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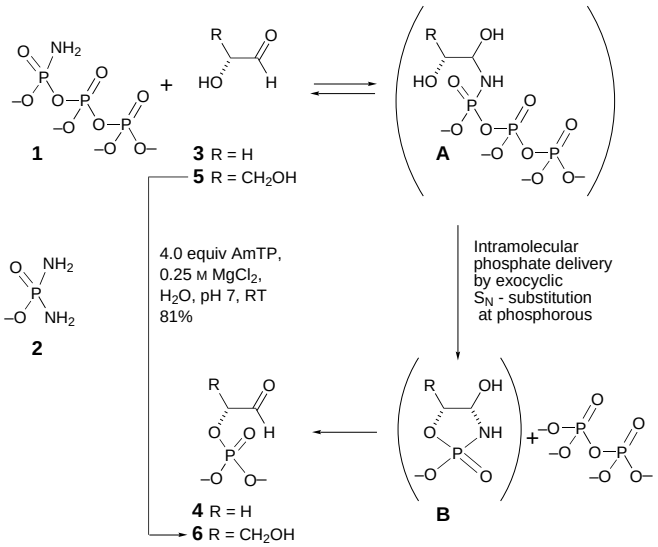
Regioselective α-Phosphorylation of Aldoses in Aqueous Solution**

Ramanarayanan Krishnamurthy, Sreenivasulu Guntha, and Albert Eschenmoser*

In the context of studies on a potentially prebiotic chemistry of glycolaldehyde,[3] we recently described an efficient conversion of this hydroxyaldehyde into its 2-phosphate in aqueous solution under very mild conditions (Scheme 1).[1] The specific phosphorylation reagent in this process is amidotriphosphate (**1**, AmTP), a compound known to be formed by ammonolysis of cyclotriphosphate ("metatriphosphate") in aqueous solution.[4] Significantly, cyclotriphosphate itself is not effective as a phosphorylation agent under the conditions where its ammonolysis product phosphorylates glycolaldehyde in essentially quantitative yields.[1] The reason for this remarkable difference in reactivity is the specific capability of the amidotriphosphate to reversibly form a carbonyl addition product **A** with glycolaldehyde and to phosphorylate the α-hydroxyl group by intramolecular phosphate group delivery from **A** to the intermediate **B** which then undergoes hydrolysis to **4** (Scheme 1).

This mechanistic concept predicts that AmTP should have the potential to regioselectively phosphorylate the α-hydroxyl groups of aldosugars. Here we report that AmTP indeed reacts with glyceraldehyde, the tetrofuranoses, and the four aldopentoses under mild conditions to form reaction products that are derived from intramolecular phosphate delivery to the hydroxyl group at the C-2 position of the sugar. We also found that a comparably efficient regioselective phosphorylation can be brought about with diamidophosphate (**2**, DAP)[5] instead of AmTP as the phosphorylating reagent; in the case of aldofuranoses, there is even a preparative advantage with regard to product isolation.



Scheme 1. Regioselective intramolecular phosphorylation of glycolaldehyde (R = H) and D-glyceraldehyde (R = CH_2OH) by amidotriphosphate (**1**, AmTP).

D-glyceraldehyde (**5**), under the reaction conditions optimized for glycolaldehyde (0.025 M aqueous solution, 0.25 M $MgCl_2$, room temperature (RT), 5 days),[1] reacts with the sodium salt of AmTP (4 equivalents, pH $\approx$ 7) slowly but cleanly and with high regioselectivity, to give D-glyceraldehyde-2-phosphate (**6**; Scheme 1; 81 % yield after isolation by ion-exchange chromatography). No discernable glyceraldehyde-3-phosphate formation takes place according to ^{1}H and ^{31}P NMR spectra of the reaction mixture.[6]

In subjecting the two aldotetroses **7** and **10** to the same treatment, a similarly regioselective phosphorylation of the α-hydroxyl groups occurs, yet this time with a twist: the products are the 1,2-cyclophosphates **8** and **12**, isolated in yields of 87 % and 80 %, respectively. In the erythrose series (2,3-diol in *cis* configuration), about a tenth of the product material is the isomeric 2,3-cyclophosphate **9**, whereas in the threose series (2,3-diol in *trans* configuration) the 1,2-cyclophosphate is free of its 2,3-isomer (Scheme 2). D-ribose (**13**) with 4 equivalents of AmTP under similar conditions reacts more sluggishly and gives the furanosyl 1,2-cyclophosphate (**15**) besides the 2,3-cyclophosphates (**16a** and **16b**), with the latter in somewhat greater proportion than in the erythrose series (Scheme 2). Overall yields are lower (29 %), presumably due to trapping of intermediates in the pyranose form.[7] According to exploratory experiments monitored by ^{1}H and ^{31}P NMR spectroscopy, the other three pentoses behave similarly to ribose. The reaction of AmTP with hexoses was explored with

[*] Prof. Dr. A. Eschenmoser, Prof. Dr. R. Krishnamurthy, Dr. S. Guntha
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-9573
E-mail: rkrishna@scripps.edu
and
Laboratorium für Organische Chemie
Eidgenössische Technische Hochschule
Unversitätstrasse 16, 8092 Zürich (Switzerland)
Fax: (+41) 1-632-1043

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from R.K. (rkrishna@scripps.edu).

