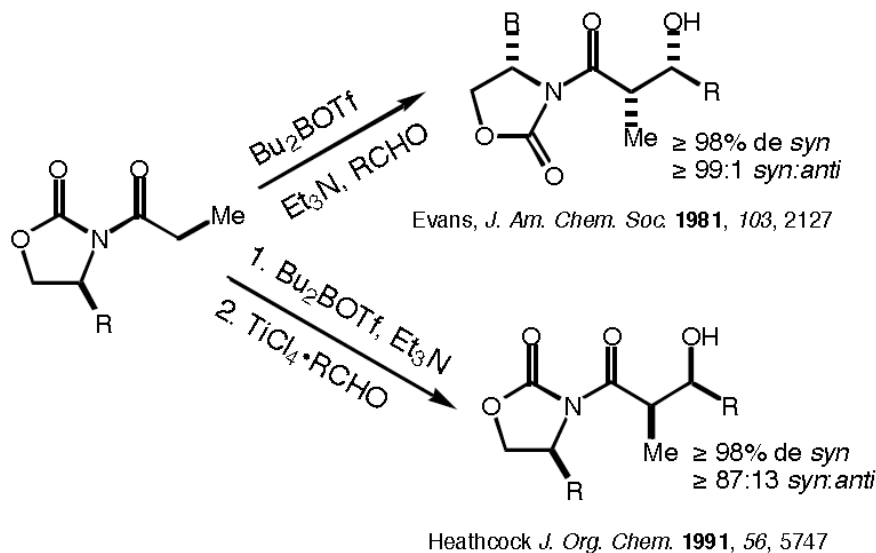
Base	equiv.	R	yield	A : B : anti
DIEA	2.5	<i>i</i> -Pr	86	86 : 14 : 0.3
DIEA	1.1	<i>i</i> -Pr	75	5 : 95 : n.a.
TMEDA	2.5	<i>i</i> -Pr	57	96 : 4 : n.a.
TMEDA	1.1	<i>i</i> -Pr	50	<1 : >99 : n.a.
Sparteine	2.5	<i>i</i> -Pr	84	95 : 5 : 0
Sparteine	1.1	<i>i</i> -Pr	63	5 : 95 : n.a.

O excesso de base (2,5 equiv.) dificulta a formação do complexo de titânio formados com oxa- ou tiozolidinona ou tiozoliditiona.

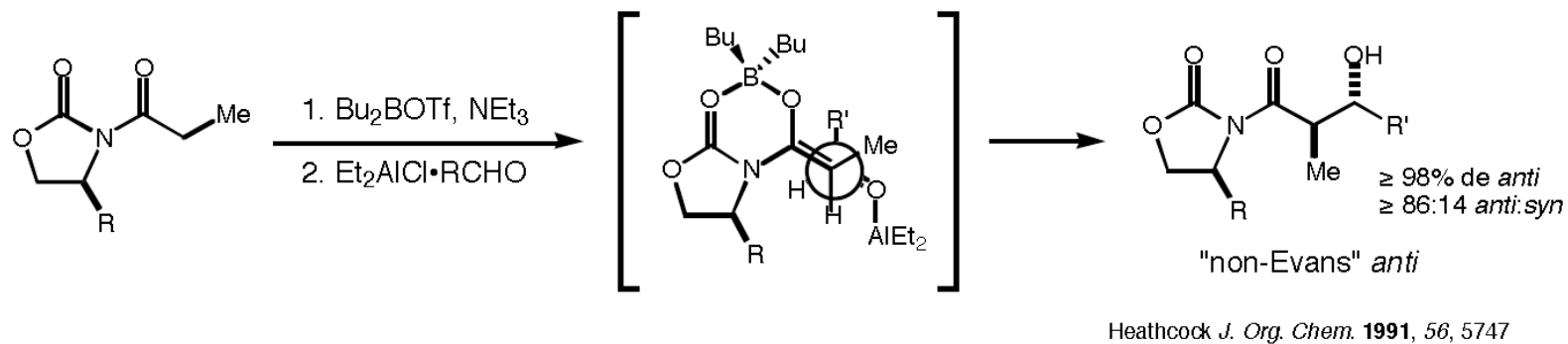
J. Org. Chem. **2001**, *66*, 894.

Evans – Resumo

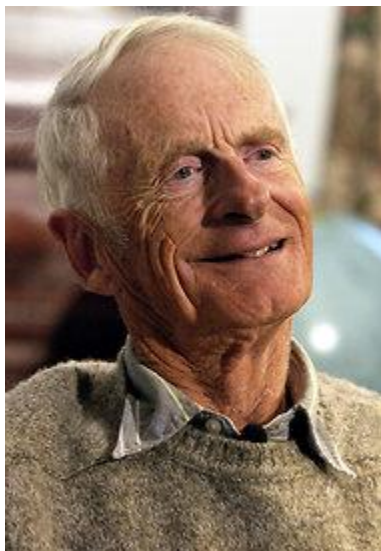
■ **Syn Aldols:**



■ **Anti Aldols:**



Catálise Assimétrica



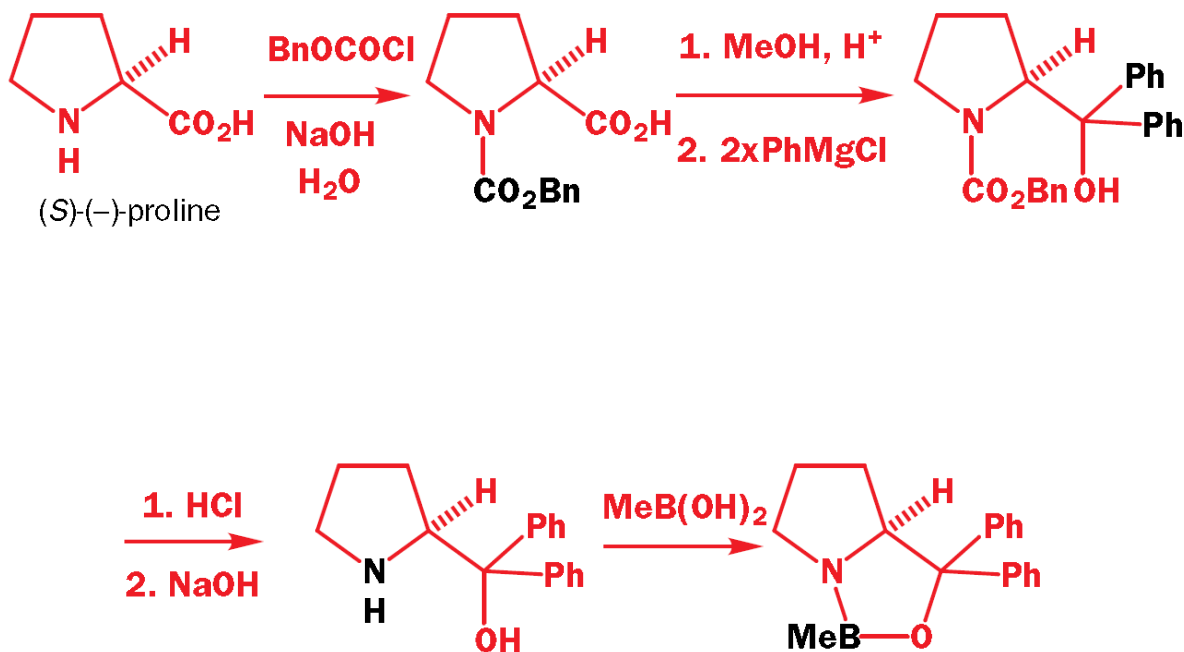
William Knowles
Prêmio Nobel 2001

“Since achieving 95% [enantiomeric excess] only involves energy differences of about 2 kcal [per mol], which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict what kind of ligand structures will be effective”

Knowles, W. S. Asymmetric hydrogenation. *Acc. Chem. Res.* **1983**, 16,106–112.

