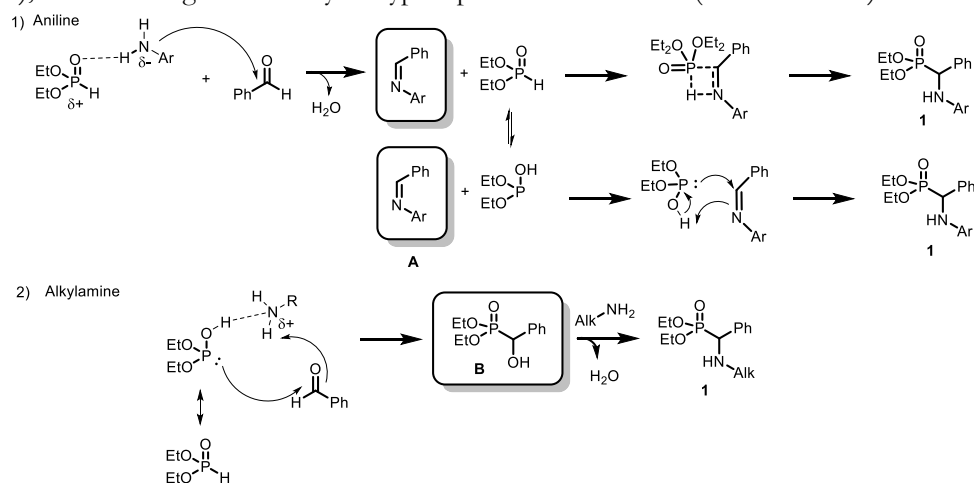


- Propose the two mechanisms to form the α -amino phosphonate **1** from the aldehyde, the amine and the phosphite and identify the two intermediates **A** and **B** formed during the reaction which depend on the amine used.

Answers: The Kabachnik-Fields reaction (also called Phospha-Mannich reaction) can proceed via two different possible mechanisms depending on the basicity of the amine. Indeed, in the presence of aniline, such as the first example, the first step involves the formation of an imine which undergoes a rearrangement via either a four or five membered transition state depending on the phosphonate/phosphite tautomerism to form the product. In the case of more basic amine (example 2), the reaction goes via α -hydroxyphosphonate mechanism (intermediate **B**).

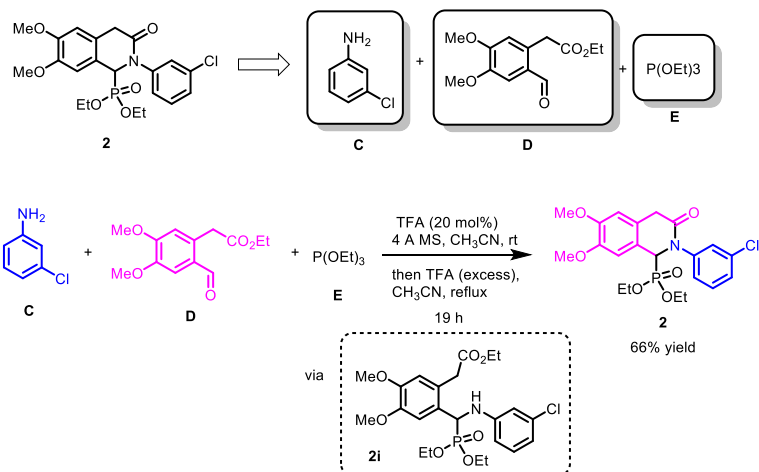


Notes: (1) Although the α -hydroxyphosphonate mechanism was supported in 1998 by Cherkasov and Galvin (*Russ. Chem. Rev.* **1998**, 67, 857-882), other groups including Keglevich and Balint (*Molecules*, **2012**, 17, 12821-12835) showed that the reaction using cyclohexylamine and benzaldehyde went *via* the imine mechanism (imine formation monitored by *in situ* FT IR spectroscopy).

(2) The imine can be pre-formed and submitted to the same reaction conditions which is known as Pudovik reaction.