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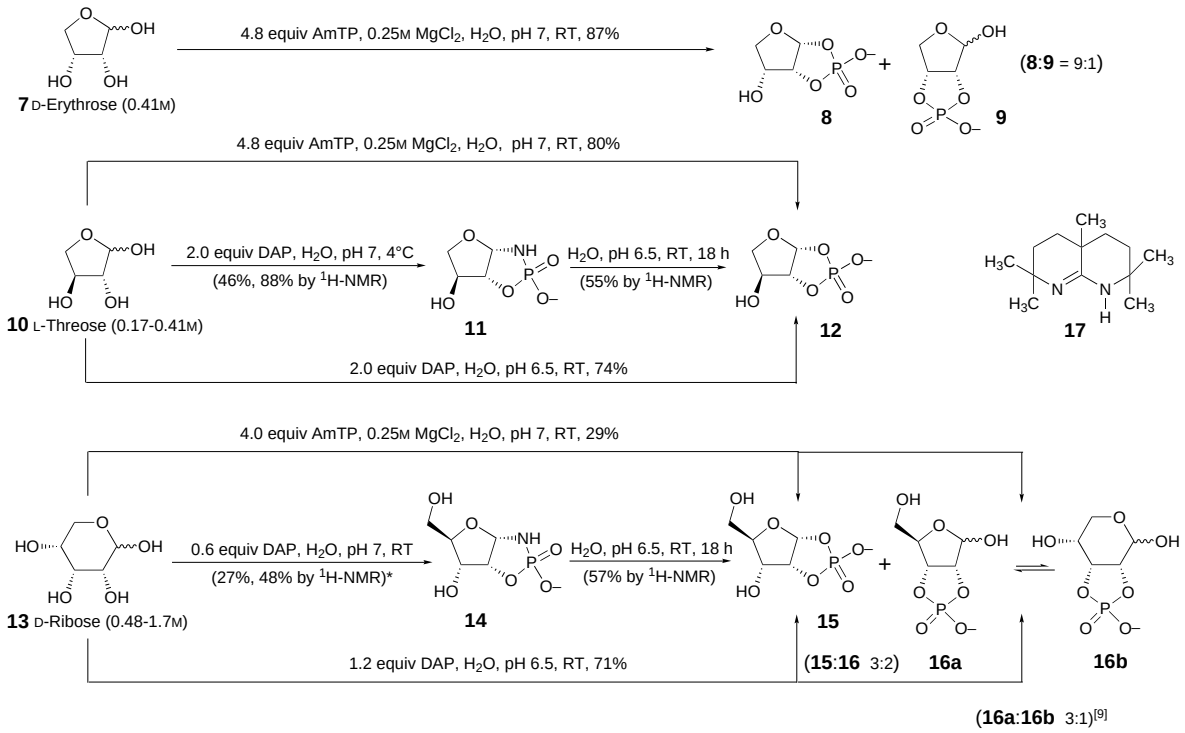

Scheme 2. Characterized products and intermediates isolated (in yields indicated) from the reaction of aldoses with either the sodium salt of amidotriphosphate (AmTP) or diamidophosphate (DAP). The experiment with AmTP in the threose series was carried out with D-threose. Yields are based on the starting aldose with the exception of the * marked value.[10]

glucose and mannose, in both cases very little phosphorylation (approximately 5%) was observed by ^{1}H NMR spectroscopy, after 14 days.

The relative reactivity of the aldoses towards AmTP is in the order of glycolaldehyde > glyceraldehyde > erythrose > threose ≫ ribose ≫≫ glucose and mannose. While the phosphorylation of the C_2-, C_3-, and C_4-sugars proceeds to completion within two to five days, the reaction with ribose progresses to about one third in two weeks (by ^{1}H NMR spectroscopy). These differences seem related to the relative stabilities of the open aldehyde form of the aldoses in aqueous solution as well as to the position of their furanose/pyranose equilibrium.[7] On the other hand, the "cyclic" aldoses (**7**, **10**, and **13**) are also phosphorylated by AmTP in the absence of $MgCl_2$, although much more slowly, whereas the "acyclic" ones (glycolaldehyde and **5**) are not.

