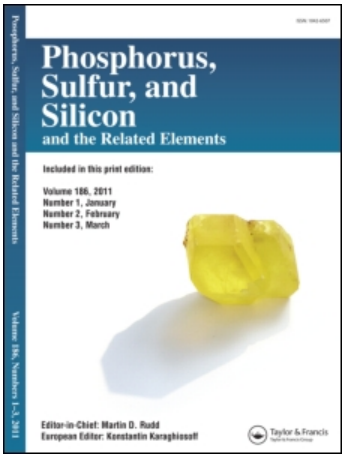

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Asymmetric Induction by Chiral Phosphorus

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ASYMMETRIC INDUCTION BY CHIRAL PHOSPHORUS

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We report on the asymmetric induction by a chiral phosphorus atom contained in a 2-oxo-1,3,2-oxazaphosphorinane ring into an adjacent keto, alkane, or alkene function.

Keywords: α-Ketophosphonate; asymmetric; oxazaphosphorinane; vinyl phosphonate

The objective of our research program is to develop asymmetric carbon-carbon bond-forming reactions of organophosphorus reagents containing a chiral phosphorus atom. We are studying the reduction and alkylation of asymetric α-ketophosphonates, such as 2-alkanoyl and 2-aroyl-2-oxo-1,3,2-oxazaphosphorinanes, because this functionality has a rich chemistry[1] which can be further exploited to prepare a wide range of interesting structural motifs. We are also interested in the chemistry of asymmetric vinyl phosphonates. Nucleophilic addition to this function gives asymmetric β-substituted phosphonates, which can take part in a Horner-Wittig reaction to afford structural motifs found in many terpenoid natural products.[2]

SYNTHESIS, CONFORMATIONS, AND REACTIONS OF 2-ALKANOYL AND 2-AROYL-2-OXO-1,3,2-OXAZAPHOSPHORINANES

2-Alkanoyl and 2-aroyl-2-oxo-1,3,2-oxazaphosphorinanes were prepared by an Arbuzov reaction of the corresponding 2-ethoxy-1,3,2-oxazaphosphorinanes and acid chlorides (Scheme 1).[3–5]

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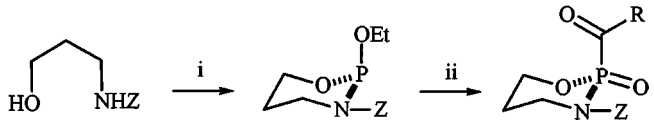
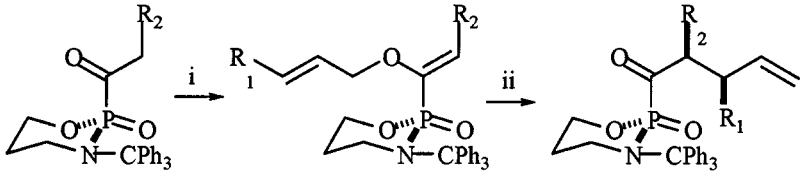


SCHEME 1 Reagents and conditions: i, $(EtO)PCl_2$, Et_3N, CH_2Cl_2; ii, Aroylchloride or alkanoylchloride (excess).

The structure of a number of these α-ketophosphonates was studied by crystallography.[5] The key structural features of these compounds is that, except when the nitrogen substituent is a trityl group, the ring adopts a pseudo-chair conformation. When the nitrogen substituent is a trityl group, the ring adopts a twisted boat conformation. In either case, the P=O bond occupies a psuedo-equatorial position[5,6] and adopts a gauche or antirelationship with the C=O bond.

We expected that the chirality at the phosphorus atom in 2-alkanoyl- and 2-aroyl-2-oxo-1,3,2-oxazaphosphorinanes would result in an asymmetric reduction of the adjacent C=O function. This has proved to be true, although to date the levels of diastereoselectivity remain modest (about 50% de). Similarly, [3,3]-sigmatropic rearrangement of phosphoenol ethers afford asymmetric α-ketophosphonates with good diastereoselectivity (Scheme 2).

