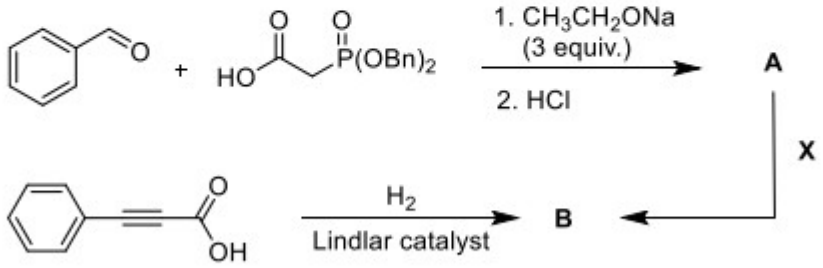
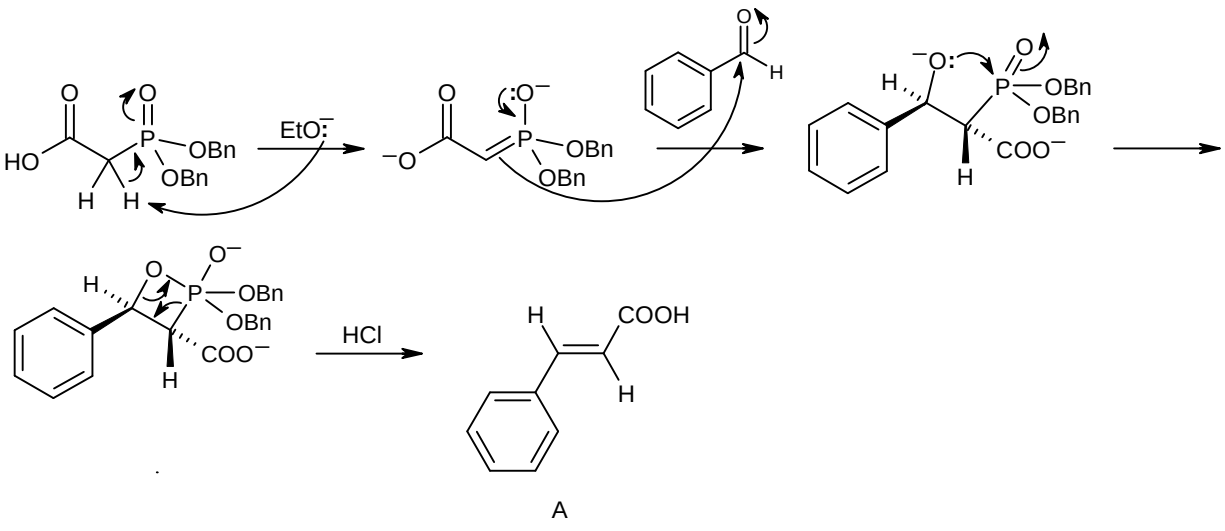
Problem 24. Cinnamon all around

Cinnamon is an important part of many dishes and desserts, including Czech apple strudel, Swedish cinnamon rolls kanelbullar, Indian spicy rice biryani and the popular winter drink mulled wine. There are several compounds in cinnamon which are responsible for its taste and smell, mainly cinnamaldehyde and cinnamic acid and its derivatives. It is noteworthy that (*E*)-cinnamaldehyde and cinnamic acid are much more abundant in nature than their respective (*Z*)-isomers. While the former have a honey, cinnamon-like odour, the latter are completely odourless. Let us first explore the syntheses of both stereoisomers of cinnamic acid.

