

An Exploration of α -Cyanocinnamate Esters as a Replacement for DEAD in the Mitsunobu Reaction

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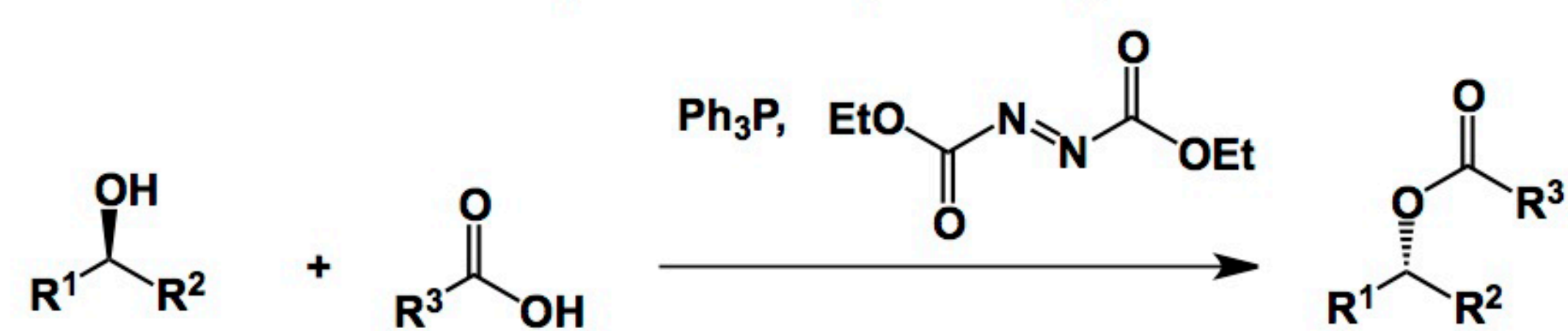
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Introduction



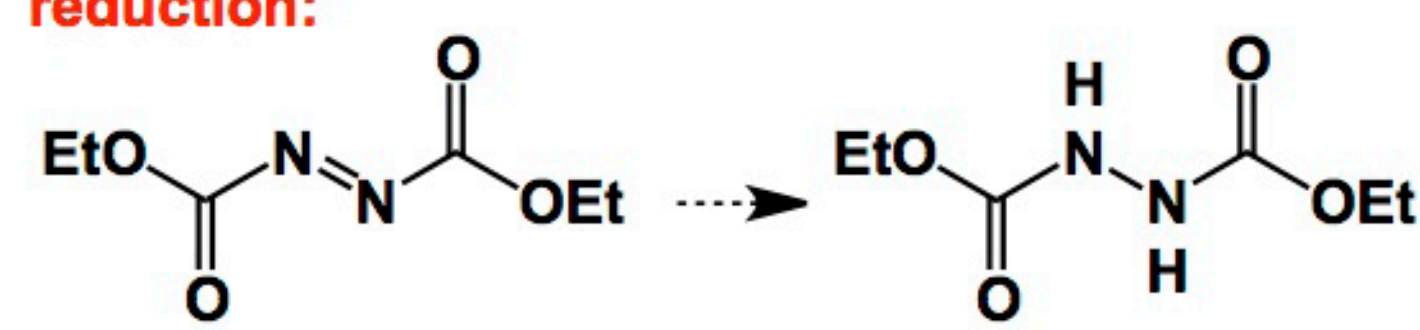
Oyo Mitsunobu (1934-2003)



oxidation:

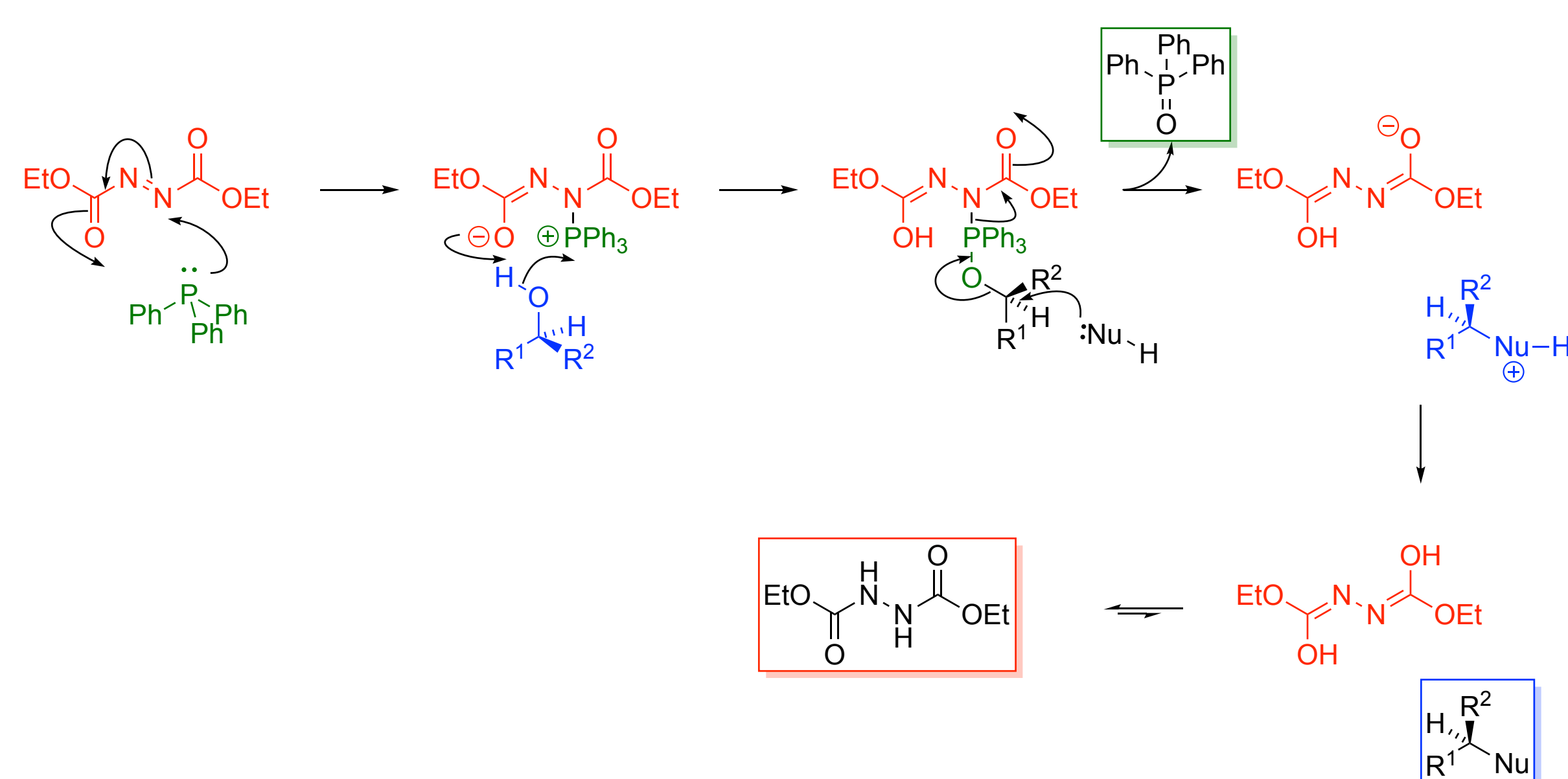


reduction:



- The Mitsunobu reaction was first reported by Oyo Mitsunobu in the *Bulletin of the Chemical Society of Japan* in 1967, with a follow-up review in *Synthesis* in 1981.
- A recent literature search using Web of Science reveals that between them, these two papers have amassed over 5,000 citations.
- The reaction proceeds by coupling the desired S_N2 substitution with an exothermic redox reaction and dehydration.
- The formation of the phosphoryl (P=O) group provides much of the driving force for the reaction.