Structural assignments in the ribose series are based on spectral comparisons to authentic samples of ribofuranosyl-1,2-cyclophosphate (**15**)[8] and the corresponding 2,3-cyclophosphate **16**,[9] while assignments for **8** and **12** in the tetrose series are supported by ^{1}H and ^{31}P NMR spectra, as well as ^{1}H–^{1}H and ^{1}H–^{13}C NMR correlation spectra. When the reaction in both the D-threose and D-ribose series is monitored by ^{1}H and ^{31}P NMR spectroscopy in D_2O in the presence of $MgCl_2$, transient signals attributed to 1,2-amidocyclophosphates **11** ($\delta(^1H) = 5.57$, CH anomeric center; $\delta(^{31}P) = 25.7$) and **14** ($\delta(^1H) = 5.35$; $\delta(^{31}P) = 25.9$) can be observed. As the reaction progresses, the intensity of these signals diminishes with concomitant rise of those for the 1,2-cyclophosphates **12** ($\delta(^1H) = 5.95$, CH anomeric center; $\delta(^{31}P) = 18.4$) and **15** ($\delta(^1H) = 5.87$; $\delta(^{31}P) = 18.8$). The constitution of the transiently formed 1,2-amidocyclophosphate **11** was assigned by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy (Figure 1). Attempts to isolate the intermediate by ion-exchange chromatography led to a mixture that contained the cyclophosphate **12** besides **11**.

According to Feldmann and Thilo,[4b] when cyclotriphosphate is ammonolyzed to AmTP, the reaction can be pushed further to form diamidophosphate (**2**). Preparatively, this compound is conveniently produced by a method starting from $POCl_3$ and stored as a crystalline pentahydrate sodium salt.[5] We have reasoned that DAP (**2**) could also serve as selective phosphorylating reagent of α-hydroxyaldehydes similar to AmTP, since one of its amino groups could act as nucleophile towards the carbonyl group and the second (after protonation) as a leaving group in the intramolecular phosphate delivery process. These expectations were realized in experiments involving L-threose and D-ribose as representative aldoses. Thereby, reaction conditions were found that not only allowed the isolation of the elusive 1,2-amidocyclophosphates **11** and **14**, but also gave better yields of final phosphorylation products in the ribose series.

When L-threose (**10**) is treated with two equivalents of DAP in aqueous solution (0.16 M **10**, RT, pH 9.6) only adduct formation, accompanied by very little phosphorylation, takes place within 24 h (^{1}H and ^{31}P NMR spectroscopy). When such an experiment is run at 4 °C and the pH value of the reaction mixture is lowered to about 7 by addition of ion-exchange resin Amberlite IR-120 (H^+), formation of the 1,2-amidocyclophosphate **11**, as well as minor amounts of **12**, is observed (^{1}H and ^{31}P NMR spectroscopy). Since the phosphorylation slowly raises the pH value of the medium (to approximately

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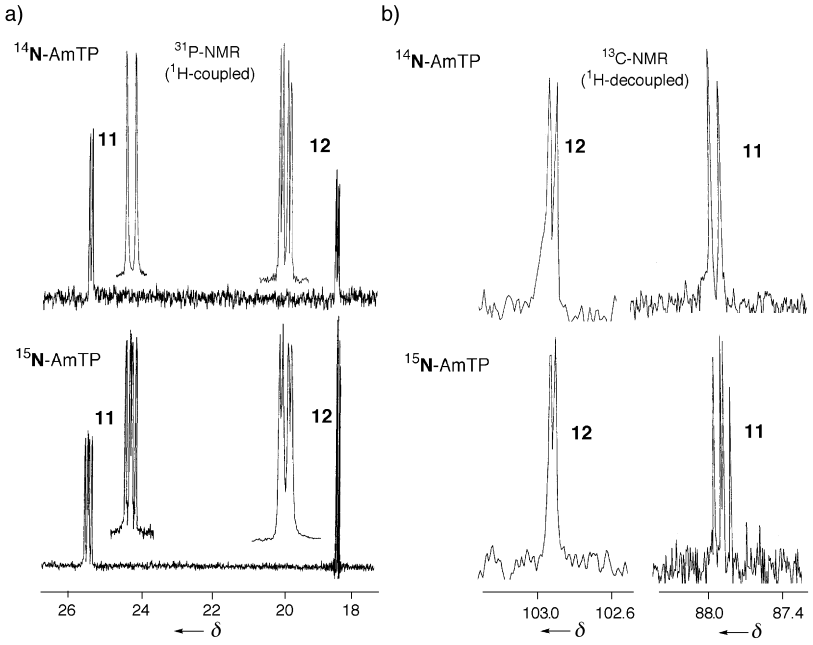

