

Topics in Current Chemistry

Fortschritte der
chemischen Forschung

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Preparative Organic Chemistry

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Aldol Condensations

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Dihetero-tricyclodecanes

G. Henrici-Olivé · S. Olivé

Olefin Insertion in Transition

Metal Catalysis



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This series presents critical reviews of the present position and future trends in modern chemical research. It is addressed to all research and industrial chemists who wish to keep abreast of advances in their subject.

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Old and New in the Field of Directed Aldol Condensations

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This paper was presented as a lecture at the meeting of the Gesellschaft Deutscher Chemiker in Köln on September 10, 1975.

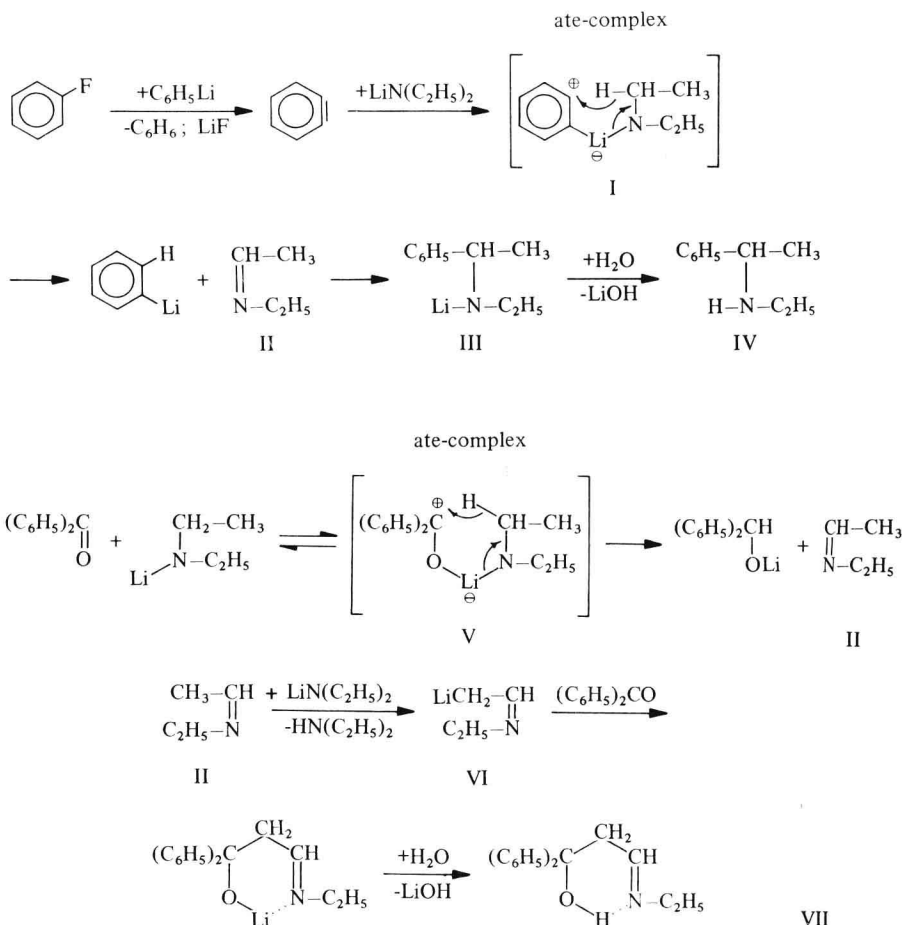
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1. Introduction

In connection with the investigation of 1,2-dehydrobenzene, phenyllithium was reacted with fluorobenzene in the presence of diethylamine¹⁾. As expected diethylaniline was among the reaction products, resulting from the addition of diethylamine to dehydrobenzene, as well as α -phenyldiethylamine IV. A more detailed investigation of these results showed that the lithiumdiethylamide which developed during the reaction also added to the intermediate dehydrobenzene forming the non-isolable ate-complex I. The anionic loosening of ligands in the neighbourhood of nitrogen causes a hydride transfer which results in the formation of phenyllithium and Schiff base II. These compounds combine irreversibly by addition of the organolithium to the C=N-bond producing lithiumamide III, which following hydrolysis yields α -phenyl-diethylamine IV.