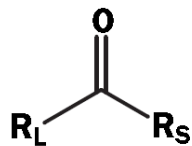
Catálise Quiral

CBS reagent (Corey-Bakshi-Shibita)

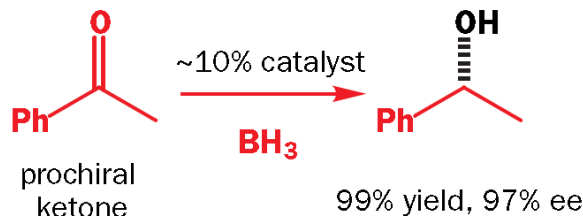
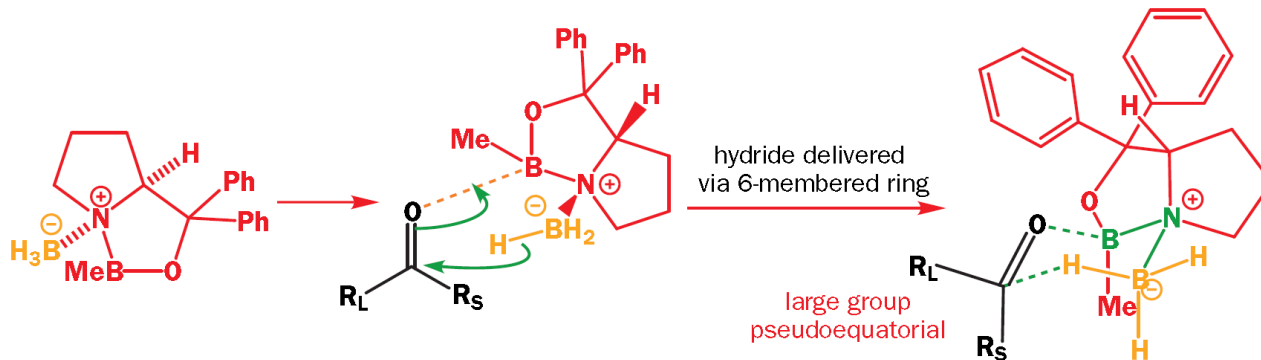
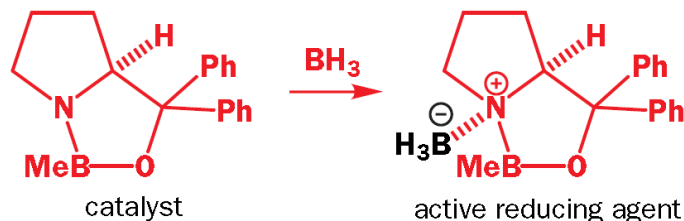


Catálise Quiral

CBS reagent (Corey-Bakshi-Shibita)

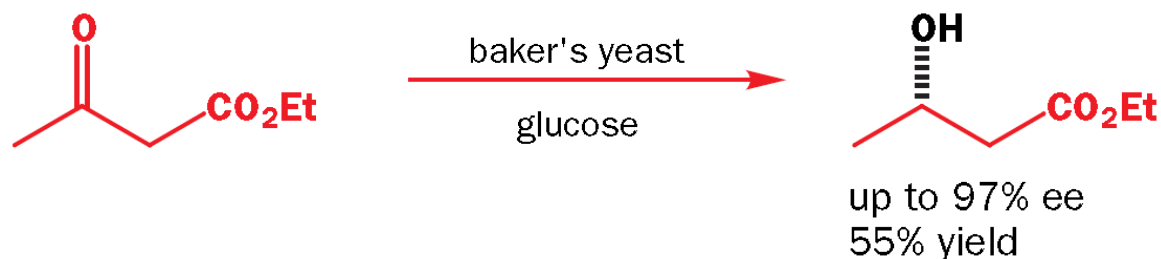


larger substituent
smaller substituent

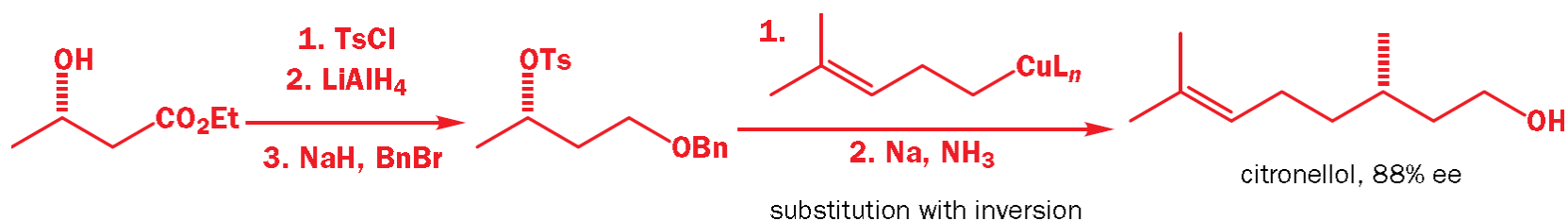


Catálise Quiral

(Enzimas)



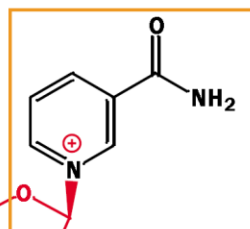
Citronela foi obtida com ee superiores ao produto isolado por fonte natural.



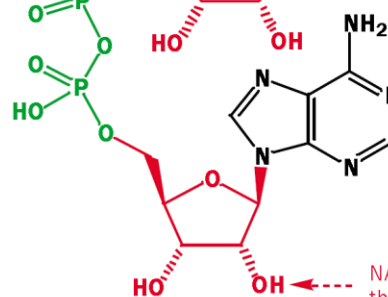
Catálise Quiral

(Bioquímica)