Figure 1. ^{31}P NMR and ^{13}C NMR spectral comparison of reaction mixtures observed in the reaction of threose with ^{14}N-AmTP (top) and ^{15}N-AmTP (bottom) (0.17 mmol **10** in 1 mL D_2O, 4 equivalents 98% ^{15}N-AmTP,[1] 0.25 M $MgCl_2$). ^{1}H-decoupled ^{31}P NMR spectrum (a) and ^{1}H-coupled ^{13}C NMR spectrum (b) recorded after 3 days at RT. a) Effect of ^{15}N-AmTP relative to ^{14}N-AmTP, in the coupling patterns of the ^{31}P{^{1}H} NMR spectrum of **11** where the phosphorous signal at $\delta = 25.9$ appears as a doublet of doublets ($J_{N,P} = 25.8$, $J_{1,P} = 16.2$ Hz), instead of the doublet ($J_{1,P} = 16.2$ Hz) that is in the spectrum when ^{14}N-AmTP is used. The signal of **12** at 18.5 ppm remains, as expected, unchanged in its splitting pattern. Over the course of time, the signal of **11** gradually disappears while that of **12** becomes larger until the end of the reaction when it remains unchanged. b) ^{13}C NMR spectra of the above reaction mixture. In the reaction with ^{14}N-AmTP, the signal at $\delta = 87$ (assigned to the anomeric carbon center of **11** by ^{13}C-^{1}H COSY experiments) appears as a doublet ($J_{C1,P} = 12.6$ Hz); with ^{15}N-AmTP it appears as a doublet of doublets ($J_{C1,P} = 12.5$ Hz, $J_{N,P} = 9.5$ Hz). The signal of **12** at 102.8 ppm (assigned to C-1) is unchanged in its splitting pattern as anticipated (d, $J_{C1,P} = 4.3$ Hz). These observations demonstrate that the nitrogen atom in **11** is attached to both the anomeric carbon atom and the phosphorous atom.

8.5) and therefore ceases to proceed, addition of Amberlite IR-120 (H^+) at 12 h intervals over 4 days is required to maintain a pH value of about 7 and allow complete consumption of L-threose. By such a procedure, **11** is formed in high yield (up to approximately 90% by ^{1}H NMR spectroscopy, as well as about 10% of **12**). About half of it (46%) could be isolated in essentially pure form by ion-exchange chromatography, the loss reflecting the lability of the primary phosphorylation product towards transformation into cyclophosphate **12**.

Isolation of the 1,2-amidocyclophosphate intermediate **14** in the D-ribose series proved more difficult due to its fast conversion into the mixture of the 1,2- and 2,3-cyclophosphates under the conditions of its (slower) formation. In an experiment starting with an excess of D-ribose[10] (1.6 M aqueous solution of **13** and 1 M DAP, RT, pH value kept at about 7 in 4 h intervals over 48 h), amidocyclophosphate **14** was isolated in 27% yield (48% by ^{1}H NMR spectroscopy, with respect to DAP). Its constitution could be fully characterized by ^{1}H NMR spectroscopy (Figure 2) in the form of its DMSO- and $CHCl_3$-soluble salt which is formed with the bicyclic amidine base **17**.[11]

When DAP phosphorylation mixtures in both series are maintained throughout at a pH value of 6.5, the phosphorylation products accumulate as cyclophosphates: in the L-threose series selectively as 1,2-cyclophosphate **12** (74% isolated), in the D-ribose series as a mixture of the 1,2- and 2,3-cyclophosphates **15** and **16** (71%, **15**:**16** ratio 3:2 according to ^{1}H NMR spectroscopy). The fact that under such reaction conditions the 1,2-amidocyclophosphates **11** and **14** convert themselves into the corresponding cyclophosphates was documented in separate experiments monitored by ^{1}H NMR spectroscopy and starting from pure **11** and **14** (Scheme 2).

Preparative phosphorylation of L-threose and D-ribose all the way to the corresponding 2-phosphates **18** and **19** is achieved by gradually lowering the pH value of the DAP reaction from pH 6.5 to about 2, under which conditions the 1,2-cyclophosphates are hydrolyzed within days to the 2-phosphates (Scheme 3). In the ribose series, a minor portion of the hydrolysis product is the 3-phosphate **20**, expected to be derived from the ribofuranosyl-2,3-cyclophosphate component **16** present in the phosphorylation mixture. Structural assignments in the ribose series are again by spectral comparison with known compounds[8, 9] and for **18** in the threose series by ^{1}H, ^{31}P, ^{1}H–^{1}H, and ^{1}H–^{13}C correlation NMR spectra.