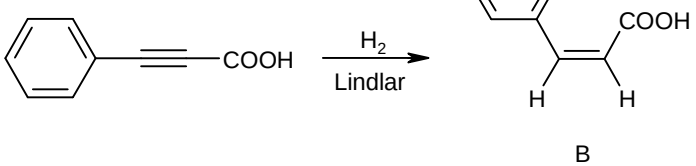


24.1 Draw the formulae of isomeric products **A** and **B**.

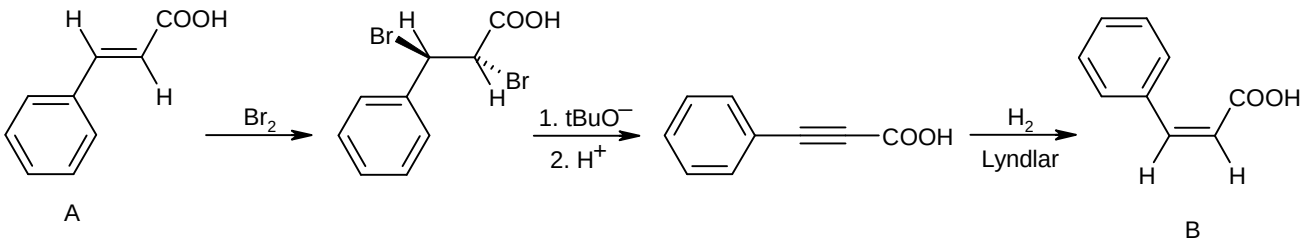
24.2 Propose reasonable reaction conditions (**X**) for the interconversion of cinnamic acid isomers (**A** → **B**).