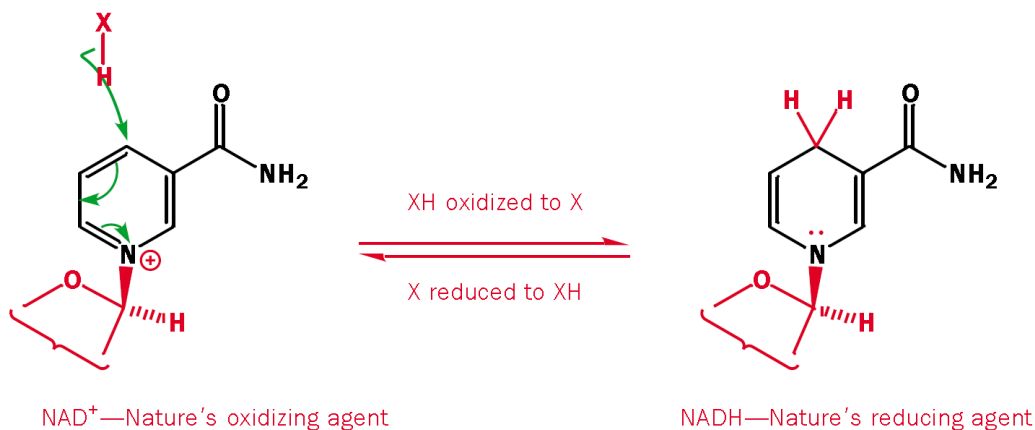
NAD
Nicotinamide Adenine Dinucleotide



the reactive part of NAD



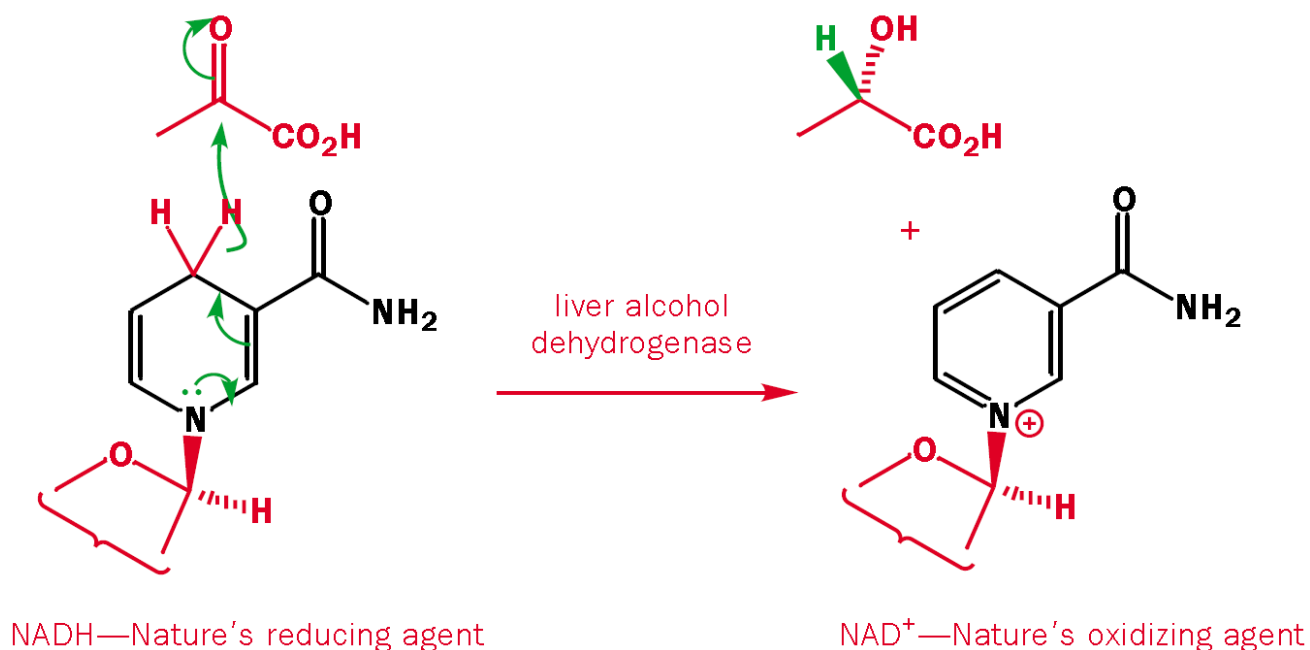
NADP has a phosphate group at the 2' position
this group does not alter the mechanism of action



Catálise Quiral

(Bioquímica)

Redução do ácido pirúvico (uma cetona) a ácido láctico (importantes metabólitos) pela enzima álcool desidrogenase

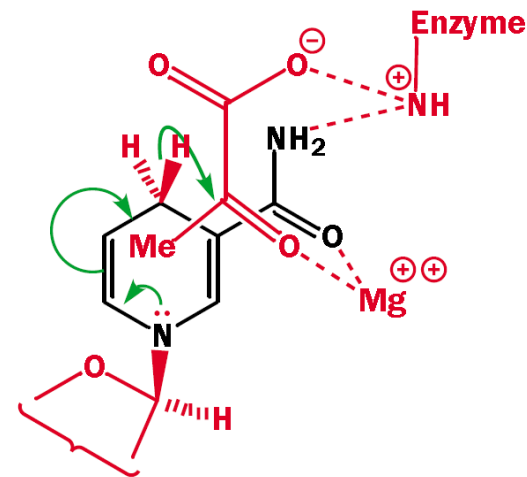


Esta reação poderia ser realizada em laboratório utilizando-se NaBH_4 como agente redutor. Porém, ácido láctico racêmico seria obtido.

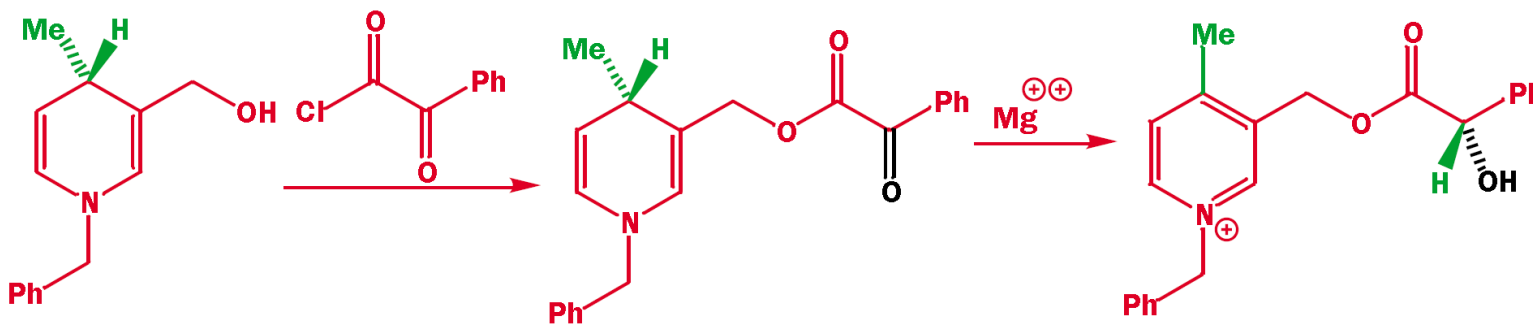
Catálise Quiral

(Bioquímica)

Hidreto é transferido apenas por uma das faces diastereotópicas do NAD⁺ ou NADP

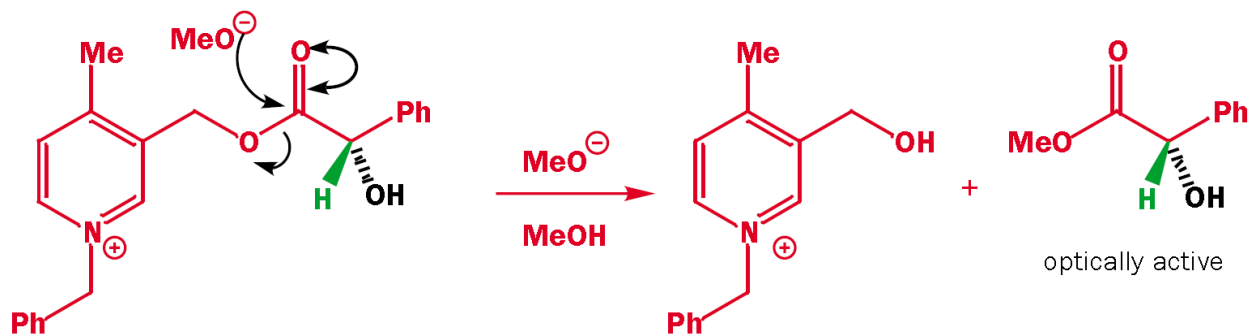


Reação Modelo

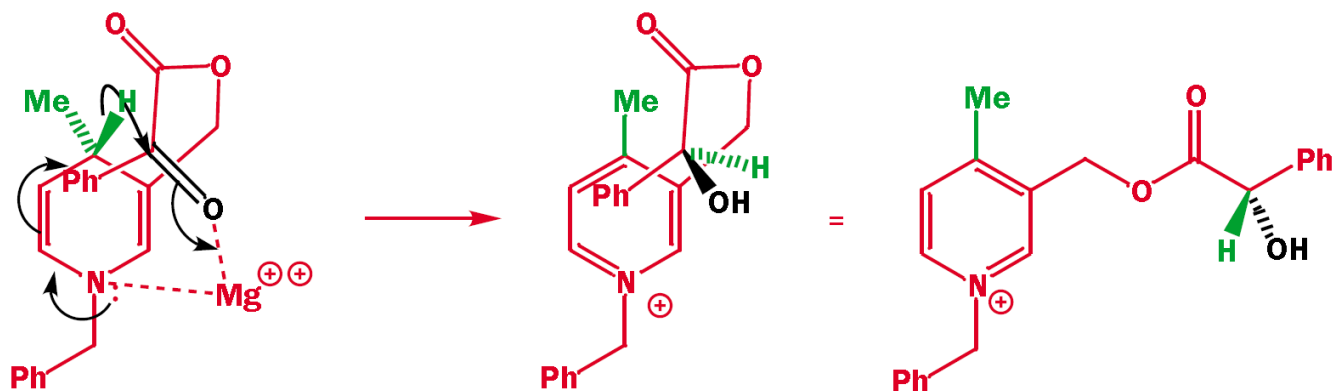


Catálise Quiral

Transesterificação leva ao álcool-éster opticamente ativo.