The reactions between the ("cyclic") aldoses and AmTP or DAP appear mechanistically transparent with the exception of open questions referring to the structurally detailed role of the magnesium ion as well as the step in which the conversion of the 1,2-amidocyclophosphate to the 1,2-cyclophosphate intermediate is taking place. What seems remarkable is that the hydrolysis of the activated

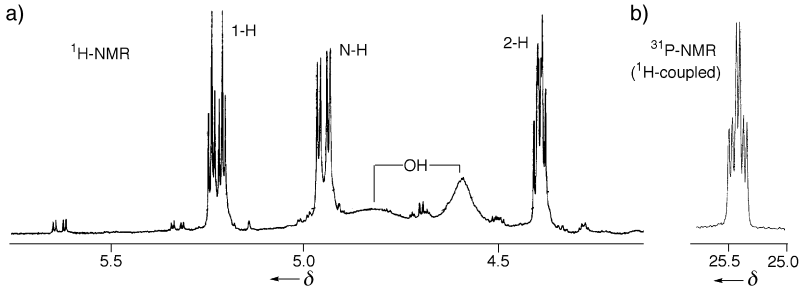

Figure 2. ^{1}H and ^{31}P NMR spectra ((a) and (b), respectively) of ribofuranosyl-1,2-amidocyclophosphate salt **14**·**17** in DMSO. The phosphoramide NH proton at $\delta = 4.96$ appears as a doublet of doublets ($J_{NH,P} = 15.4$, $J_{1,NH} = 5.0$ Hz). The signal at $\delta = 5.25$ which is the 1-H (anomeric center) signal appears as a multiplet ($J_{1,P} = 16.5$ Hz, $J_{1,NH} = 5.0$, $J_{1,2} = 4.9$ Hz). In the ^{31}P NMR spectrum the signal appears at $\delta = 25.5$ as doublet of doublet of doublets ($J_{1,P} = 16.5$ Hz, $J_{NH,P} = 15.4$, $J_{2,P} = 7.4$ Hz). On addition of D_2O, the signal at $\delta = 4.96$ disappears, along with signals assigned to the OH groups, with a concomitant change in the splitting pattern of the signal at $\delta = 5.25$, reverting back to a doublet of doublets. At the same time the ^{31}P NMR signal at $\delta = 25.5$, reduces to a doublet of doublets.

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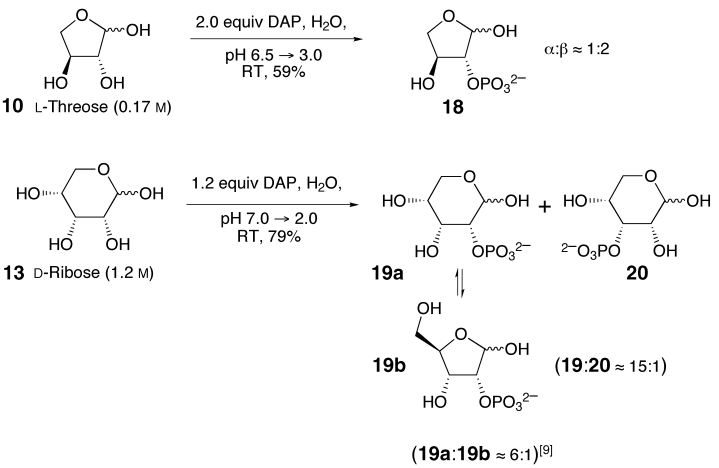

Scheme 3. One-pot transformation of selected aldoses into 2-phosphate derivatives with diamidophosphate (DAP). In separate experiments it was demonstrated by ^{1}H NMR spectroscopy that **11** and **12** (see Scheme 2) react to give **18** and **14**, and the mixture of **15**/**16** (Scheme 2) reacts to give **19**/**20**, under the same reaction conditions but in the absence of DAP.

amidocyclophosphate group takes the path through a primary product in which the phosphate group is still activated (the 1,2-cyclophosphates), before the final hydrolysis products, the stable 2-phosphates, are formed. Such a stepwise deactivation path clearly reflects a transient kinetic control of the hydrolysis process by anchimeric assistance in the cycle forming steps.[12]

