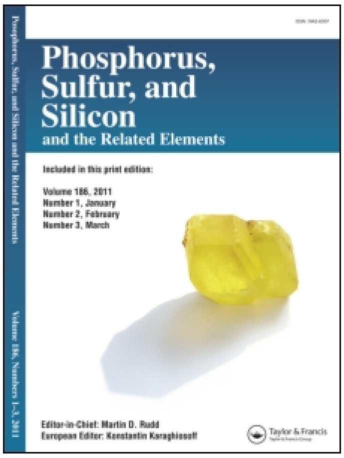

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Phosphinoglycines and Phosphinoglycolates

J. Heinicke[a]; J. Lach[a]; N. Peulecke[a]; P. G. Jones[b]; I. Dix[c]
[a] Institut für Biochemie—Anorganische Chemie, Universität Greifswald, Greifswald, Germany [b] Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Braunschweig, Germany [c] Institut für Anorganische Chemie, Universität Göttingen, Göttingen, Germany

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Phosphinoglycines and Phosphinoglycolates

J. Heinicke,[1] J. Lach,[1] N. Peulecke,[1] P. G. Jones,[2] and I. Dix[3]
[1]Institut für Biochemie—Anorganische Chemie, Universität Greifswald, Greifswald, Germany
[2]Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Braunschweig, Germany
[3]Institut für Anorganische Chemie, Universität Göttingen, Göttingen, Germany

We describe an easy one-pot three-component access to novel asymmetric α-phosphino amino acids and α-phosphino glycolates; properties, crystal structures, reactions, and examples of use in transition metal catalysis are presented.

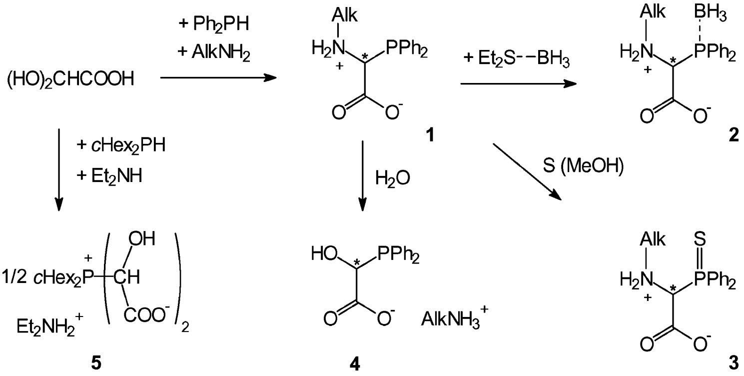
Keywords Amino acids; asymmetric phosphines; diastereoselectivity; glycolates; transition metal catalysis

Phosphino-substitution of α-amino acids offers a tool for generating asymmetric phosphine ligands from the natural pool of chiral compounds. Early reports concern the phosphinomethylation of α-amino acids at the nitrogen atom by secondary phosphines and formaldehyde,[1] later extended to primary phosphines yielding heterocyclic condensation products.[2–4] In the late 1990s, first examples of phosphinylation at carbon atoms of the α-amino acids in β-, γ- and δ-position to the chiral α-CH center were reported. Some were introduced into small peptides and tested in transition metal catalysis.[5–11]

We recently found a simple way to synthesize α-phosphino α-amino acids **1** by one-pot three-component condensation of secondary phosphines with primary amines and glyoxylic acid. The compounds allow derivatization by reaction in methanol (e.g., addition of BH_3 or oxidation with sulfur at phosphorus to **2** and **3**) but are easily hydrolyzed by water to **4**. Decarboxylation occurs in tetrahydrofuran (THF) and rapidly in hot $CDCl_3$. Crystalline **1** decarboxylates only on heating above 100°C.

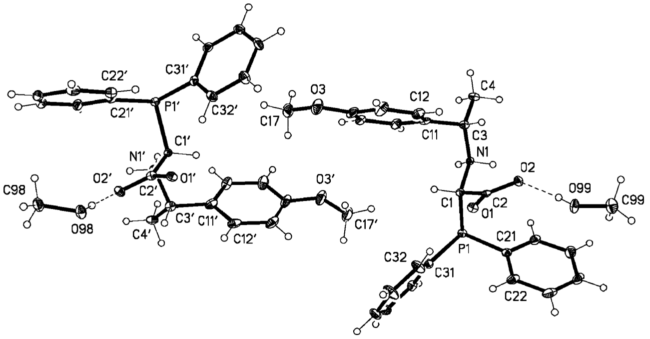
Address correspondence to J. Heinicke, Institut für Biochemie—Anorganische Chemie, Universität Greifswald, D- 17487 Greifswald, Germany. E-mail: heinicke@uni-greifswald.de

Secondary amines do not usually form phosphino amino acids but tend to furnish diorganoammonium phosphonium bis(glycolates) **5**. Combinations of **1**, **2**, **4,** or **5** with Ni(COD)$_2$ in THF or toluene lead to efficient catalysts for oligomerization of ethylene.[12,13]

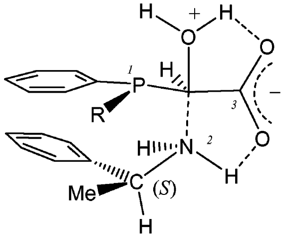


Two-component reactions of 2-phosphino- and homologous 2-arsinoalkylamines with aldehydes and ketones,[15] and also with pyruvic acid to form the first heterocyclic phosphino and arsino amino acids[14–18] have been known for a long time. However, three-component reactions seemed to be restricted to formaldehyde[1,2–4,19] and for less reactive aldehydes and ketones to five-valent P-H functional phosphorus compounds (Kabachnik-Fields reactions[20–22]). Secondary phosphines add easily to aldehydes or ketones,[23] but addition of primary amines usually leads to replacement of the phosphine, and $R_2PCH(R')NR''_2$ derivatives are synthesized by addition of phosphines directly to imines.[19] The formation of **1** in diethyl ether at room temperature occurs by primary substitution of an OH group of glyoxylic acid hydrate by the phosphine and precipitation of an organoammonium phosphinoglycolate. This is followed by a slow salt condensation, usually complete within 15 h (overnight) to 1 d at room temperature. The driving force might be the lower solubility of the zwitterionic amino acid. The water probably remains hydrogen bonded to the COO$^-$ group and is replaced only by crystallization from methanol (marked change of solubility). Monosolvates with MeOH hydrogen bonded to COO$^-$ were detected by X-ray crystal structure analysis.[12] The replacement of OH by a primary amino group is higly diastereoselective and allows access to chiral phosphino amino acids simply by use of suitable commercially available chiral primary amines (Scheme).

If diphenylphosphine is added to optically active 1-phenylethylimino glyoxylic ethylester the diastereoselectivity is lost and a 1:1 mixture of



diastereoisomers formed. This gives evidence that the formation of **1** does not proceed via imines but by substitution of the hydroxy group by the amine. Control by hydrogen bonding interactions as depicted, perhaps complemented by π-interactions, may be implied.



(*pre-S* at α-CH)

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