In order to establish the reducing agent function of the dialkylamide it was reacted with benzophenone²⁾. We expected a reduction by way of the ate-complex V



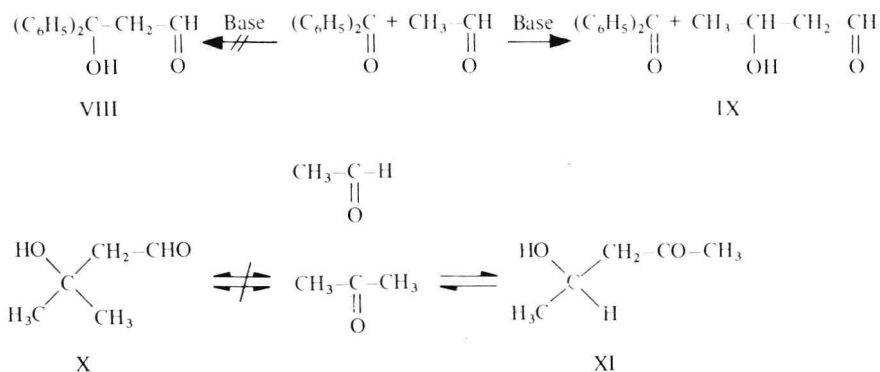
to benzhydrol coupled with the oxidation of the amine to Schiff base II. Although following hydrolysis, approximately 35% yield of benzhydrol was isolated; a complicated compound was obtained instead of ethyldienethylamine II. A meticulous structural determination and a later synthesis showed the unexpected compound to be the Schiff base VII, *i.e.* the aldimine adduct with benzophenone.

Evidently a fraction of the benzophenone is reduced to benzhydrol in a redox reaction in which an equivalent amount of Schiff base II is formed. After metallation of II by the remaining lithiumdiethylamide, the metallated Schiff base VI reacts with the reduced benzophenone to yield the aldimine adduct VII. Surprisingly, the entire process is completed within one minute at 0 °C.

Since the final product can be easily converted with a mineral acid to β -phenylcinnamaldehyde, the total reaction is an aldol condensation. The methyl group of the acetaldehyde is specifically condensed with the carbonyl group of the ketone. This opportunity of achieving a directed aldol condensation was now put into practice and the method was quickly shown to be capable of a wide application with generally high yields.

Previously, it was not possible to control the aldol condensation so that aldehydes would combine with the carbonyl groups of ketones with their α -CH-groups. For example, acetaldehyde does not react with benzophenone under the usual base catalyzed conditions to give adduct VIII because the aldehyde undergoes a much more rapid self addition to acetaldol IX.

Even the reaction with more active ketones, such as acetone, does not lead to adduct X but, as has been proven, to compound XI. Acetaldehyde has the more easily accessible carbonyl group and acetone, following anionization, possesses the more strongly nucleophilic α -carbon.

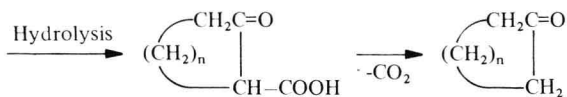
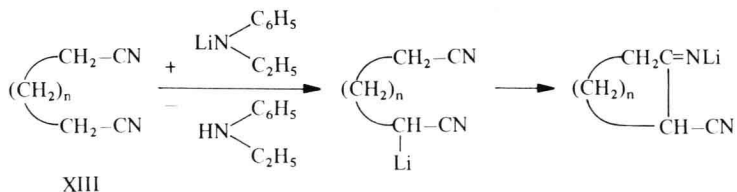
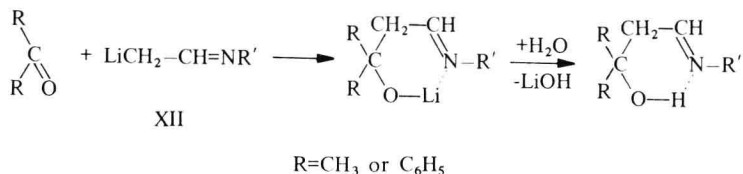


2. Directed Aldol Condensation

2.1. General Procedure for Directed Aldol Condensation

As the aldol condensation described at the outset has clearly shown, these difficulties can be avoided if the aldehyde carbonyl group is converted to an azomethine group.