A

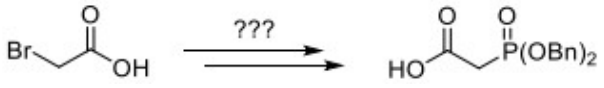


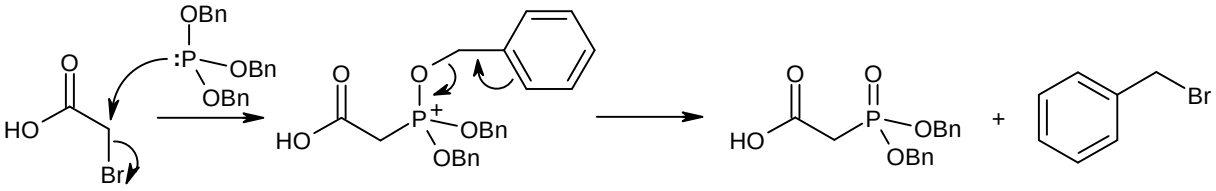
B



A B

24.3 Starting from 2-bromoacetic acid, how would you prepare the phosphonate used in the above-mentioned synthesis?

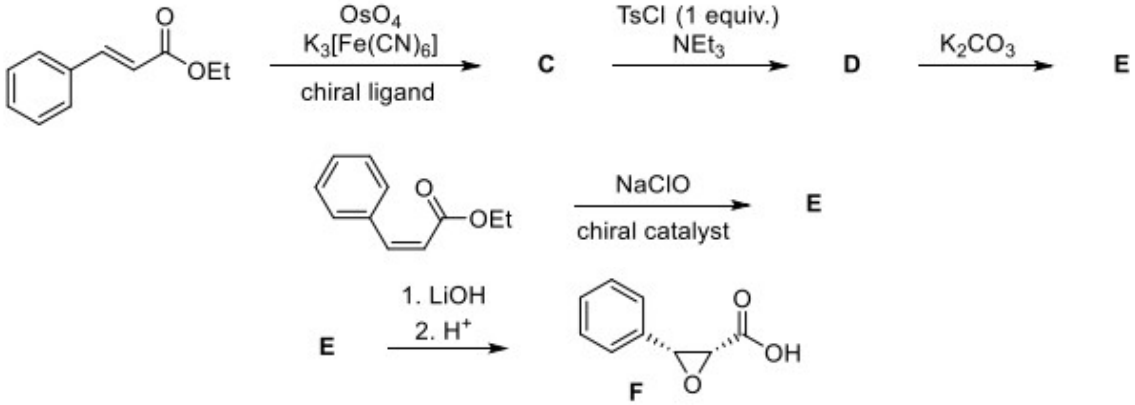




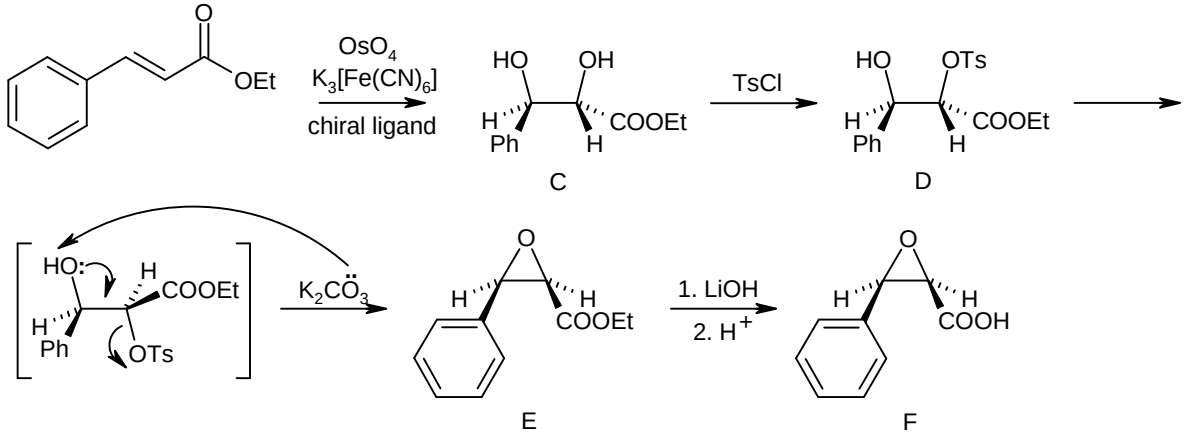
Both stereoisomers of cinnamic acid and their derivatives are often used as starting material in numerous syntheses. Let us have a look at some examples.

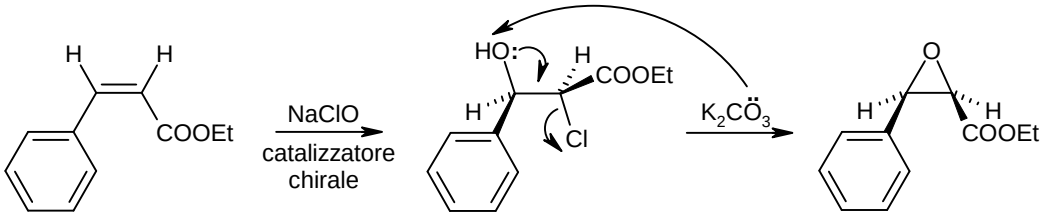
Docetaxel (**J**), sold under the brand name Taxotere, is a semisynthetic chemotherapy drug used to treat numerous cancer types. While the core structure, 10-deacetylbaccatin III (**G**), is extracted from yew leaves, the side chain is prepared synthetically from ethyl cinnamate.

A key intermediate, epoxyacid **F**, can be prepared from both *(E)*- and *(Z)*-ethyl cinnamate. *(E)*-Ethyl cinnamate is first reacted with osmium tetroxide in the presence of a chiral ligand. Only one enantiomer of **C** is formed. The reaction of **C** with one equivalent of tosyl chloride leads to compound **D** in which the hydroxyl group at position 2 is tosylated. In a basic environment, tosylate **D** is converted to compound **E**. Alternatively, compound **E** can be prepared in one step from *(Z)*-ethyl cinnamate by hypochlorite-mediated oxidation. A chiral catalyst ensures the formation of a single enantiomer. Hydrolysis of **E** then provides acid **F**.



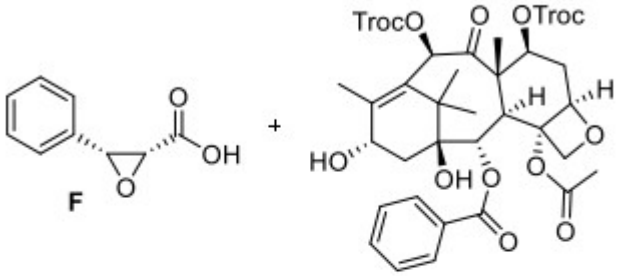
24.4 Draw the structures of compounds **C**, **D** and **E**, including stereochemistry. The absolute configuration of all compounds can be deduced from the known structure of acid **F**.