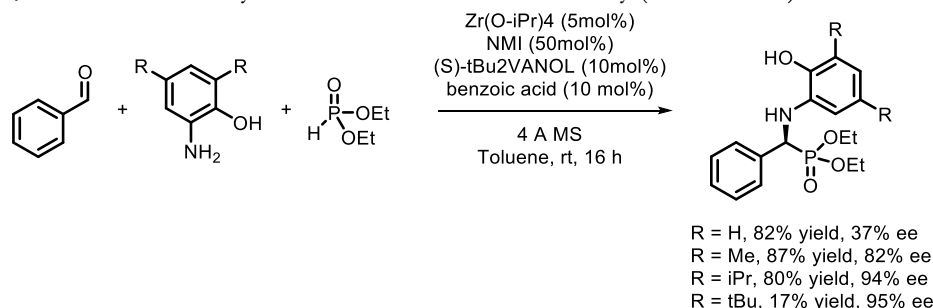
- The Borse group reported the synthesis of compound **2** (*Tetrahedron Lett.*, **2012**, 53, 6940-6942). How would you synthesize the following compound by using Kabachnik-Fields reaction?

Answers: The authors started with the aniline **C**, the aldehyde **D** and triethylphosphite **E** in the presence of TFA as catalyst in acetonitrile which undergoes a Kabachnik-Field reaction to give intermediate **2i**. Treatment with a large excess of TFA in reflux gave the lactam **2**.

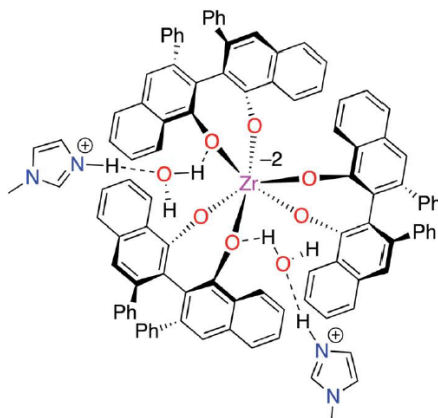


- Borhan and Wulff groups developed an enantioselective Kabachnik-Field reaction (*Chem Sci.* **2021**, 12, 12333-12345). Rationalize the asymmetric induction seen when the substituent goes from H to Me. Propose another substituent that would give higher enantioselectivity.

Answers: The size of substituent at the ortho position of the OH has the biggest impact on the asymmetric induction. Indeed, going from H to iPr, the enantiomeric excess has increased from 37 to 94%, respectively. Only the substituent at the ortho position is important to give high enantiomeric excess. It is thought that a steric clash with the zirconium complex can occur, which reduces the yield if the substituent is too bulky (17% for tBu).



In their study, authors found the optimal conditions being 1:3 ratio of Zr(OiPr)₄/(S)-Bu₂VANOL and therefore proposed the following complex of zirconium with 3 ligands. Although they don't have direct proof whether it is the active catalyst, crystal structures obtained from both mixtures 1:2 and 1:3 (Zr/L) gave the same complex.

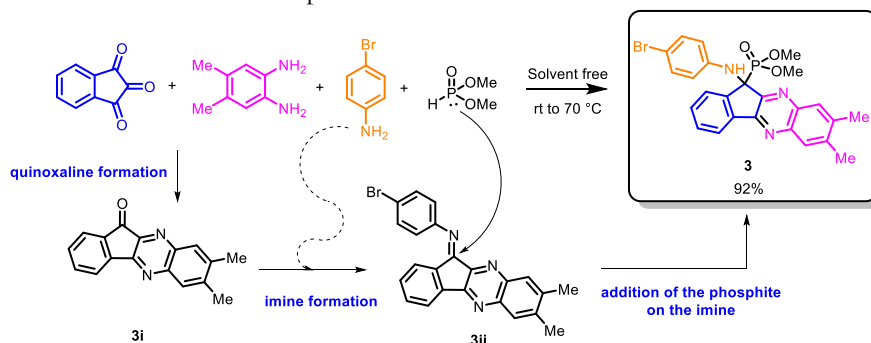


Finally, this methodology has been applied to alkyl aldehyde and gave good ee (90%).

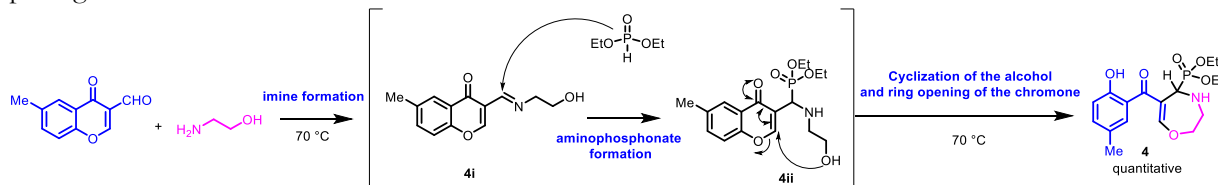
Notes: 10 mol% of benzoic acid was used and found to help both yield and enantiomeric excess (+10%). Unfortunately, the authors don't propose any explanation.

