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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t713618290

Double Asymmetric Induction as Method for the Synthesis of Chiral Organophosphorus Compounds

Oleg I. Kolodiazhnyi^a

^a National Academy of Sciences of Ukraine, Ukraine

Online publication date: 27 October 2010

To cite this Article Kolodiazhnyi, Oleg I.(2002) 'Double Asymmetric Induction as Method for the Synthesis of Chiral Organophosphorus Compounds', Phosphorus, Sulfur, and Silicon and the Related Elements, 177:8,2111-2114

To link to this Article: DOI: 10.1080/10426500213410 URL: http://dx.doi.org/10.1080/10426500213410

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Phosphorus, Sulfur and Silicon, 2002, Vol. 177:2111–2114 Copyright © 2002 Taylor & Francis 1042-6507/02 \$12.00 + .00

DOI: 10.1080/10426500290094837



DOUBLE ASYMMETRIC INDUCTION AS METHOD FOR THE SYNTHESIS OF CHIRAL ORGANOPHOSPHORUS COMPOUNDS

Oleg I. Kolodiazhnyi National Academy of Sciences of Ukraine, Ukraine (Received July 29, 2001; accepted December 25, 2001)

New examples of multistereoselective syntheses of organophosphorus compounds are described.

Keywords: Asymmetric Michael addidion; chiral aminophosphonic acids; chiral phosphoric acid esters; double asymmetric synthesis; multistereoselectivity

Multistereoselectivity is the reaction process proceeding under the control of several chiral auxiliaries effecting the asymmetric induction. Stereoselectivity of reagents can be estimated as a difference of reaction rates or activation energies leading to two opposite stereoisomers.^{1,2}

The individual diastereofacial preferences of the two chiral reactants may reinforce one another (matched asymmetric synthesis (AS)), or, on the contrary, oppose one another (mismatched AS).

In the present work the following versions of multistereoselective syntheses have been studied:

- a chiral reagent reacts with a chiral substratum;
- a chiral reagent containing two chiral auxiliaries reacts with an achiral substratum; and
- · AS of a chiral reagent in the presence of asymmetric catalyst.

Thus, the addition of chiral di-and trialkylphosphites (R*O=Menthyl, Bornyl, Gluco-D-furanosyl) to chiral C=N compounds is accompanied by double asymmetric induction at the α -carbon atom,

This work is supported by the State Foundation of Basic Research of Ukraine (DFFD). Address correspondence to Oleg I. Kolodiazhnyi, Institute of Bioorganic Chemistry, National Academy of Sciences of Ukraine, Murmanska, 1, Kyiv, 02094, Ukraine. E-mail: oikol123@bpci.kiev.ua

FIGURE 1

with formation of optically active aminophosphonic acid ethers of $\sim\!100\%$ de in case of reagents having matched asymmetric induction and of 80% de in case of reagents possessing mismatched asymmetric induction. The reaction of di- and trimenthylphosphites gives aminophosphonic acids of opposite configuration, that allows to prepare all four possible diastereomers. The menthyl esters by acidic hydrolysis were converted to N-substituted aminophosphonic acids and then by catalytic hydrogenation under Pd/C to 1-aminobenzylphosphonic acids. 3,4

Addition of chiral esters of trivalent phosphorus acids to chiral esters of crotonic or cinnamic acids proceeds more stereoselectively than in the case when only one of these reagents is chiral. The reaction of dimenthyl phosphite with menthyl crotonoate proceeds with $\sim\!96\text{--}98\%$ stereoselectivity. 2,5

MntO
$$POX + RCH=CHCO_{2}R' \longrightarrow (MntO)_{2}P(O) \qquad OR'$$

$$MntO$$

$$X= Na, ZnEt$$

$$MntO$$

$$R'=Mnt, de = 96.98\%$$

$$HCI$$

$$(HO)_{2}P(O)$$

$$R'$$

$$R'=Mnt, de = 96.98\%$$

$$HCI$$

$$(HO)_{2}P(O)$$

$$R'$$

FIGURE 2

$$(R^*O)_3P \xrightarrow{a} R^*O \xrightarrow{D} (HO)_2P(O) \xrightarrow{D} (HO)_2P(O) \xrightarrow{D} NO_2 \xrightarrow{C} (HO)_2P(O) \xrightarrow{NH_2} Ph$$

 $R^* = (1R, 2S, 5R)$ -menth-2-yl (+)-(R) a = BF₃ Et₂O; b = Me₃SiBr; H₂O; c H₂/Ni(Re)

FIGURE 3

The addition of nitrostyrene to trimenthylphosphite leads to the formation of optically active β -nitroalkylphosphonates and β -aminophoshonic acids 3,5.²

Reduction of dimenthyl acylphosphonate with LiAlH₄ or NaBH₄ affords a mixture of chiral (R)- and (S)-diastereomers in the ratio of $\sim 3:1.^5$ Meantime catalytic hydrogenation of the acylphosphonate by complex of lithium alumohydride with chiral ligand (A = cinchonin or cyclohexylidene 1,2-gluco-D-furanose) furnishs predominantly one diastereomer of dimenthyl 1-oxybenzylphosphonic acid.⁵

This diastereoface selectivity is explained by effect of menthyl group of the compounds which closes one of the sides of carbonyle group in such a manner that *Si*-side of ketone is shielded more than *Re*-party and lithium alumohydride attacks preferentially this side.

Chiral reagents containing two asymmetric auxiliaries in one molecule, increasing asymmetric induction, are especially interesting. ⁶ Thus, the lithium derivative of Schiff base, formed from (R)- camphor and diethyl aminomethanephosphonate, was allowed to react with alkyl and benzyl halides to yield the corresponding esters of (S)- α -aminoalkanephosphonic acids.

Acidolysis of the chiral di-alkylaminophosphines by formic acid leads in good yield to the formation of optically pure phosphonic acid amides.^{7–9}

So multistereoselectivity represents effective methodology to increase the asymmetric synthesis of chiral organophosphorus compounds using in one reaction two or three asymmetric auxiliaries

FIGURE 4

$$\begin{array}{c} O \\ O \\ O \\ O \\ O \\ \end{array} \begin{array}{c} O \\ P \\ \end{array} \begin{array}{c} O \\$$

FIGURE 5

R*= (S)- or (R)-CH*(Me) Ph or (R)-CH*(Bu-i)CO₂Me

FIGURE 6

reinforcing one another. In some cases this methodology allows to increase the stereoselectivity of reactions up to 100% de.

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