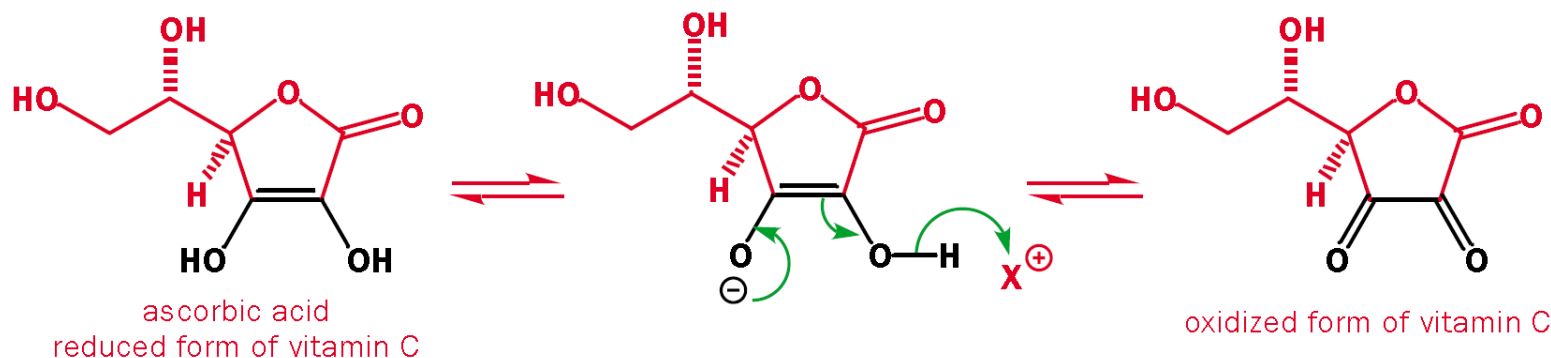
O ET envolve quelação com Mg^{2+} e pode ser utilizado como para explicar a redução com NAD^+ .



Catálise Quiral

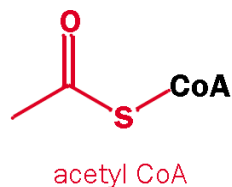
(Vitamina C)

Como visto anteriormente, vitamina C pode formar um enolato estável que é utilizado como redutor (muitas vezes chamado de antioxidante) em inúmeros processos bioquímicos.

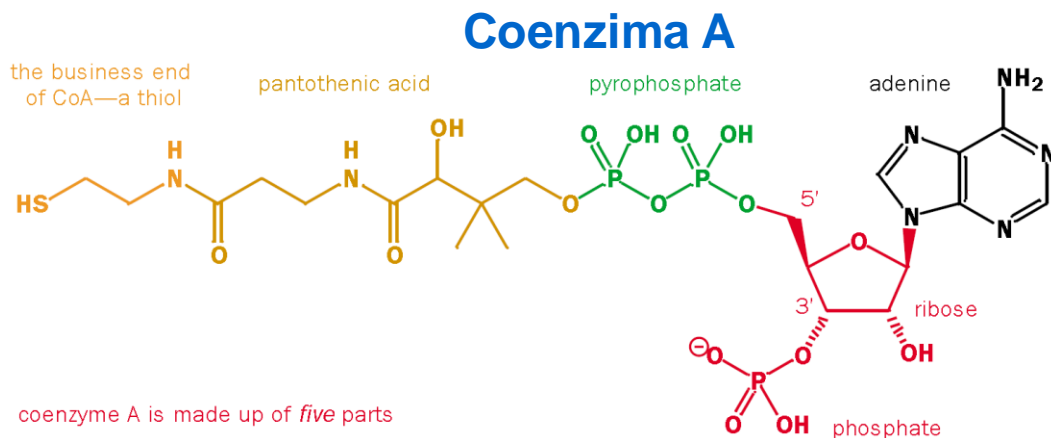


$X = \text{Fe(III)}, \text{peróxidos reativos} \dots$

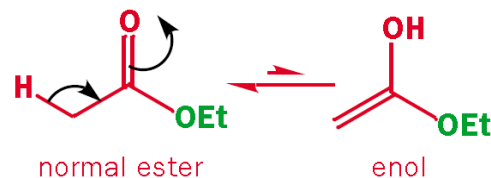
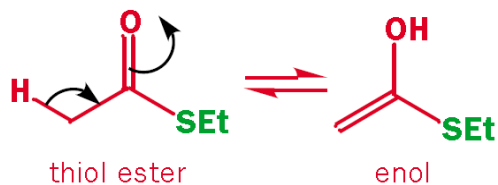
Catálise Quiral



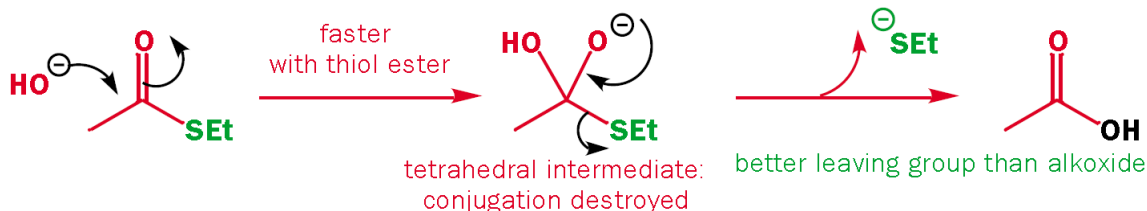
CoA represents the rest of the coenzyme A molecule



Conjugação menos efetiva nos tioésteres permite maior formação do enol do que em ésteres.

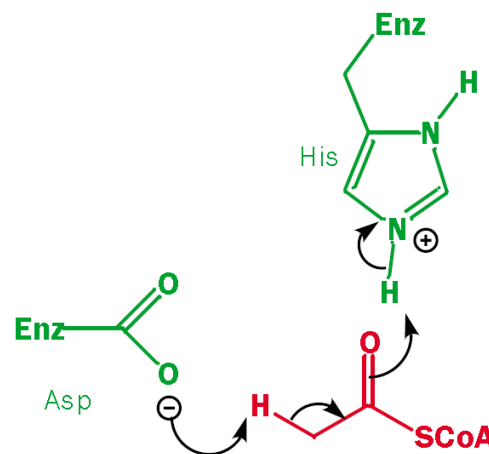
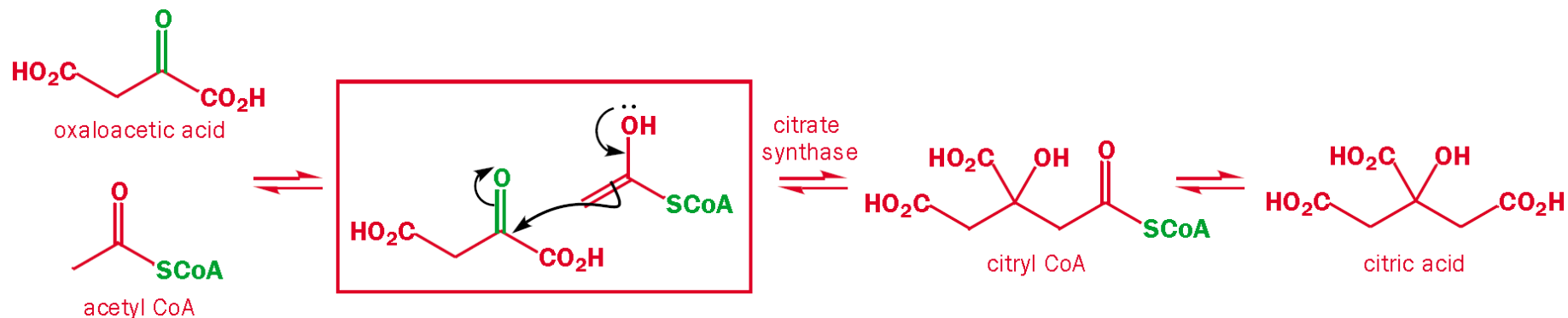


Menor conjugação também torna a carbonila do tioéster mais reativa aumentando a velocidade da reação (adição - etapa limitante). Finalmente, tiolato é melhor grupo de saída do que alcoxido.