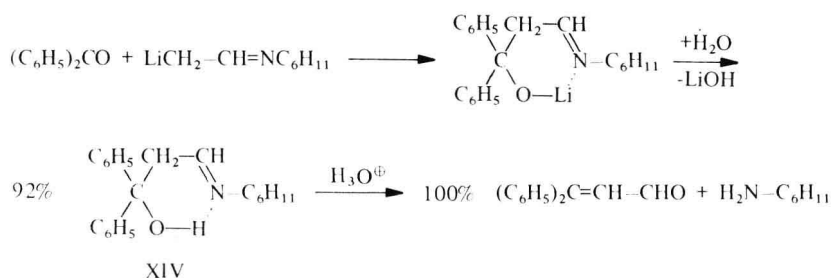
This Schiff base is metallated with an appropriate lithium compound to XII and subsequently reacted with benzophenone or acetone. Since the protective group can be removed following the aldol addition, this method is a means of bringing about organometallic directed aldol condensations³⁾.



In this connection it should be remembered that Karl Ziegler⁴⁾ had already used metallated secondary amines for condensation purposes. For the synthesis of larger ring compounds he applied the lithium ethylanilide in a type of Dieckmann reaction to ring close dinitriles, such as XIII. Since the metallated amine is soluble in ether, he succeeded in forcing the cyclization by the principle of dilution.

The resulting product led to cyclic ketones such as Exaltone (Cyclopentadecanone) or Dihydrocivetone (Cycloheptadecanone) in yields of 60–70%, after hydrolysis with saponification of the ketimine group and cleavage of CO₂. What an ingenious move in a successful operation!

Returning to our problem, we determined the following optimal conditions under which the metallation of the Schiff base and the succeeding reaction with carbonyl compounds, to give the aldime adducts, should proceed. Cyclohexylamine has proved to be effective as the amine component of the Schiff base, because Schiff bases with branched alkyl substituents on nitrogen have a lesser tendency of self-addition than those with unbranched groups. Further, it was shown, also for steric reasons, that lithium diisopropylamide was a more appropriate metallating agent than lithium diethylamide. When accordingly, ethylidene cyclohexylamine was reacted with lithium diisopropylamide in ether at 0 °C and after 10 minutes benzophenone was added at –70 °C, the Schiff base XIV could be recovered in 92% yield following hydrolysis⁵⁾.



These favourable results can probably be traced back to the stable chelates formed by the lithium salts of the aldol adducts. In the hydrolysis product the nitrogen of the aldimine group is linked through an intramolecular hydrogen bond bridge, as was established by the IR spectrum. Since the aldimine adduct could finally be converted by treatment with acid in a nearly quantitative yield to β -phenylcinnamaldehyde, the preparative problem of subjecting aromatic ketones to the directed aldol condensation was solved.

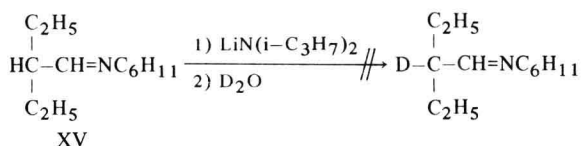
However, even in the singularly smoothly operating directed aldol condensation with aromatic ketones, there is no such thing as perfection. In order to determine the influence of inductive and steric effects on the new process, the Schiff bases of α -substituted acetaldehydes were metallated under the standard conditions with lithium diisopropylamide, and the aldimine adducts with benzophenone were isolated. Table 1⁶⁾ shows the measured yields.

Table 1

Schiffbase	Aldimine-adduct	m. p.
$\text{CH}_3\text{--CH=NR}$	92%	127–128°
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2\text{--CH=NR} \end{array}$	91%	82–83°
$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{CH}_2\text{--CH=NR} \end{array}$	71%	104–105°
$\begin{array}{c} \text{CH}_3 \\ \\ \text{HC--CH=NR} \\ \\ \text{CH}_3 \end{array}$	29%	107–108°
$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{HC--CH=NR} \\ \\ \text{C}_2\text{H}_5 \end{array} \text{ XV}$	0%	