The phosphorylation processes reported here exemplify a general strategy for attaining regioselectivity in synthesis, namely, to reversibly attach an activated reagent to a reactant in the structural neighborhood of the site to be functionalized, and to achieve the desired structural transformation by an irreversible intramolecular delivery of the functionalizing group.[13] Apart from the interest the reported reactions can have for the chemistry of carbohydrates[14], the demonstration of the existence of such robust and regioselective phosphorylation processes in aqueous solution is also intended to be a contribution to prebiotic chemistry.[1, 15]

Experimental Section[19]

10 →**12** (Example of a phosphorylation with AmTP): An aqueous solution of sodium salt of AmTP[1] (5 mL, 10.0 mmol) was added to D-threose, **10** (250 mg, 2.1 mmol; Sigma-Aldrich) followed by anhydrous $MgCl_2$ (119 mg, 1.25 mmol). The reaction mixture (pH 8.5) was shaken at RT until a clear solution resulted. After five days (pH 7.1) the turbid solution was diluted with 500 mL of water and subjected to ion-exchange chromatography (DEAE-A25-Sephadex, 40–120 mesh, HCO_3^- form, 5 × 20 cm, washed with 300 mL water, final elution with 0 →0.5 M $Et_3NH.HCO_3$ in 0.01M increments of 50 mL). Fractions containing the product (after concentration to approximately 10 mL, detected by thin layer chromatography: *n*BuOH:AcOH:H_2O 5:3:2, anisaldehyde stain) were combined and concentrated in vacuo (10 mm Hg), coevaporated with water 4 times to remove excess buffer, and dried to constant weight (high vacuum, RT, approximately 24 h) to afford 512 mg of pale yellow powder which contained the triethylammonium salt of **12** (477 mg, 80% yield based on pentaerythritol as the ^{1}H NMR internal reference; purity > 95% according to ^{1}H NMR spectroscopy). **12** · Et_3NH^+: R_f = 0.60; ^{1}H NMR (600 MHz, D_2O): δ = 1.16 (t, J = 7.4 Hz, 9H, CH_3), 3.07 (q, J = 7.4 Hz, 6H, CH_2), 3.86 (dd, J_{gem} = 10.6, $J_{3,4}$ = 1.1 Hz, 1H, 4-H), 4.06 (dd, J_{gem} = 10.6, $J_{3,4}$ = 2.6 Hz, 1H, 4-H), 4.28 (br.m, 1H, 3-H), 4.70 (m, partially masked by HDO signal, 1H, 2-H), 5.95 (ddd, $J_{1,P}$ = 15.7, $J_{1,2}$ = 4.0, $J_{1,3}$ = 1.7 Hz, 1H, 1-H); ^{13}C NMR (151 MHz, D_2O): δ = 8.58 (CH_3), 46.98 (CH_2), 73.19 (C4), 74.54 ($J_{C3,P}$ = 6.9 Hz, C3), 84.27 (C2), 102.78 ($J_{C1,P}$ = 4.3 Hz, C1); ^{31}P NMR (243 MHz, D_2O): 18.7 (dd, $J_{H1,P}$ = 15.7, $J_{H2,P}$ = 5.5 Hz); MS (pos., FAB): *m*/*z* (%): 306 (10, $[M+Na]^+$), 102 (100, $[Et_3NH]^+$); high resolution MS: found: 306.1084 $[M+Na]^+$; calcd: 306.1082.