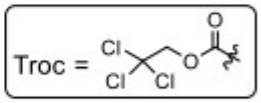


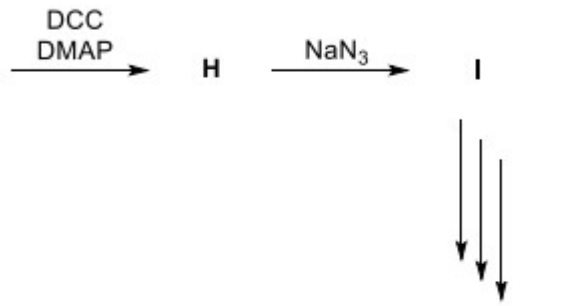
E

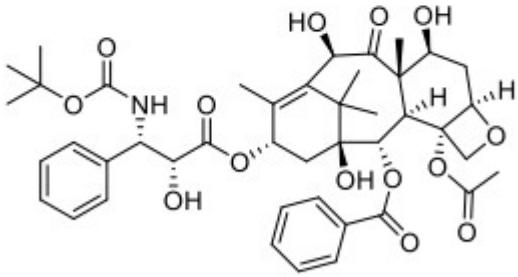
Epoxyacid **F** reacts with 10-deacetylbaccatin III (**G**) in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to provide compound **H**. A subsequent reaction with NaN_3 leads to compound **I**, which is easily converted to docetaxel (**J**).



G
10-Deacetylbaccatin III
(partially protected with Troc)