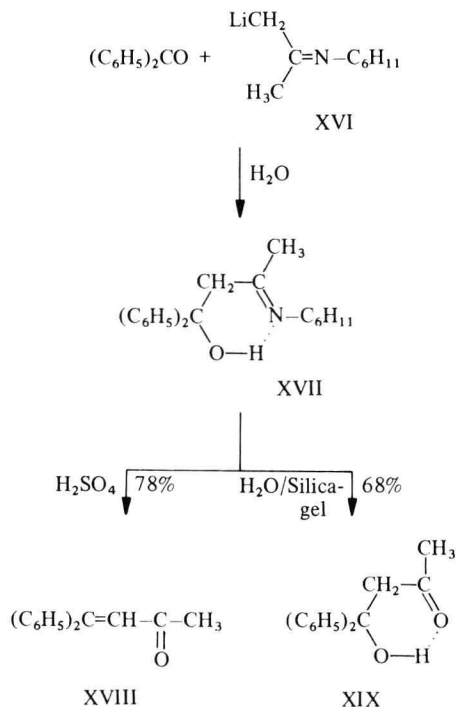
According to these values, the yields decrease with increasing branching on the α -carbon of the Schiff base until they reach 0% with 2,2-diethyl-ethylidene cyclohexylamine XV.

The basis for these findings can be shown by the following: When the Schiff base XV was treated with lithium diisopropylamide for two hours in ether (the Schiff base of the unsubstituted acetaldehyde is instantly metallated in ether) and then reacted with D_2O , the starting material XV was recovered almost quantitatively. Since the compound does not contain any deuterium, as shown by NMR, it can be concluded that it was not metallated.



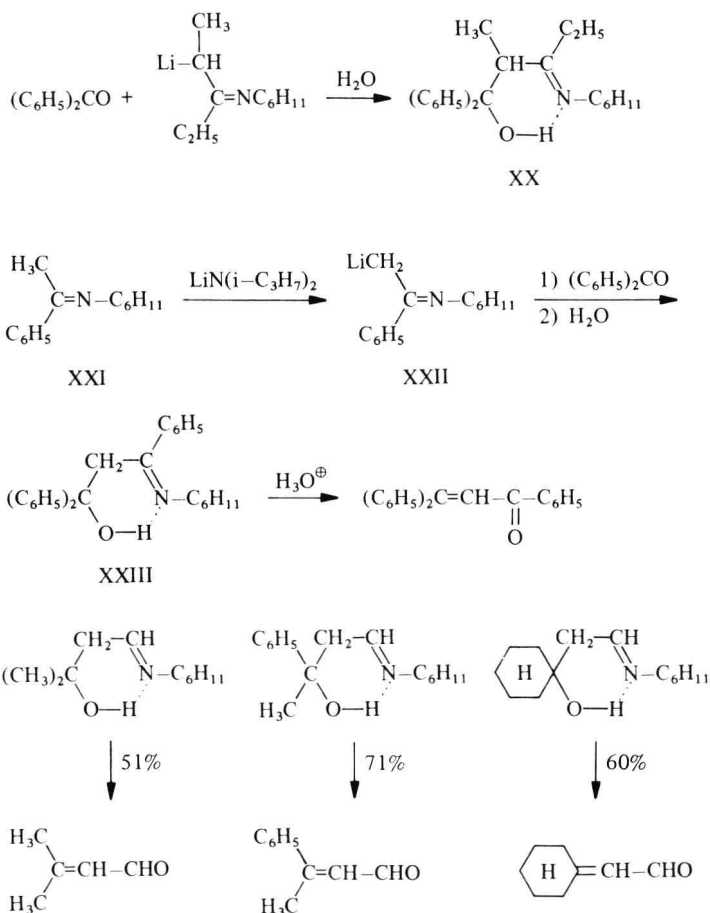
The increasing alkylation of the aldimine leads to a reduced suitability for being metallated. This is likely to be explained by the interaction of the growing steric hindrance and the hyperconjugation effect which lowers the mobility of the α -proton.

The Schiff bases of ketones can also be condensed with aromatic ketones, such as benzophenone, by the method under discussion⁷⁾. Using the standard conditions, isopropylidene cyclohexylamine was metallated to XVI and combined with benzophenone. The ketimine adduct XVII could be isolated in 65% yield. Following the decomposition of XVII with diluted sulphuric acid the unsaturated ketone XVIII was recovered. It proved to be identical with a comparable compound which was synthesized by a more cumbersome procedure. The nitrogen free ketol could also be obtained from XVII. During thin layer chromatography of XVII on silica gel, benzo-



phenone was found as well as a compound with a shorter path of travel. This substance had a melting point of 85 °C and the elemental formula $C_{16}H_{16}O_2$. On the basis of the NMR spectrum and the proton ratios ($CH_{\text{aromatic}} : OH : CH : CH_3 = 10 : 1 : 2 : 3$), it is the previously unknown ketol XIX.