13 →**15** + **16** (Example of a phosphorylation with DAP): D-Ribose (**13**, 600 mg, 4.0 mmol) was dissolved in water (3.4 mL) and $NaPO_2(NH_2)_2 \cdot 5H_2O$ (500 mg, 2.4 mmol) was added at RT. The pH value of the solution (9.4) was lowered to and maintained at 7, over a 24 h period, by addition of ion-exchange resin Amberlite IR-120 (H^+) at 4 h intervals. Another batch of $NaPO_2(NH_2)_2 \cdot 5H_2O$ (500 mg, 2.4 mmol) was added and pH 7 maintained as before, over a 24 h period. Subsequently the pH of the reaction mixture was lowered to 6.5 and maintained, over 24 h, by addition of Amberlite IR-120 (H^+) as before. The reaction mixture was diluted to 10 mL with 0.05 M aqueous $Et_3NH \cdot HCO_3$, filtered, and the resin washed 3 times with 0.05 M aqueous $Et_3NH \cdot HCO_3$ (10 mL). The washings were combined with the filtrate and subjected to ion-exchange chromatography (Dowex 1X8, HCO_3^- form; 7.5 × 10 cm, elution with 0.05 →0.2 M $Et_3NH \cdot HCO_3$ in 0.01-M increments of 50 mL volume each). The fractions containing the product (after each was concentrated in vacuo, analyzed by ^{31}P NMR spectroscopy (D_2O)) were combined and worked up as described for **12** to yield 960 mg of a white powder containing the triethylammonium salt of **15** + **16** (883 mg, 71% yield based on sodium benzoate as a ^{1}H NMR internal reference; **15**:**16** = 3:2, ^{1}H NMR spectroscopy). **15**(Na^+): R_f = 0.31; ^{1}H NMR (600 MHz, D_2O): δ = 3.64 (dd, J_{gem} = 12.5 Hz, $J_{4,5}$ = 4.5 Hz, 1H, 5-H), 3.88 (d, J_{gem} = 12.5 Hz, 1H, 5-H), 4.04 (br.m, 2H, 3-H, 4-H), 4.82 (m, 1H, 2-H), 5.86 (dd, $J_{1,P}$ = 17.0 Hz, $J_{1,2}$ = 4.1 Hz, 1H, 1-H); ^{13}C NMR (151 MHz, D_2O): δ = 59.68 (C5), 69.74 ($J_{3,P}$ = 6.1 Hz, C3), 78.76 (C2), 80.37 (C4), 101.34 ($J_{1,P}$ = 4.1 Hz, C1); ^{31}P NMR (243 MHz, D_2O): δ = 19.89 (dd, $J_{H1,P}$ = 16.9 Hz, $J_{H2,P}$ = 4.9 Hz); MS (pos., FAB): *m*/*z* (%): 257 (100, $[M+Na]^+$); MS (neg., ESI): *m*/*z* (%): 211 (100, $[M]^-$). Diagnostic signals for **16** (as a mixture of α/β-pyranose and -furanose anomers): ^{1}H NMR (600 MHz, D_2O): δ = 4.88 (d, $J_{1,2}$ = 6.9 Hz, 0.25H, 1-H, β-pyranose), 5.43 (br.s, 0.55H, 1-H, β-furanose), 5.49 (dd, $J_{1,2}$ = 5.1, $J_{2,P}$ = 0.9 Hz, 0.20H, 1-H, α-furanose); ^{31}P NMR (243 MHz, D_2O): δ = 17.73 (d, J = 18.1 Hz, β-pyranose), 21.49 (dd, J = 8.9 Hz, J = 8.7 Hz, β-furanose), 22.89 (t, J = 7.6 Hz, α-furanose).

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[6] Signals of glyceraldehyde-3-phosphate would be expected at δ = 3.95–4.05 (for 2-H and 3-H) in the ^{1}H NMR spectrum and at 3.5 ppm in the ^{31}P NMR spectrum (Data taken from an authentic sample, Sigma-Aldrich). On a related note, D-2-deoxyribose was observed not to be phosphorylated by AmTP under conditions where D-ribose is.

[7] The β-pyranosyl form of the primary AmTP addition product is not expected to undergo intramolecular phosphate delivery and may only slowly equilibrate with the furanosyl form under the reaction conditions. Primary adduct formation of **13** with AmTP (in contrast to the experiments with DAP) is inferred, but could not be reliably monitored by ^{31}P NMR, due to signal overlap. The much higher yield of **15**/**16** obtained by the DAP procedure (see below) is presumably related to acid catalysis in the equilibration of primary adducts. Hexopyranoses with DAP under such conditions again give only a little phosphorylation.

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[10] In this experiment, excess ribose was used in order to facilitate separation of the product from the reagent in the ion-exchange chromatography.
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[12] This can either be a nucleophilic assistance by an adjacent hydroxyl group in a proton-catalyzed substitution of the NH_2 group in a non-cyclic 2-amidophosphate (formation of 2,3- and 1,2-cyclophosphates in the ribose and erythrose series), and/or a (N →O) exchange at the anomeric center through proton-catalyzed C,N dissociation →C,O recombination and subsequent hydrolytic loss of ammonia.
[13] Examples in synthetic chemistry where this strategy has used are legion. For early examples, see Ref. [16] (regioselectivity in the formation of the porphyrin skeleton in Woodward's chlorophyll synthesis) and Ref. [17] (regioselectivity of a Michael addition step in a colchicine synthesis).
[14] Note that, as the procedures described here involve separation and isolation by ion-exchange chromatography requiring large volumes, scaling up these reactions may therefore have its limits.
[15] High concentrations of substrates and reagents (up to 20% and 30%, respectively) are necessary in order for the reactions to be completed within days (instead of weeks, using lower concentrations). For the special case of ribose, the transformation to the cyclophosphates **15** and **16a** belongs to those functionalizations of the ribose molecule which select the furanose form from the sugar's pyranose/furanose equilibrium (see also Footnote 61 in Ref. [18]).
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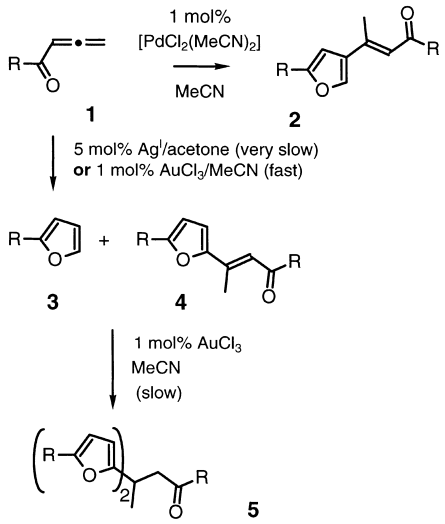
[17] a) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, A. Eschenmoser, *Angew. Chem.* **1959**, *71*, 637 – 640; b) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall A. Eschenmoser, *Helv. Chim. Acta* **1961**, *44*, 540 – 597.
[18] A. Eschenmoser, *Science* **1999**, *284*, 2118 – 2124.
[19] Further experimental details of the preparation of and spectral data for **6**, **8** + **9**, **11**, **14**, **18**, and **19** + **20** are given in the Supporting Information.

