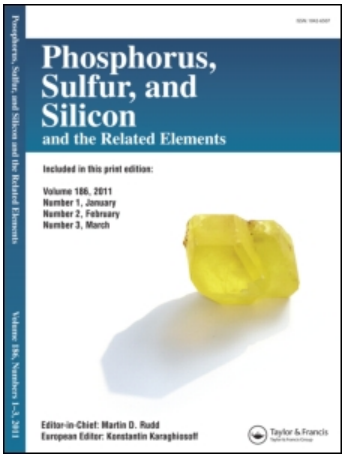

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Chelate Complexes with the P=O-Double Bond - A New Concept for Asymmetric Synthesis

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A new strategy for asymmetric synthesis uses highly efficient cyclic phosphorus amidate auxiliaries capable of forming a rigid chelate complex with a metal enolate.

Keywords: asymmetric synthesis; phosphorus amidates; cyanohydrins; amino acids

Cyanohydrins can be regarded as umpoled carbonyl compounds, because their deprotonation results in formation of cyanohydrin carbanions so that the a^1-carbonyl reactivity has been switched to d^1.[1] If these reactive intermediates are allowed to react with electrophiles, at least one new stereogenic center is formed at the α-C-atom of the cyanohydrin; often several stereocenters are created according to the choice of the appropriate electrophile (Figure 1). Effective stereocontrol of this umpolung reaction opens the path to a wide variety of optically active compounds, which are otherwise only obtained with difficulty.[2] To the best of our knowledge a stereoselective version of this important C-C-bond formation has not been reported to date.

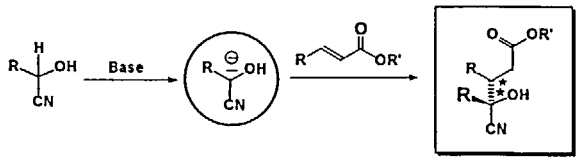

FIGURE 1. Example for the stereochemical potential of cyanohydrin alkylations.

We have recently presented a solution for the above-mentioned problem by linking the cyanohydrin-oxygen with a chiral cyclic phosphate (Figure 2).[3] Deprotonation results in formation of a lithiated keteneimine which is conformationally locked by means of a Li-*O*- (and perhaps a Li-*N*)-chelate. Thus, one diastereotopic face becomes sterically shielded and the attack of an electrophile should be directed towards the opposite face. After alkylation, it should be possible to remove the auxiliary hydrolytically by selective P-O-cleavage. This sequence outlines our new concept for asymmetric synthesis: reversible linkage of a *P*-chiral auxiliary to the substrate, generation of a metallated reactive intermediate with a metal-P=O-chelate, that undergoes a diastereoselective transformation, and final recycling of the auxiliary. The synthetic potential of auxiliaries based on chiral phosphonates or phosphonamides would thus be substantially enlarged.[4]

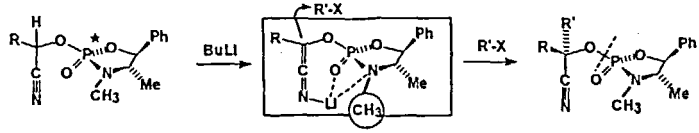

FIGURE 2. The new concept applied to the alkylation of cyanohydrin phosphates.

Reactions of ephedrine derivatives with phosphoryl chloride lead to intermediates, which are esterified in the same pot with a racemic cyanohydrin (e.g. benzaldehyde cyanohydrin) with complete retention of configuration at the stereogenic phosphorus atom (Figure 3). The acidic α-proton can then be mildly removed with *n*-butyllithium; the resulting carbanion is alkylated by many different electrophiles. Thus, tertiary cyanohydrin phosphates are obtained with up to 94% *de*. Among others, long chain alkyl, benzyl, phenylalkyl, propargyl, and especially allyl rests can be attached to the cyanohydrin in good chemical and very good optical yields. Almost every ketone cyanohydrin phosphate can be obtained in diastereomerically pure form after one single recrystallization step. The *(R)*-configuration at the cyanohydrin α-C-atom could be proven by X-ray structure analysis; it corresponds to the predicted conformation of the reactive intermediate. So, the attack of the electrophile was indeed directed towards the opposite face of the lithiated keteneimine.