By reaction of the Schiff base of the homologous diethylketone with benzophenone, the ketimine adduct XX could indeed be isolated in 60% yield, but the respective ketol could not be obtained by thin layer chromatography. The same lack of success resulted from the attempted acid decomposition of XX to the corresponding unsaturated ketone. In both cases only benzophenone was recovered because here the branching from the α -carbon atom also counteracts the stability of the ketol adduct.



The Schiff base of acetophenone XXI, after anionization with lithium diisopropylamide to the deep yellow solution of XXII, led to the adduct XXIII (55% yield) upon combination with benzophenone. Treatment with diluted mineral acid converted XXIII in 95% yield to 1,1-diphenyl-2-benzoylethylene⁶⁾.

At first this new technique of adding metallated Schiff bases appeared problematical for the possible synthesis of natural products, because during its application to methylketones, such as β -ionone, it could be expected that the proton active $-\text{COCH}_3$ system would undergo a transmetallation or transanionization with the metallated Schiff base. Fortunately, this was not the case³⁾, as was shown by model experiments with acetone, acetophenone, and cyclohexanone.

2.2. Application to the Synthesis of Natural Products

In general, the aldimine adducts of natural products can be converted in one step to the corresponding α , β -unsaturated aldehydes or ketones. They are subjected to a steam distillation in the presence of oxalic acid, in which the final product distils over. Under these conditions the more thermodynamically stabile product is formed, usually the trans olefin.

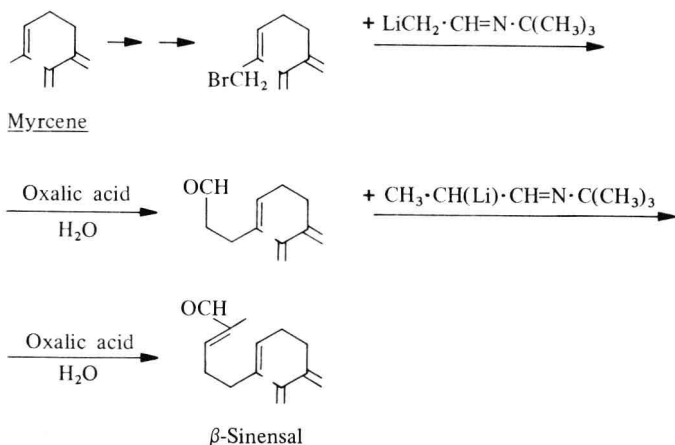
The compounds listed in Table 2 can be synthesized relatively simply by the method under discussion⁷⁾. The yields given relate to the starting aldehyde or ketone.

Table 2

Carbonyl component	Aldimine adduct m. p. and yield	α , β -Unsaturated aldehyde b.p. and yield
Butyraldehyde		2-Hexene-1-al, (Leafaldehyde) b.p. ₁₅ 42–48 °C, 65%
β -Cyclocitral	92–93 °C 58%	β -Cyclocitrylidene-acetaldehyde b.p. _{0.1} 72.5–75 °C, 50%
6-Methyl-5-heptene-2-one	32–33.5 °C 76%	Citral (<i>cis-trans</i> -mixture) b.p. _{0.5} 68–74 °C, 64%
β -Ionone	46–47 °C 80%	β -Ionylidene-acetaldehyde b.p. _{0.001} 115–120 °C, 42%

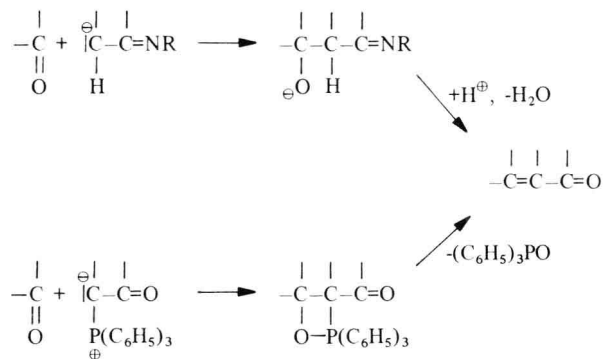
The β -cyclocitrylidene acetaldehyde synthesized in this way was recovered for the first time in crystalline form. The two aldehydes, citral and β -ionylidene acetaldehyde, are of special value because they are intermediate products in the synthesis of Vitamin A and other carotinoids.