Catálise Quiral

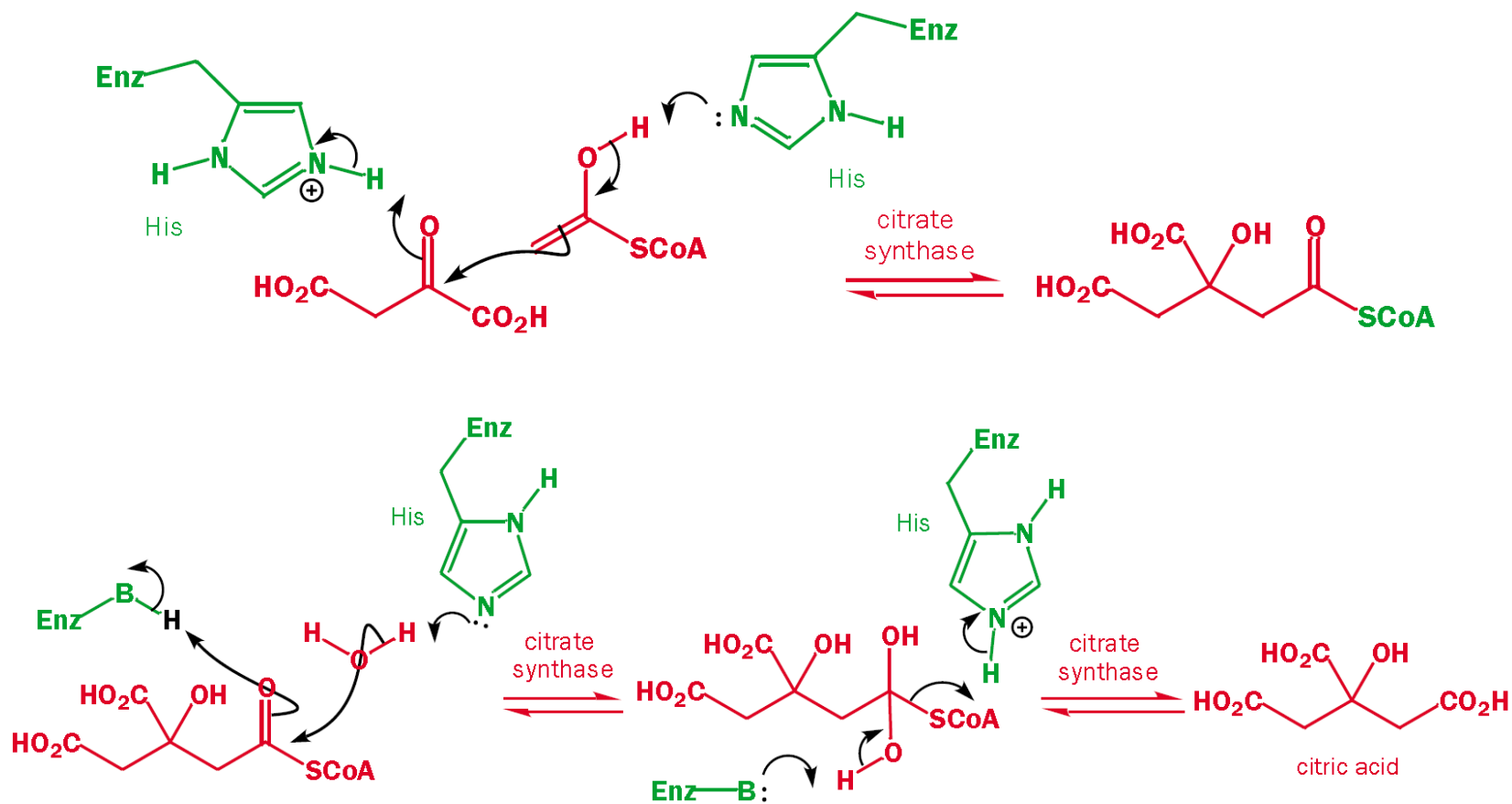
(Coenzima A)



Catálise Quiral

(Coenzima A)

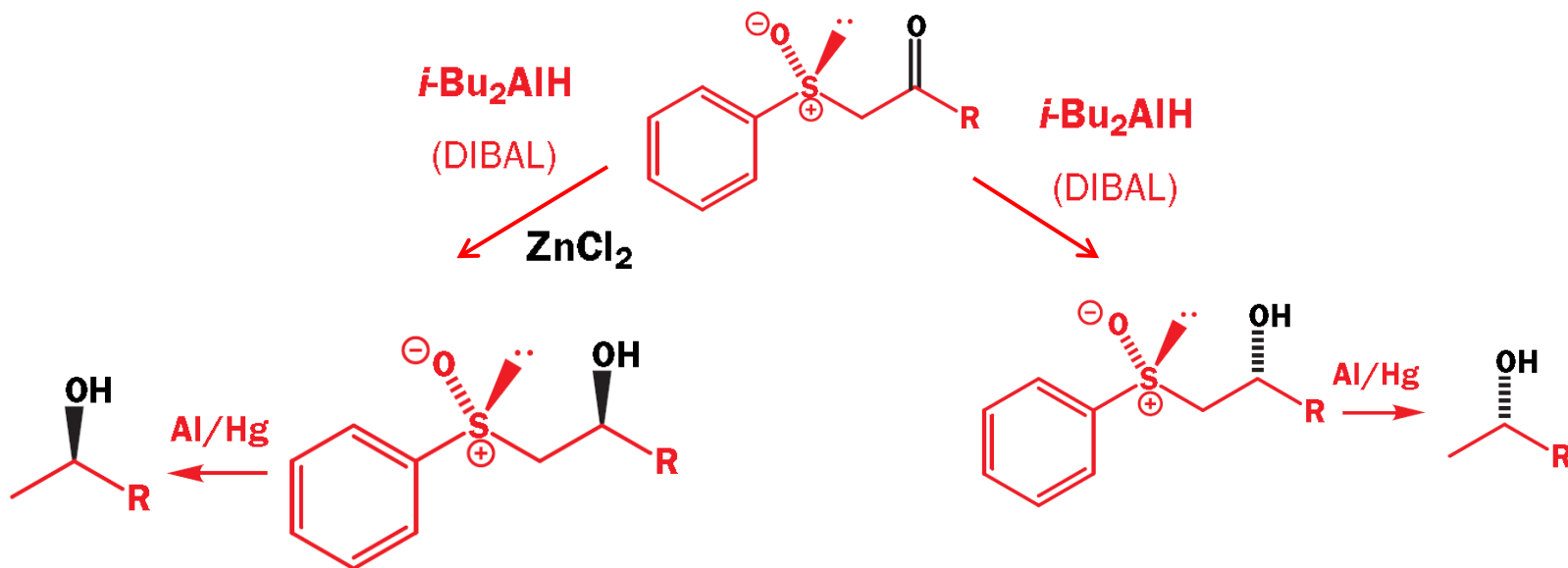
Mecanismo



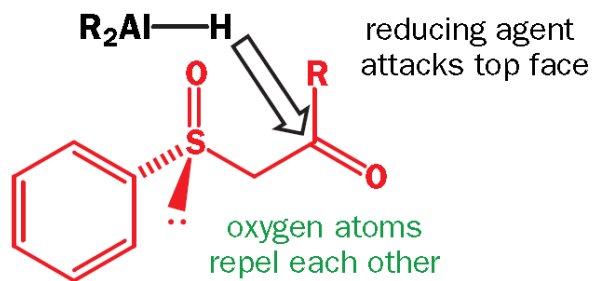
Method	Advantages	Disadvantages	Examples
chiral reagent	often excellent ees; can recrystallize to purify to high ee	only a few reagents are successful and often for few substrates	enzymes, CBS reducing agent