Mechanism of the Mitsunobu Reaction



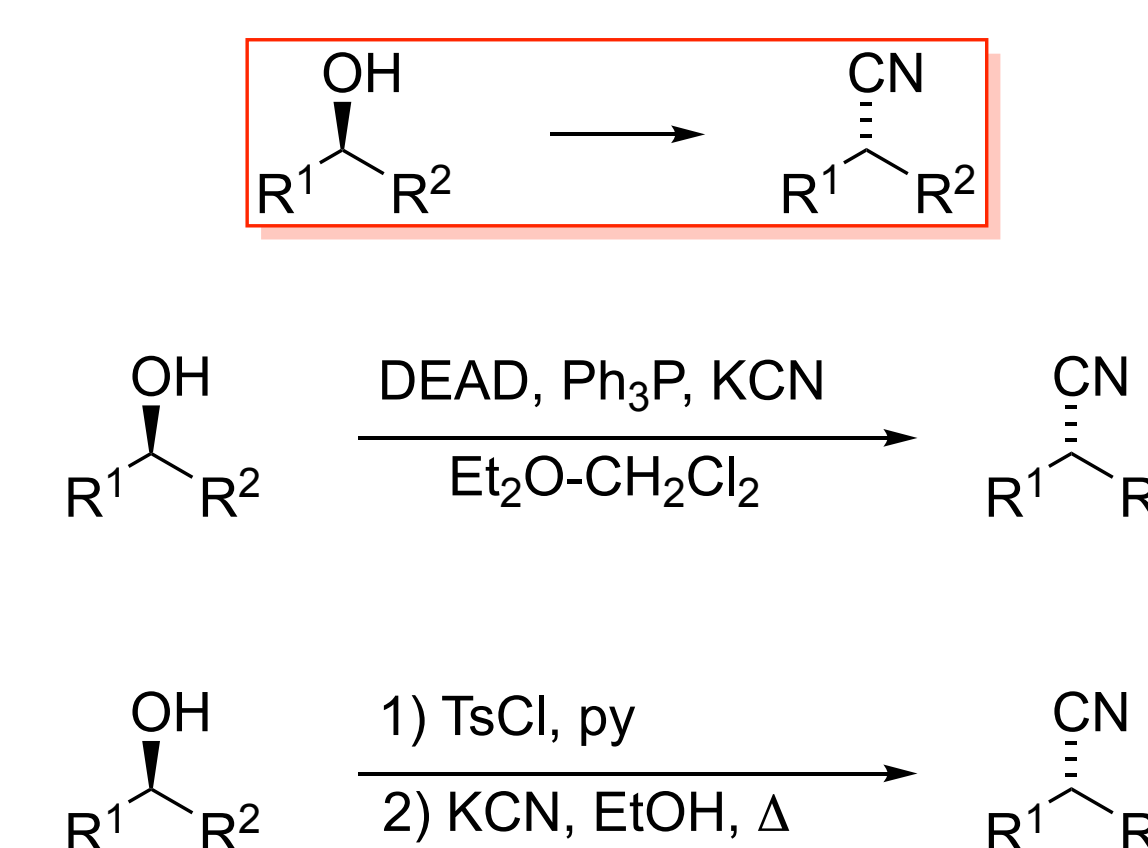
- The reaction is the method of choice for the conversion of primary or secondary alcohols to substitution products with inversion of configuration.
- The reaction works best when the pK_a of $H-Nu$ is below 12.

Our Target Transformation

- We are seeking to prepare nitriles from alcohols with inversion of configuration at the carbinol carbon.

- This can be accomplished by:
 - the Mitsunobu reaction with potassium cyanide.
 - initial conversion of the alcohol to the tosylate, followed by displacement of the sulfonate by cyanide anion.

- Both these methods involve the use of hazardous cyanide anion.