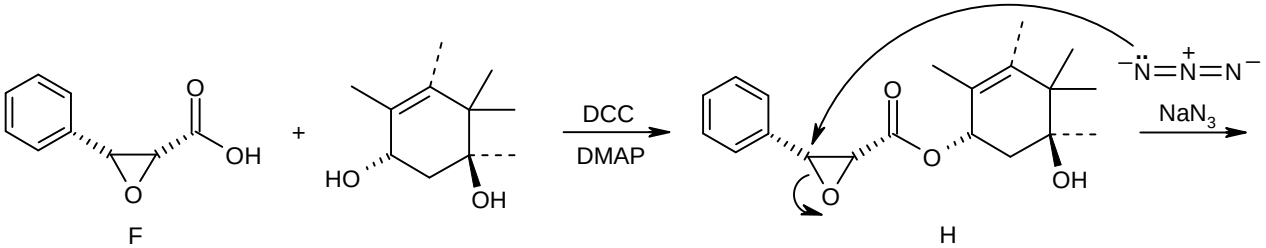




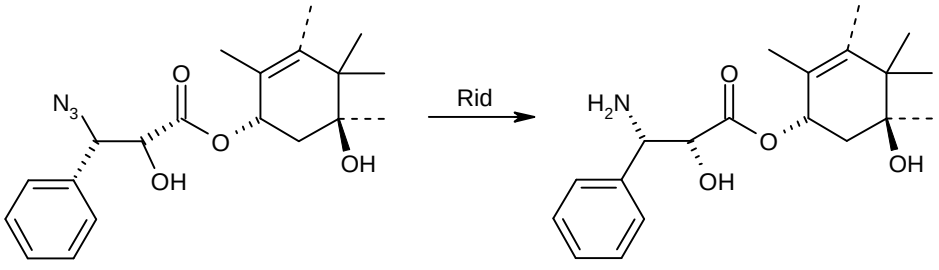
J Docetaxel

24.5 Draw the structures of compounds **H** and **I**, including stereochemistry.

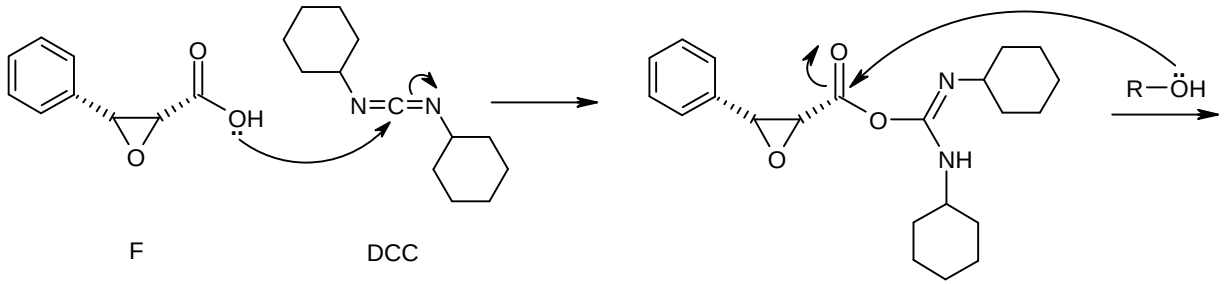
24.6 What is the role of DCC in the first step? Write the appropriate chemical equation.

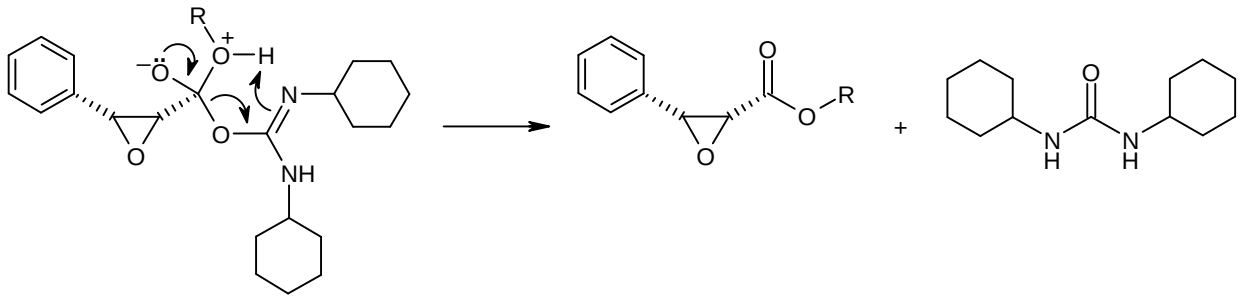


F H

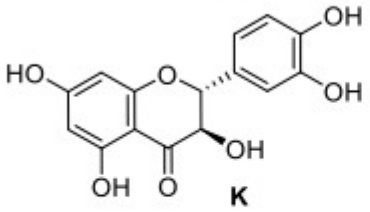


I



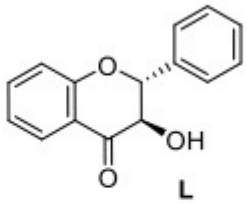


Taxifolin (**K**) is an inhibitor of ovarian cancer with strong hepatoprotective properties. It belongs to 3-hydroxyflavanone (**L**) family of natural products.