Enxofre

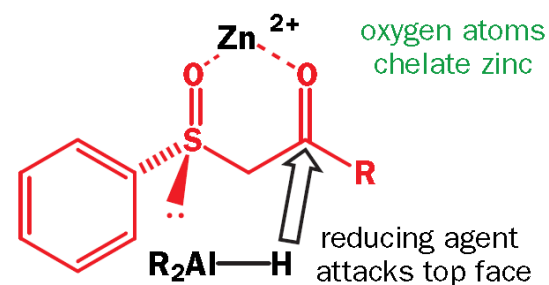
(Sulfóxidos)



reduction in the absence of ZnCl_2

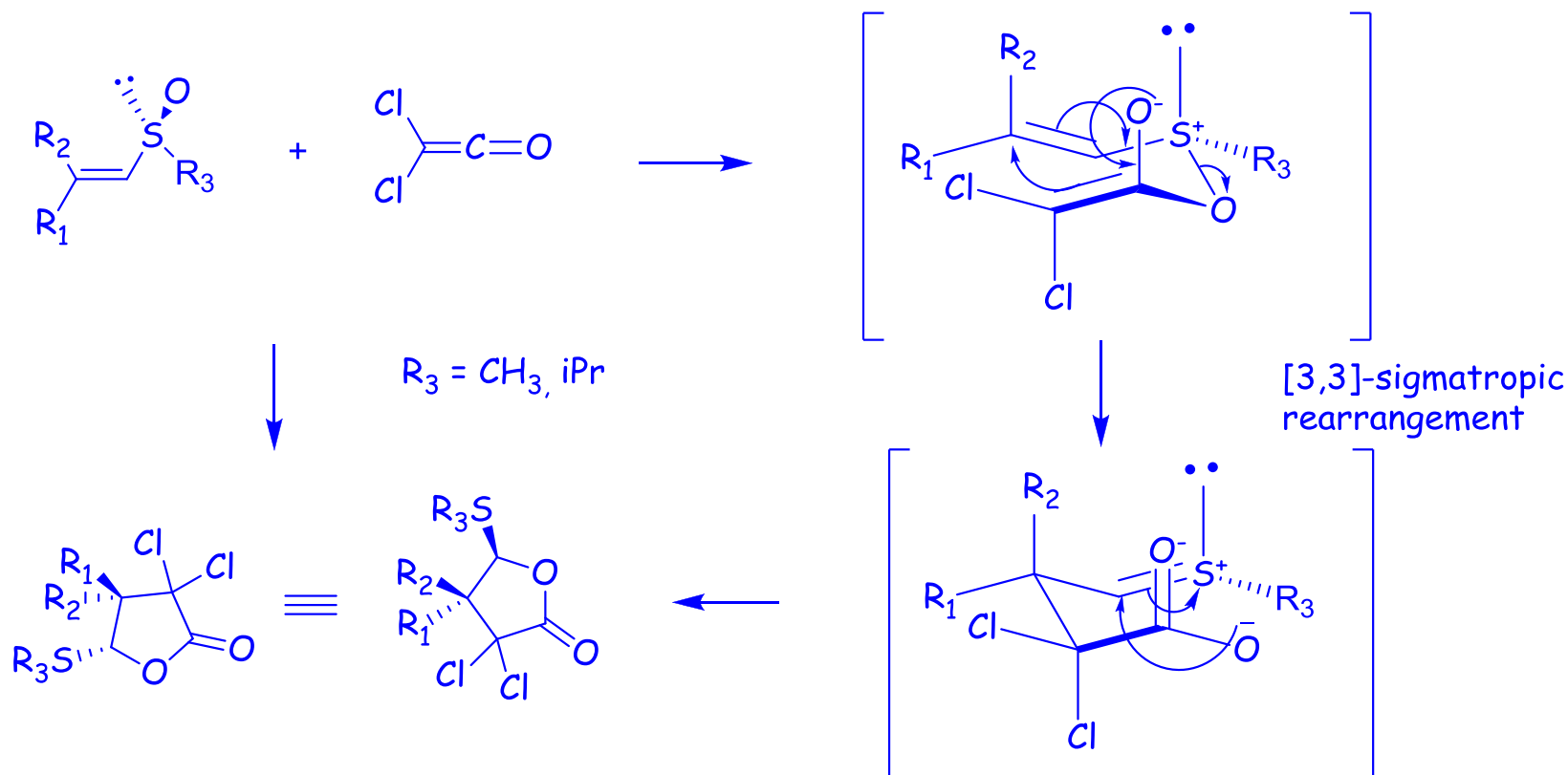


reduction in the presence of ZnCl_2

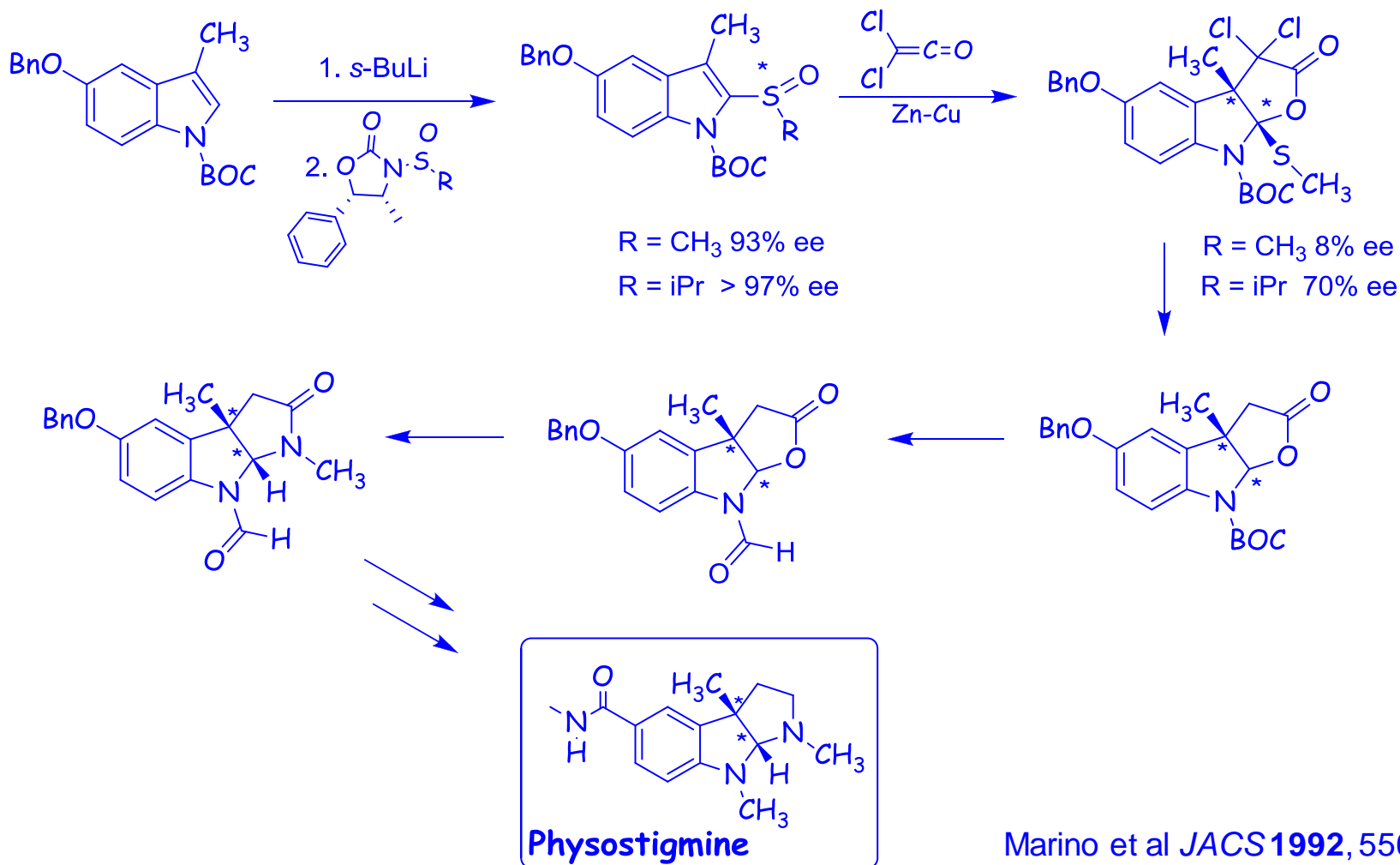


Enxofre

(Sulfóxidos Quirais – Lactamização de Marino)