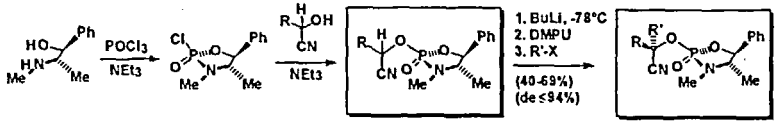

FIGURE 3. Synthesis and alkylation of aldehyde cyanohydrin phosphates.

For the regioselective cleavage of the cyanohydrin phosphates we use a mild Lewis acid activation by titanium chloride triisopropoxide (Figure 4). Subsequent addition of water produces a two-layer-system, which contains only the free ketone cyanohydrin in the organic phase. From the aqueous phase the ring-opened primary product shown below is isolated. In this manner the free optically active ketone cyanohydrins are obtained in high yields. From the primary product pure (+)-pseudoephedrine can be recycled with 5 N hydrochloric acid.

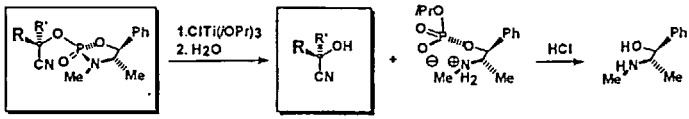

FIGURE 4. Cleavage to free ketone cyanohydrines and recycling of the auxiliary.

The optical purity of the final products could be proven by NMR-experiments with TADDOL as shift reagent.[5] To prove the expected retention of configuration in the hydrolysis step, we converted the optically active acetophenone cyanohydrin into the corresponding 1,3-oxazolidin-4-one, which showed a positive specific rotation *[α]* corresponding to the the literature value for the *R*-compound.

Recently we found that under Pd-II-catalysis the olefinic cyanohydrin phosphates undergo a highly stereospecific rearrangement which leads to phosphate protected γ-hydroxy methacrylic nitriles (Figure 5). The cyanoallylphosphate moiety is perfectly designed for a [3,3]-sigmatropic rearrangement, which would be in our case the first example of a Phospha-Claisen-version.[6]

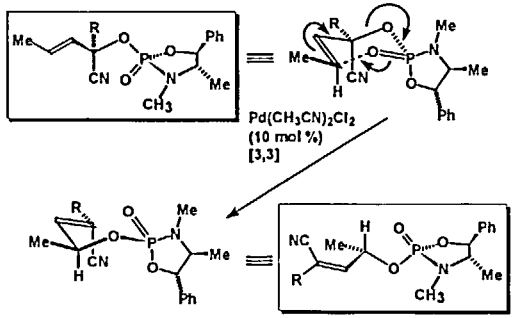

FIGURE 5. Pd-II-catalyzed rearrangement of α-cyanoallylphosphates.

Can we transfer the concept of conformationally locking a reactive intermediate by the P=O double bond to other asymmetric syntheses? If the hydroxyl group of a cyanohydrin is replaced by an amine and the nitrile by a carboxylic acid, the basic structure of an amino acid comes out. The shortest possible version of an asymmetric amino acid synthesis with internal asymmetric induction attaches the chiral auxiliary as *N*- or *C*-terminal protecting group to glycine. In our three-step procedure we protect sarcosine with a bicyclic auxiliary based on the renewable ressource glutamic acid (Figure 6).[7] Mild deprotonation with sodium hexamethyldisilazide generates the ester enolate which is alkylated by methyl iodide with a high chemical yield and a *de* of 92%. Final hydrolysis should afford the free amino acid and the auxiliary, which may be recycled. To our surprise, we were not able to alkylate the ester enolate with higher homologous alkyl halides. Even allyl iodide as well as tosylates and triflates did not react. In the future we will therefore use C_2-symmetrical auxiliaries with a smaller steric demand based on binaphthol or TADDOL. Alternatively we will replace the *N*-methyl group by a "slim" oxygen atom in order to develop a new strategy for the synthesis of α-hydroxy carboxylic acids.

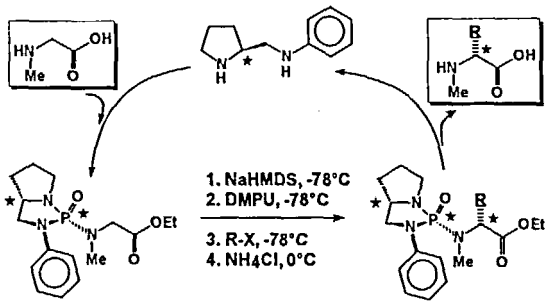

FIGURE 6. Asymmetric synthesis of *N*-methyl-α-amino acids.

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