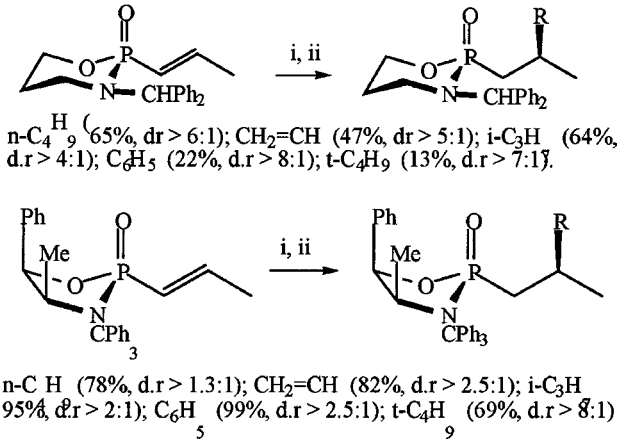


SCHEME 2 Reagents and conditions: i, KHMDS, THF, 0°C, R_2 CH=CHCH$_2$Br; ii, Toluene, reflux, 5 h.

ASYMMETRIC NUCLEOPHILIC ADDITION TO 2-PROPENYL-2-OXO-1,3,2-OXAZAPHOSPHORINANES

We have previously reported on the nucleophilic additions to chiral vinylphosphonates using organocuprates, with chlorotrimethylsilane and tetramethylethylenediamine as rate-accelerating additives.[7,8] The diastereomeric purity of the products, after chromatography and a single crystallization from petroleum ether, were excellent (Scheme 3).[8a]

We have also investigated addition to enantiopure vinyl phosphonates derived from N-trityl-(1R,2S)-norephedrine. The S_P isomer was



SCHEME 3 Reagents and conditions: i, RMgBr, CuI, TMSCl, TMEDA, −78°C to −10°C; ii, TBAF, THF, r.t.

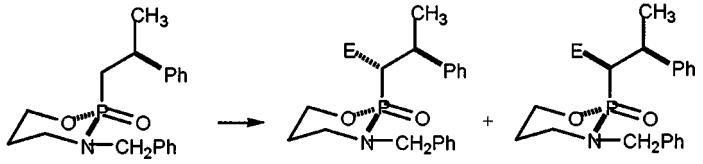
isolated as a single enantiomer. However, the diastereoselectivity of the additions to this five-membered ring analogue proved significantly less than the six-membered ring analogue.[9]

ALKYLATION OF 2-OXO-1,3,2-OXAZAPHOSPHORINANES

As described before, we intend to use the asymmetric β-substituted phosphonates prepared in the previous section in Horner-Wittig reactions. As a preamble to this study, we were interested in investigating the diastereoselectivity of the reaction of these phosphorus stablized anions with electrophiles.

We prepared a series of 2-alkyl-2-oxo-1,3,2-oxazaphosphorinanes with and without a substituent at their β position and investigated the diastereoselectivity in the alkylation at the α position.

Alkylation of 2-alkyl-2-oxo-1,3,2-oxazaphosphorinanes without a substituent at their β position proceeds with good selectivity. This selectivity is influenced by the steric bulk of the nitrogen substituent as expected. Stereochemistry of the β-substituent either enhances (in the case of R,R/S,S pair) or counteracts (in the case of R,S/S,R pair) the stereoselectivity arising from the asymmetric phosphorus atom itself. Cooperative effects from the chirality of the phosphorus atom and its β substituent results in excellent degrees of stereoselectivity in these reactions (Scheme 4).



E = Allyl (35%, d.r. > 15); E = Me (58%, d.r. > 4); E = Bn (38%, d.r. > 7);
E = Me_3Si (44%, d.r. =1)

SCHEME 4 Reagents and conditions: LDA, toluene, E-Br −78°C to 0°C.

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