K

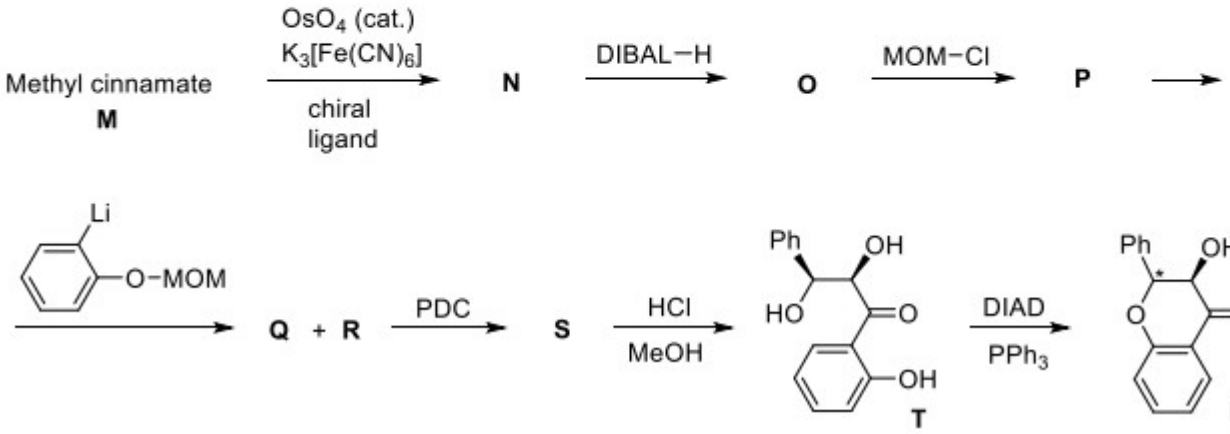
Taxifolin



L

(2*R*,3*R*)-3-Hydroxyflavanone

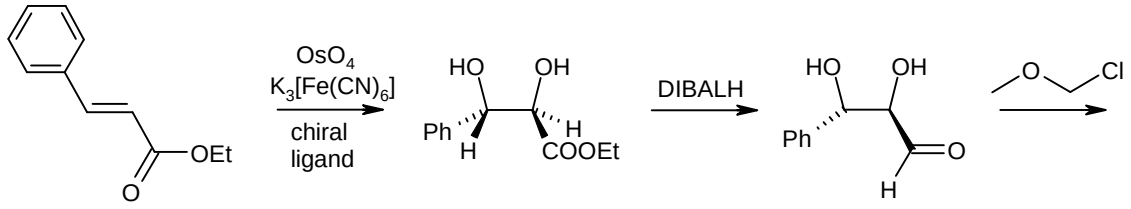
The synthesis of compound **L** starts with asymmetric dihydroxylation of methyl cinnamate **M** using osmium tetroxide as catalyst, potassium ferricyanide as oxidant and a chiral ligand. The synthesis continues with the transformation of the ester group in compound **N** to compound **O** and subsequent reaction of hydroxyl groups in the presence of an excess of chloromethyl methyl ether (MOM–Cl), yielding compound **P**. Compound **P** reacts with a protected aryllithium reagent in a non-stereoselective manner, giving a mixture of two compounds **Q** and **R**. The reaction of the mixture of compounds **Q** and **R** with PDC yields a single compound **S**, which upon acidic treatment provides compound **T**. Finally, the reaction of **T** with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine proceeds by formal S_N2 substitution of one hydroxyl group with the other to furnish target compound **L**.



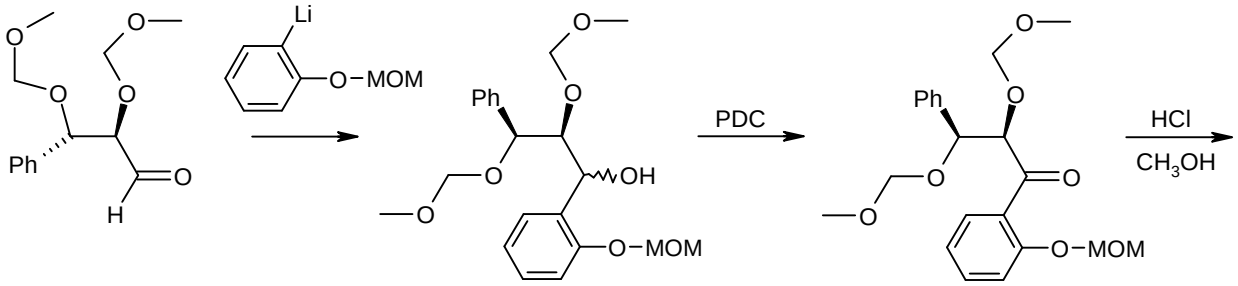
24.7 From the known configuration of product **T**, decide whether compound **M** is the ester of (*E*)- or (*Z*)-cinnamic acid.

24.8 Draw the structures of compounds **N**–**S** and **L**, with the correct configuration on the benzylic oxygen.

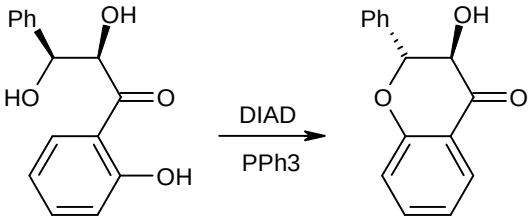
24.9 Decide whether compounds **Q** and **R** are a) constitutional isomers, b) diastereoisomers or c) enantiomers.