Also worth mentioning is a natural product synthesis performed by Büchi⁸⁾. It concerns β -sinensal, a constituent of the aroma of the chinese orange. Starting from myrcene, the bromination derivative was prepared in two steps. This was condensed with the metallated Schiff base, derived from ethylidene-*t*-butylimide and lithium diisopropylamide, and hydrolyzed to the aldehyde in 60% yield with aqueous oxalic acid. The resulting aldehyde was now reacted with metallated propylidene-*t*-butylimide, in the same way as the directed aldol condensation, and again hydrolyzed with aqueous oxalic acid (60% yield). The final product was identical in all properties with the naturally occurring β -sinensal. Through chemical modification of the intermediate product it was proven, that the sesquiterpene has the trans-trans configuration.



3. Directed Aldol Condensation and Modified Carbonyl-Olefination with Phosphorus Ylids – a Comparison

The essential point of the directed aldol condensation⁹⁾ is that it makes a desired extension of the chain of an aldehyde or ketone to an α,β -unsaturated ketone or aldehyde possible. It could be argued that such a chain extension is also possible by means of an olefination using phosphorus ylids. Certainly, this latter method has a broad range of application and it was used by Trippett¹⁰⁾ to obtain α,β -unsaturated aldehydes similar to those under discussion. It has an added advantage in that the dehydration of the carbonyl-alcohol resulting from the directed aldol condensation, which does not always progress smoothly, can be avoided.



However, the olefination by way of the phosphorus ylid also has its disadvantages particularly in this sphere. The scope of both methods is compared in Table 3⁹⁾ in which the yields, as before, are based on the starting aldehyde or ketone.

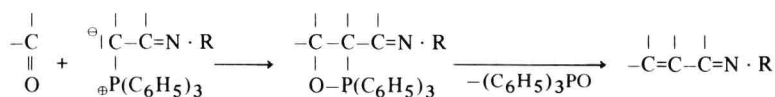
It is readily apparent that the olefination through the phosphorus ylid gives good results with aldehydes as the substrate. On the other hand, it fails utterly when ap-

Table 3

Final product	Prepared by	
	directed aldol condensation	phosphorus ylids
$\text{CH}_3\text{--CH}_2\text{--CH}_2\text{--CH=CH--CHO}$	65%	81%
$\text{C}_6\text{H}_5\text{--CH=CH--CHO}$	72%	60%
$(\text{CH}_3)_2\text{C=CH--CHO}$	40%	0%
$\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{C=CH--CHO} \\ \diagup \\ \text{CH}_3 \end{array}$	71%	0%
$(\text{C}_6\text{H}_5)_2\text{C=CH--CHO}$	78%	0%
$\begin{array}{c} \text{CH}_3 \\ \\ (\text{C}_6\text{H}_5)_2\text{C=C--CHO} \end{array}$	81%	0%
$\begin{array}{c} \text{CH}_3 \\ \\ (\text{C}_6\text{H}_5)_2\text{C=CH--C=O} \end{array}$	50%	0%

plied to ketones. It is just these condensations with ketones which are made possible by the directed aldol condensation using metallated Schiff bases. It thus finds its proper sphere of application.

The reason for the failure of the carbonyl-olefination with ketones by way of the phosphorus ylid lies in the resonance stabilization of the ylid. The charge distribution is concentrated in the direction of the oxygen atom. Therefore, it also appeared fitting here to introduce a C=N--R group in place of the C=O group in phosphorane.



4. Combination of the Directed Aldol Condensation and the Carbonyl-Olefination with Phosphorus Ylids

This idea, published by us in 1968⁹⁾, has in the meantime (in 1969), been put into practice by Japanese scientists¹¹⁾.

The phosphonate XXIV was converted to the respective ylid with sodium hydride and yielded on reaction with ketones or aldehydes the corresponding Schiff bases XXV. These products, in contrast to the aldehyde or ketimine adducts with their intramolecular hydrogen bonds, can easily be converted to the unsaturated carbonyl compound in good yield.

Since the realization of our ideas concerning the triphenylphosphoranes has only recently begun and the experimental work is not yet finished, I can only give a short preliminary report on the subject¹²⁾.