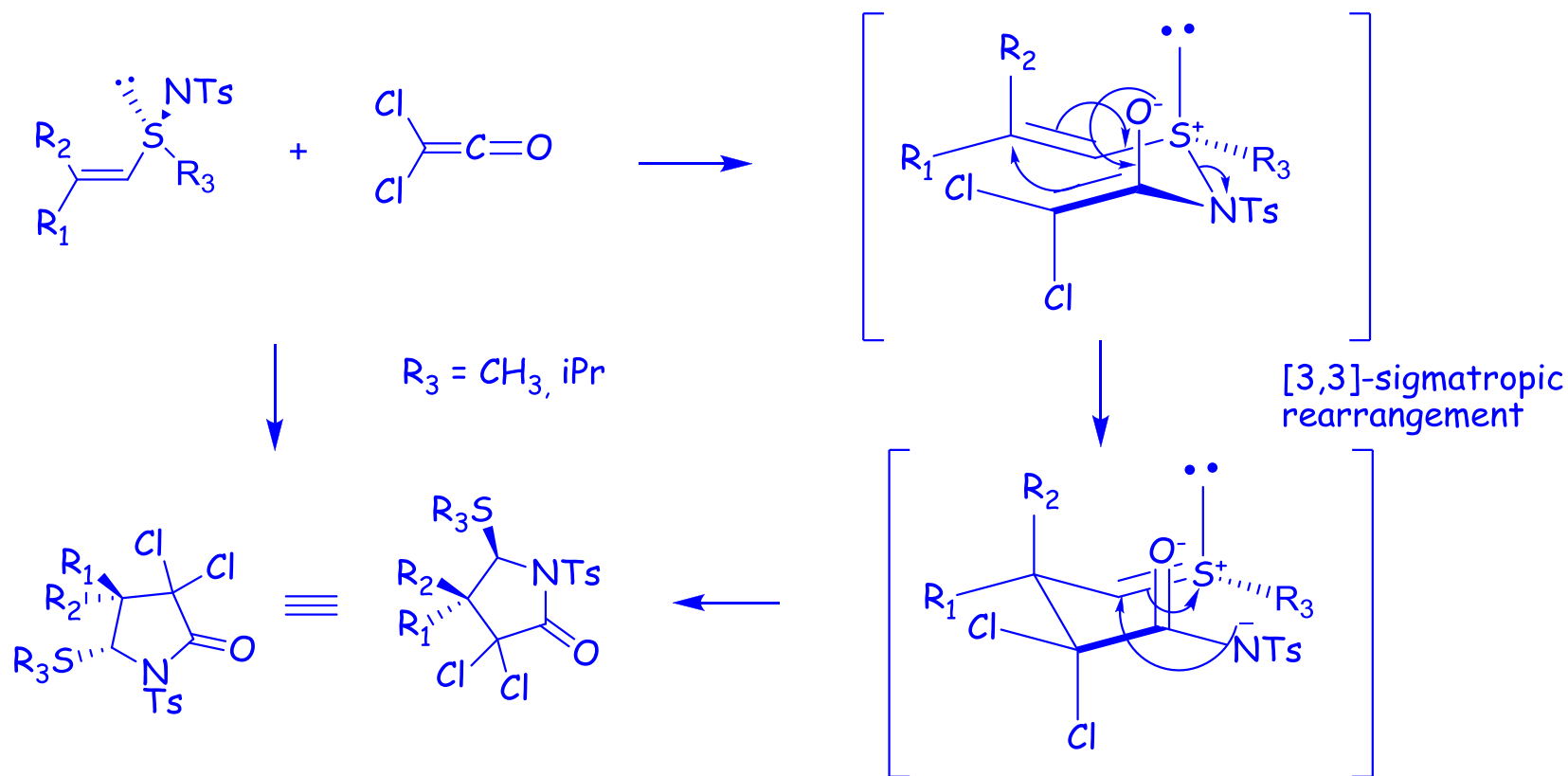


Síntese Enantiosseletiva da (-)- Fisostigmina - Marino



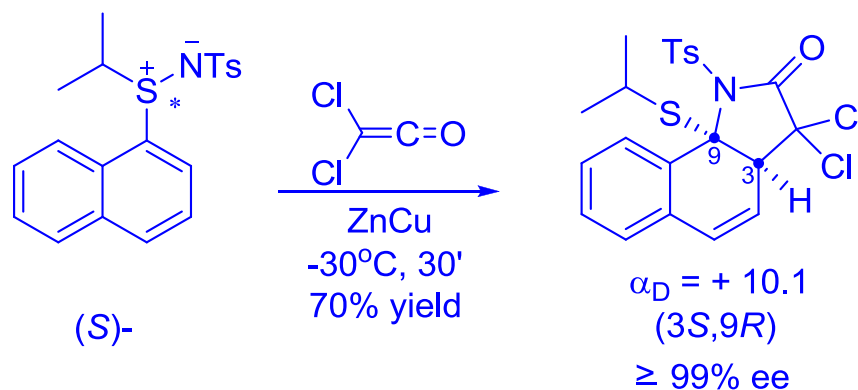
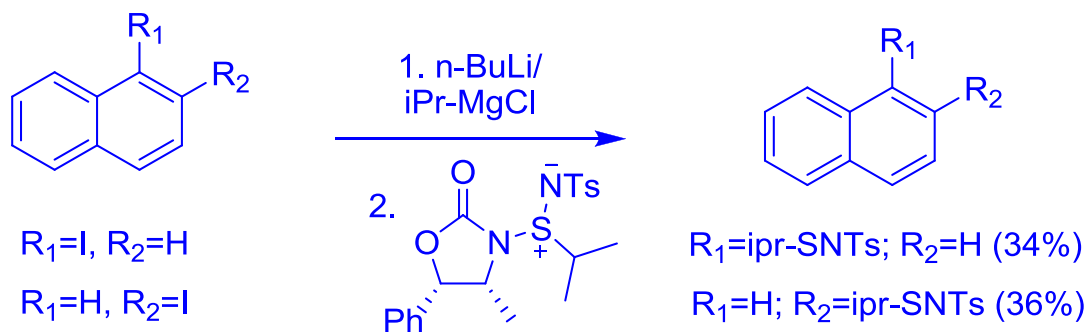
Enxofre

(Lactamização)