M N O



P Q + R enantiomeri S



T L

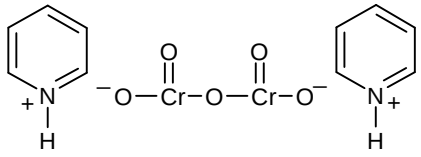
24.10 Why can we not react compound **O** with the aryllithium reagent directly?

24.11 Draw the structure of the PDC reagent.

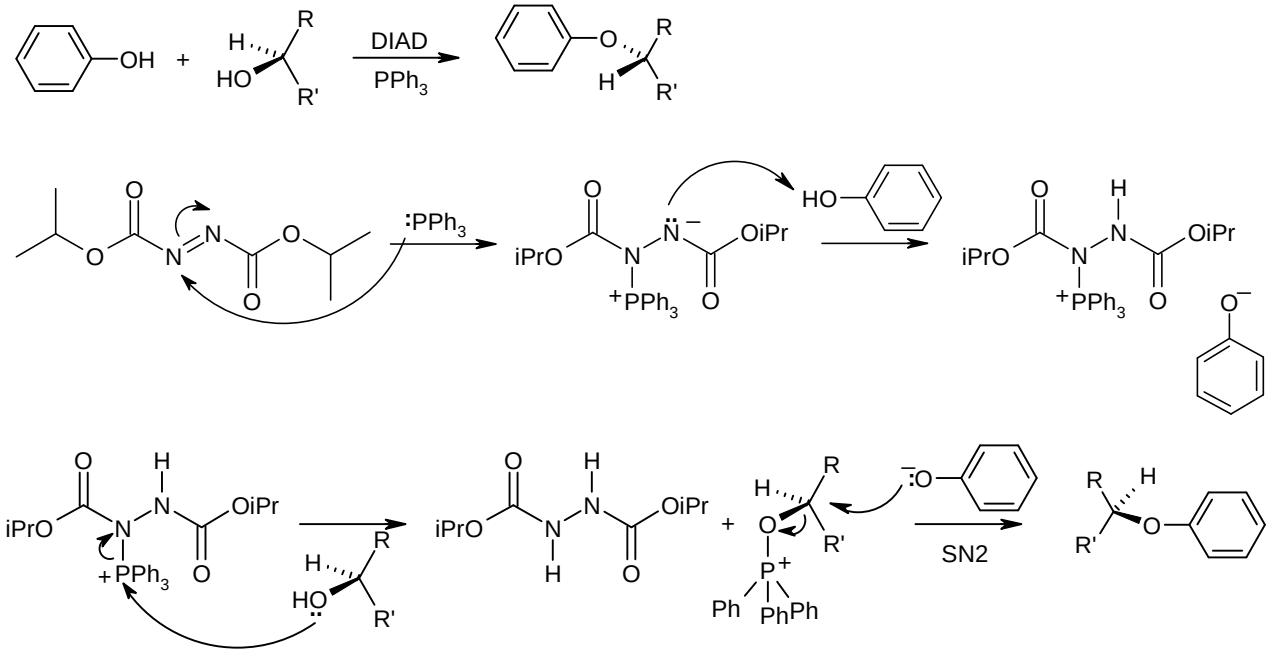
24.12 After whom is the reaction converting compound **T** to compound **L** named?

24.10 I gruppi alcolici sono lievemente acidi e distruggono il reattivo litio-organico trasformandosi in alcossidi. Questi sono nucleofili e possono attaccare l'adeide. I gruppi alcolici vanno quindi protetti trasformandoli in eteri con MOM-Cl.

24.11 PDC è piridinio dicromato con formula: $(HPy)_2\ Cr_2O_7$. E' un ossidante blando degli alcoli primari e secondari che ossida a composti carbonilici. In solvente opportuno ossida gli alcoli primari solo fino ad aldeidi.



24.12 Si tratta della reazione di Mitsunobu che converte un alcol in un estere o in un etere con inversione di configurazione usando DIAD (diisopropil-aza-dicarbossilato) e trifenilfosfina.



Soluzione proposta da Mauro Tonellato – Padova