Hazards of the Mitsunobu Reaction

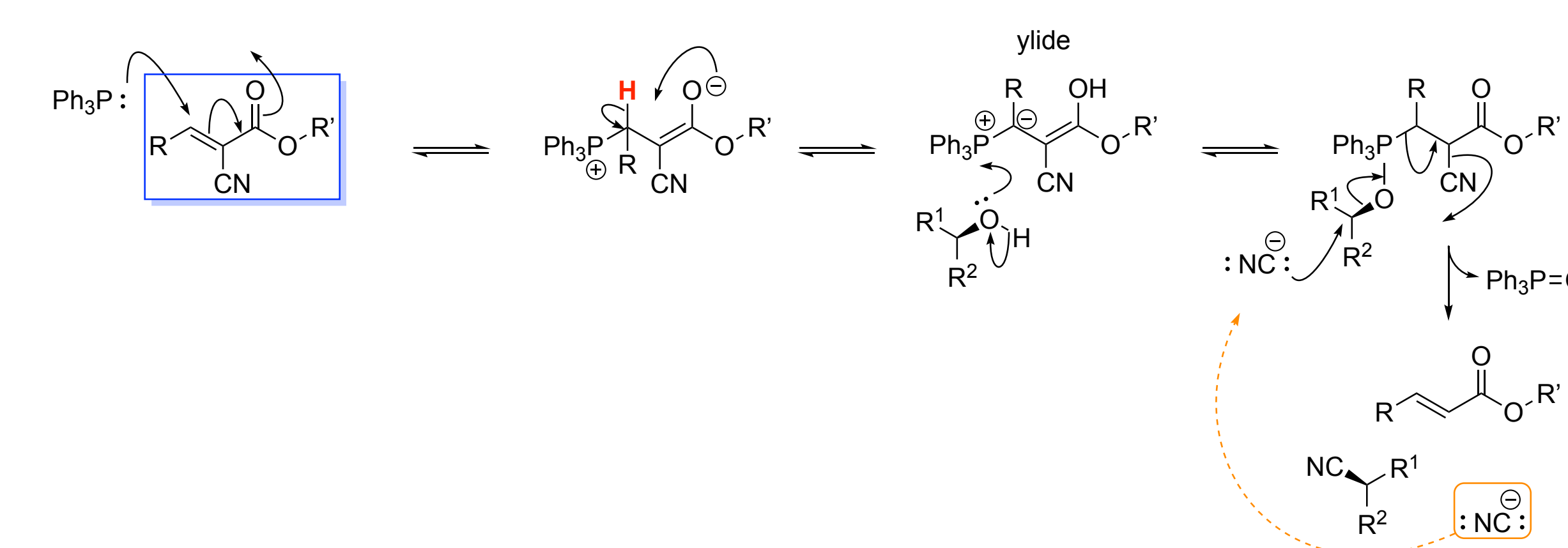
DEAD

SAFETY DATA SHEET	
DETHYL AZODICARBOXYLATE	
Section 1: Identification of the substance/mixture and of the company/undertaking	Section 2: Hazards identification
Section 3: Composition information on ingredients	Section 4: First aid measures
Section 5: Fire and explosion	Section 6: Accidental release measures
Section 7: Handling and storage	Section 8: Exposure controls and personal protection
Section 9: Physical and chemical properties	Section 10: Stability and reactivity
Section 11: Toxicological information	Section 12: Ecological information
Section 13: Disposal	Section 14: Transport information
Section 15: Regulatory information	Section 16: Other information

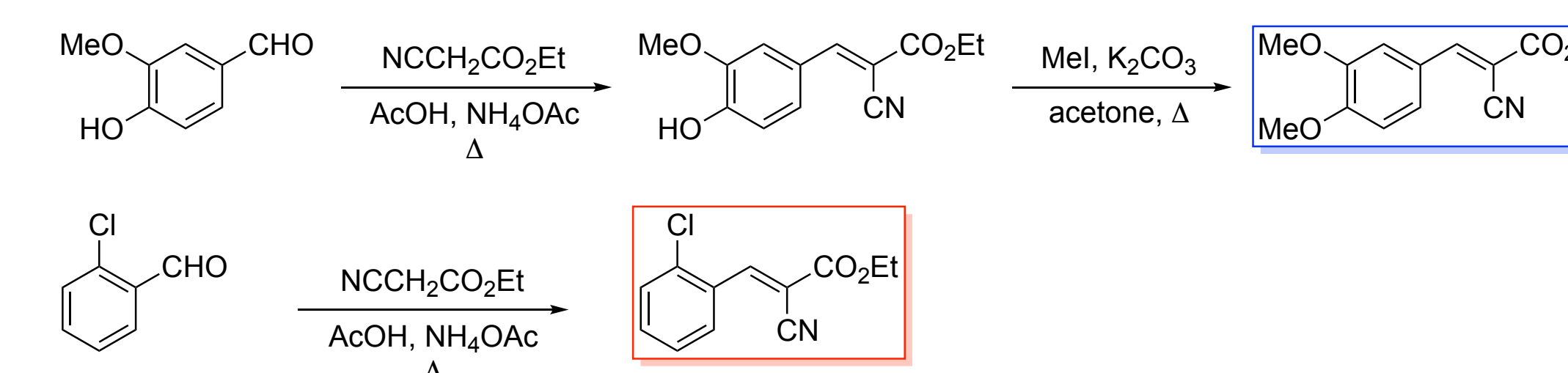
Is There a Way to Avoid the Use of Both DEAD and Cyanide?

- The ideal reagent should:
 - Be of relatively low toxicity.
 - Be relatively non-volatile.
 - React with triphenylphosphine to generate a zwitterionic intermediate capable of reacting with the alcohol, in a manner similar to DEAD.
 - Maintain a low level of free cyanide anion *in situ*.
 - Generate low-toxicity or recyclable by-products.
- It would be especially nice if the triphenylphosphine could also be replaced, but this is not viable at this time.

Our Potential Solution



- The α -cyanocinnamate esters are readily prepared by the Doebner reaction between the aromatic aldehyde and ethyl cyanoacetate in acetic acid with ammonium acetate.
- These esters have an electron-deficient double bond that will react like DEAD with triphenylphosphine to give a zwitterion intermediate.
- The β - position of the original ester is now positioned to generate a very stabilized phosphorus ylide.
- We expect this ylide to react with the alcohol to give the alkylated cyanoacetate, which will then react with cyanide anion in a reaction that generates cyanide ion.
- We have now completed the synthesis of ethyl *E*- α -cyano-3,4-dimethoxycinnamate and ethyl *E*- α -cyano-2-chlorocinnamate from the corresponding aldehydes.
- We have begun our preliminary explorations of the reaction using 2-octanol and ethyl *E*- α -cyano-3,4-dimethoxycinnamate, with diethyl malonate as the starter nucleophile.



Future Directions

- We will continue our preliminary examination of this reaction.
- We will explore the effects of the aromatic ring substituents on the course of the reaction
- We will determine the stereochemistry of the reaction using a chiral alcohol of known configuration.

Acknowledgments

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