A New Gold-Catalyzed C–C Bond Formation**

A. Stephen K. Hashmi,* Lothar Schwarz, Ji-Hyun Choi, and Tanja M. Frost

While a manifold on the stoichiometric organometallic chemistry of gold is known, only a few catalytical applications have been reported.[1] As far as the *homogeneous* catalysis of organic reactions is concerned, there exist only two reactions that have reached any importance. The first forms C–X bonds (X = heteroatom) by the addition of O- or N-nucleophiles to alkenes or alkynes, as developed by Utimoto et al.[2] and Teles et al.[3] The second application forms C–C bonds by the asymmetric aldol reaction, as developed by Ito and Hayashi et al. and Togni et al.[4] We now report a new gold-catalyzed reaction that combines both C–O and C–C bond formation and allows the selective cross cycloisomerization/dimerization of terminal allenyl ketones and α,β-unsaturated ketones.

In the course of our investigation of transition metal catalyzed reactions of the readily available allenyl ketones **1**,[5] we observed that certain substrates such as **1a**, in which electron-rich substituents in the Ag^I-catalyzed Marshall reaction[6] lead to **3** as the major product, also form cycloisomers/dimers **4** as minor side products. Compound **4** is a constitutional isomer of the cycloisomer/dimer **2** obtained from the Pd^{II}-catalyzed conversion of **1** (Scheme 1).[7]



1-5	yield [%] of 2	3	4	5
a: R = 4-(TBDMSO)C_6H_4				
Pd^{II}	59	-	-	
Ag^I	-	22	14	
gold catalysis		**3**[a]	**4**[a]	**5**[b]
b: R = CH_2-4-(MeO)C_6H_4		60	31	-
c: R = CH_2-4-(TBDMSO)C_6H_4		35	5	42
d: R = CH_2CH_2-4-(TBDMSO)C_6H_4		38	6	31
e: R = 3-(MeO)C_6H_4		34	38	-
f: R = 4-(O_2N)C_6H_4		88	4	-
g: R = 2-(O_2N)C_6H_4		72	8	-
h: R = 3,4-(OCH_2O)C_6H_3		29	24	-
i: R = 4-(MeS)C_6H_4		48	51	-
k: R = CH_3		47[c]	47	-
m: R = 2,5-$(MeO)_2C_6H_3$		45	36	-

Scheme 1. Cycloisomerization, dimerization, and trimerization of **1**. a) Immediate workup after consumption of the starting material. b) Workup after several hours. c) Determined in the crude product by ^{1}H NMR.

In order to make **4** the major product, we tested Au^{III} catalysts, which combine a Pd^{II}-like d^8 system, with a silver-like metal of the copper triad. These gold catalysts prove to be extremely active and allow the reactions to be conducted under very mild conditions at room temperature or below. Because of the absence of paramagnetic species, the reactions could be easily monitored by NMR. For 1 mol% of catalyst, the required reaction times at 20 °C were, depending on the substrate, over one week for $AgNO_3$, about one hour for $[PdCl_2(MeCN)_2]$, and about one minute for $AuCl_3$! The

[*] Priv.-Doz. A. S. K. Hashmi, Dipl.-Chem. L. Schwarz, J.-H. Choi, T. M. Frost
Institut für Organische Chemie
Johann Wolfgang Goethe-Universität
Marie-Curie-Strasse 11, 60439 Frankfurt a. M. (Germany)
Fax: (+49) 69-79829464
E-mail: hashmi@chemie.uni-frankfurt.de

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