4. In 2015, the group of Ghahremanzadeh reported one-pot four-component Kabachnik-Field reaction. (*RSC Adv.* **2015**, 5, 99148-99152) Identify the product formed in this case.

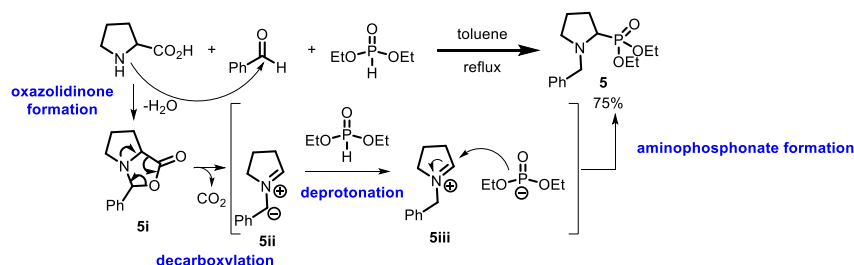
Answers: The first step is the formation of quinoxaline **3i** followed by the imine formation with the aniline. Ultimately, the phosphite is added onto the imine to form product **3**.



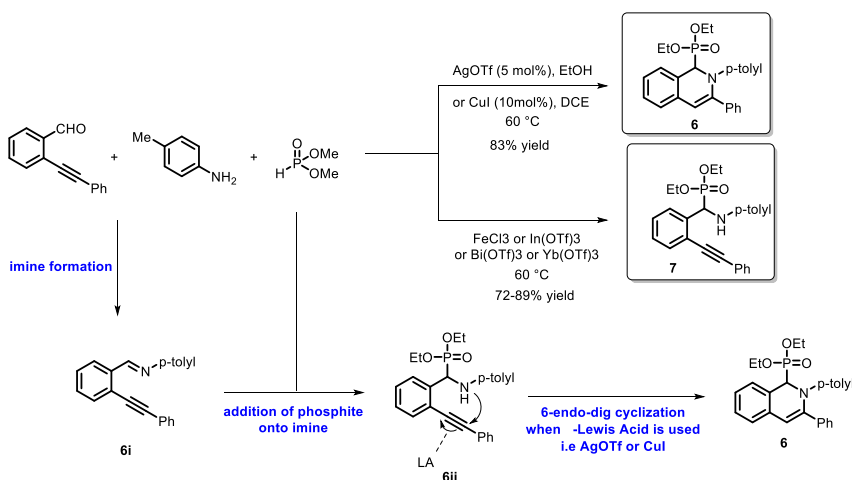
5. Ali *et. al.* reported the synthesis of the following oxazepine **4** (*Heterocycles*, **2013**, 87, 2513-2532). Propose a mechanism.
Answers: The reaction starts with the imine formation from the ethanolamine and the chromone followed by the addition of the diethylphosphite to give the aminophosphonate **4ii**. This non-isolated intermediate is converted to the product **4** via an intramolecular nucleophilic attack of the hydroxy group at the 2-position of the pyrone followed by ring opening.



6. Kaboubin *et. al.* reported the synthesis of the following aminophosphonate **5** by using a Kabachnik-Fields reaction starting from the proline (*Tetrahedron Lett.*, **2013**, 54, 4872-4875). Propose a mechanism.
Answers: the reaction was proposed to proceed through a decarboxylation of the oxazolidinone **5i** which was formed from the proline and the aldehyde. The resultant ylide **5ii** then deprotonates the diethylphosphite which adds onto the imine **5iii** to give the product **5**.



7. Wu's group in 2007 (*Tetrahedron*, **2007**, 63, 12166-12171 and *J. Comb. Chem.* **2007**, 9, 690-694) reported the following transformation. Identify the two products **6** and **7** and rationalize their formation.
Answers: The aminophosphonate **7** is being formed the same way as before. In the presence of π -Lewis acid such as AgOTf or CuI, the nitrogen cyclizes on the alkyne through a 6-endo-dig cyclization to form the hydroisoquinoline **6**. Whereas when using oxophilic (also called σ -)Lewis acid (FeCl_3 , $\text{In}(\text{OTf})_3$...) the linear aminophosphonate **7** is obtained exclusively.



Notes: See *J.Org.Chem.* **2007**, 72, 21, 7817-7831) for more information about σ and π -electrophilic Lewis acid.