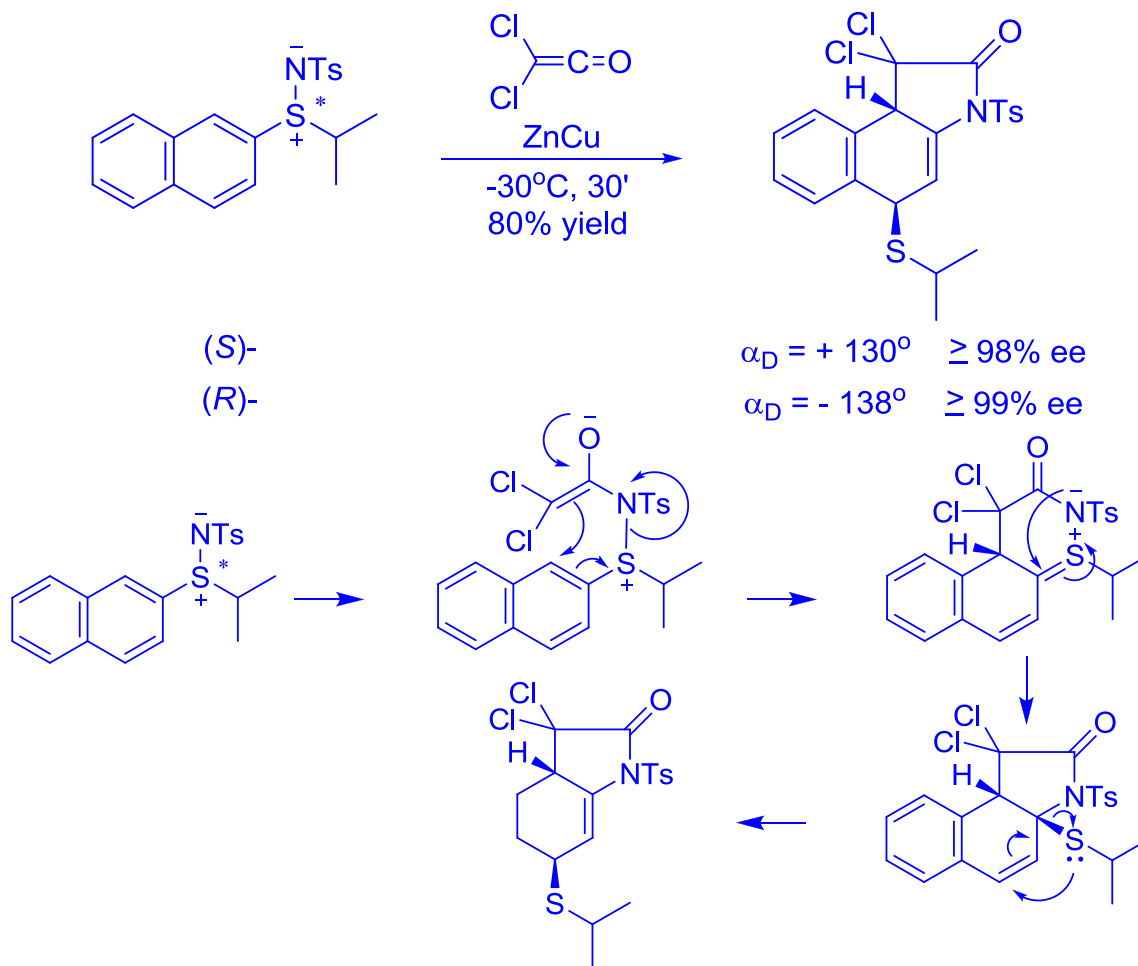
Silveira, G. P.; Marino, J. P. *J. Org. Chem.* 2013, 78, 3379.

Primeiras lactamas obtidas com alta *re* por γ -lactamização



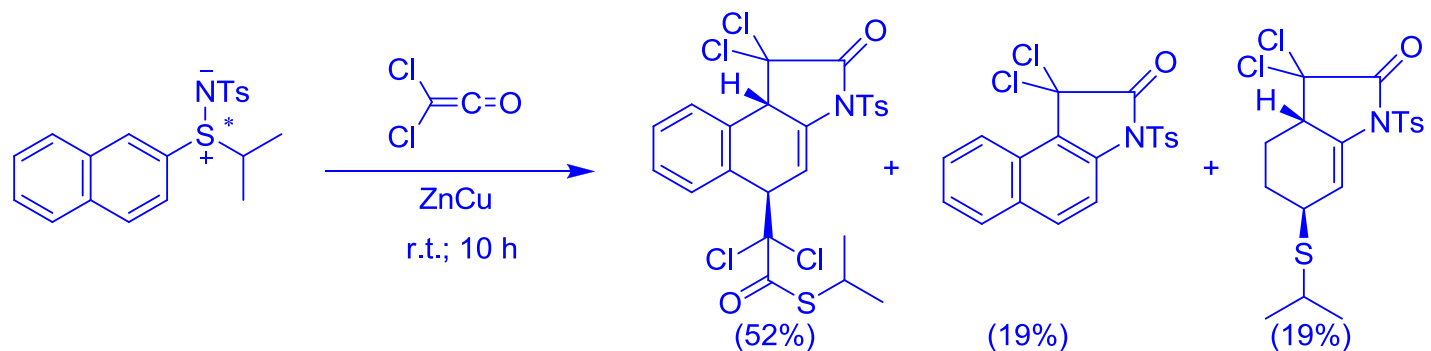
Silveira, G. P.; Marino, J. P. *JOC* **2013**, 3379

Primeiras lactamas obtidas com alta *re* por γ -lactamização



Silveira, G. P.; Marino, J. P. *JOC* 2013, 3379

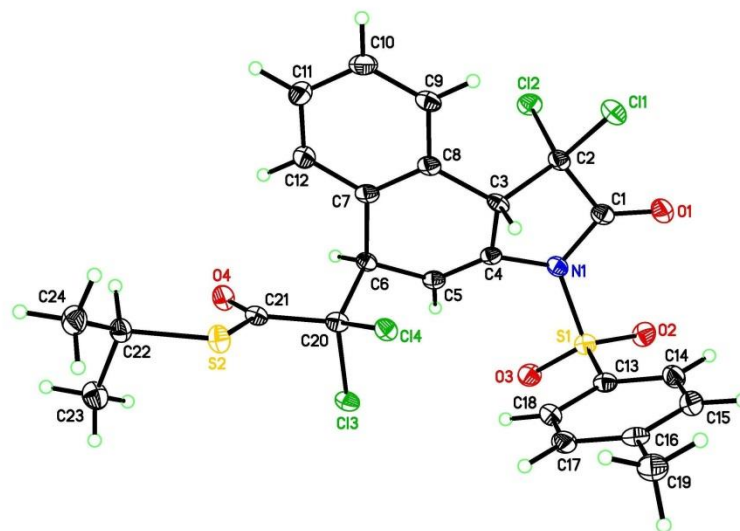
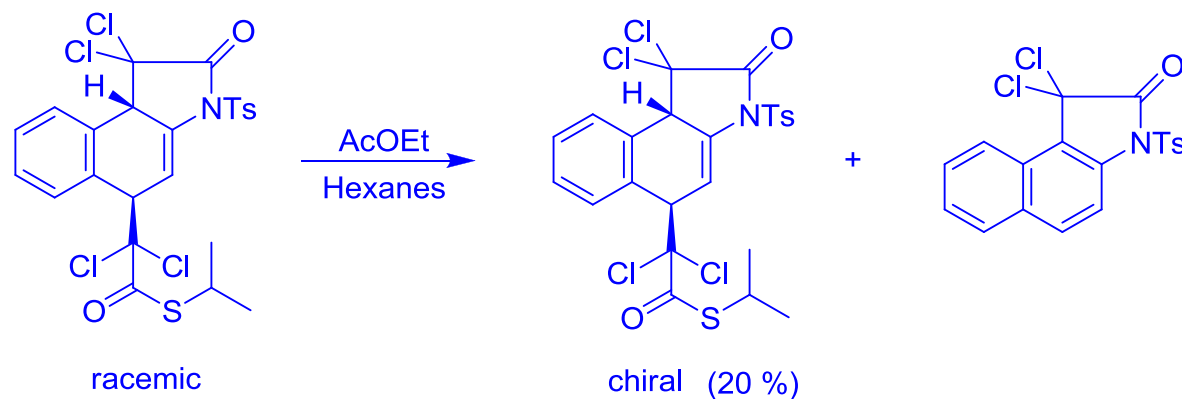
Primeiras lactamas obtidas com alta *re*



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Silveira, G. P.; Marino, J. P. *JOC* **2013**, 3379

Primeiras lactamas obtidas com *alta re*



Silveira, G. P.; Marino, J. P. *JOC* 2013, 3379