Table 1. Initial Transport Rate[a]

substrate	carrier	pH (Aq I)[b]	initial transport rate 10^{-9} mol/(cm^2·h)
GMP	OEP (1)	2.5	≤0.001
	sapphyrin (2)	2.5	86.9
		3.0	51.9
		3.5	22.9
		4.0	1.87
	rubyrin (3)	2.5	16.6
AMP	sapphyrin	3.1	262.1
Ara-AMP	sapphyrin	3.1	183.9

[a] Transport experiments were performed in a manner similar to those reported in ref 6: [substrate] = 10 mM and [carrier] = 0.1 mM. Initial transport rates were calculated from the linear region of concentration vs time curve (cf. supplementary material). Estimated errors ≤5%. [b] The pH of Aq I was adjusted by adding 1 N NaOH to the GMP diacid solution. Aq II was basified with NaOH to give an initial pH = 10.0.

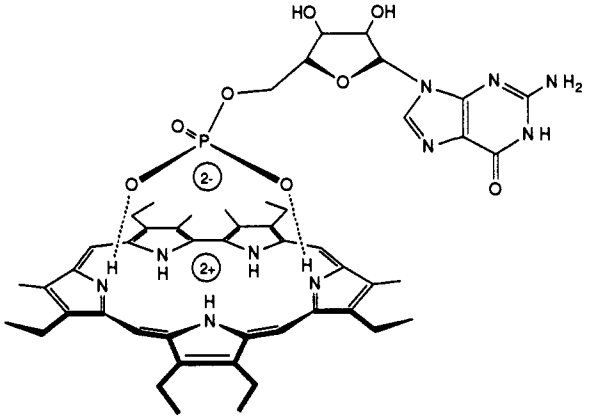
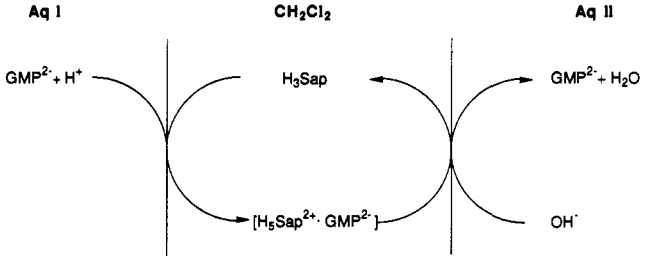


Figure 1. Schematic representation of proposed 1:1 complex formed between sapphyrin 2 and GMP diacid. Under the conditions of transport, higher order aggregates and sapphyrin species with different degrees of protonation could be contributing; see text.

Scheme 1



paired, *overall neutral* [H_5Sap^{2+}·GMP^{2-}] complex (Figure 1). However, the participation of other entities, including dimers such as [H_4Sap^+·GMP^{2-}·H_4Sap^+] and/or other higher aggregates[13] cannot at present be entirely ruled out.[14]

Sapphyrin **2** also appears to effect transport of other monophosphate species. Both AMP and Ara-AMP, for instance, are transported efficiently. In fact, as might be expected for these more lipophilic adenosine derivatives, the actual transport rates are slightly higher than those observed for GMP (Table I). Interestingly, the transport of both AMP and GMP appears to be inhibited by certain other small anions. The addition, for instance, of NaCl or NaF (1-2 molar equiv relative to Sap) to Aq I leads to long induction periods (1-2 h) for nucleotide transport. Presumably, this reflects the fact that these anions are also bound and transported by the protonated forms of sapphyrin.[15]

In conclusion, we have demonstrated effective transport of nucleotides and analogues through a dichloromethane membrane with protonated sapphyrin as the carrier. Currently, we are exploring the range and scope of this expanded porphyrin approach to nucleotide transport. In preliminary work, we have found that the new rubyrin system (**3**)[16] is able to transport GMP but is less effective than sapphyrin **2** for this purpose (Table I). However, this larger macrocyclic system appears relatively more effective for the transport of diphosphorylated species such as, e.g., GDP.[17] This leads us to suggest that specific structural effects could be important in regulating this general expanded porphyrin approach to nucleotide transport and recognition.

Acknowledgment. This work was supported by the Texas Advanced Research Program (Grant No. 3658-016). J.L.S. also thanks the National Science Foundation (PYI 1986), the Camille and Henry Dreyfus Foundation (Teacher-Scholar Award 1988-1993), and the Sloan Foundation (Fellowship 1989-1991).

Supplementary Material Available: pH titration curve for sapphyrin and time course of GMP, AMP, and Ara-AMP transport (3 pages). Ordering information is given on any current masthead page.

(13) Since the free-base sapphyrin (H_3Sap) is strongly basic, it generates the mono cation [H_4Sap^+·OH^-] in the presence of a small amount of water. In the presence of larger amounts of water, dimerization and/or aggregation occurs to give a species with λ_{max} = 461.5 nm. Similar effects have been observed in the diacid (H_5Sap^{2+}) form: Maiya, B. G.; Cyr, M. J.; Harriman, A.; Sessler, J. L. *J. Phys. Chem.* **1990**, *94*, 3597-3601.

(14) During transport, the absorption maximum of the CH_2Cl_2 layer in the U-tube was found to shift from 446 to 450 nm; this is consistent with the existence of both mono- and diprotonated sapphyrin species.

(15) Fluoride anion transport is also enhanced by sapphyrin: Sessler, J. L.; Ford, D.; Cyr, M. J.; Furuta, H. To be submitted for publication.

(16) For the synthesis and X-ray structure of rubyrin, see: Sessler, J. L.; Morishima, T.; Lynch, V. *Angew. Chem.* In press.

(17) Furuta, H.; Morishima, T.; Sessler, J. L. Unpublished results.

Palladium-Mediated Stereocontrolled Reductive Amination of Azido Sugars Prepared from Enzymatic Aldol Condensation: A General Approach to the Synthesis of Deoxy Aza Sugars[1]

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We report in this study the diastereoselective Pd-mediated reductive amination of azido ketoses or aldoses prepared (on 1-10-mmol scales) from aldolase reactions to five- or six-membered-ring deoxy aza sugars. Although only four aldolases have been used in this study, it appears to be general that this combined chemical and enzymatic approach is a very effective way for the construction of deoxy aza sugars structurally related to many natural and unnatural monosaccharides.

Aza sugars[2] are useful inhibitors of enzymes associated with carbohydrate processing.[2,3] Synthesis of aza sugars based on

(1) Supported by the NIH (GM44154).

(2) (a) Paulsen, H.; Todt, K. *Adv. Carbohydr. Chem.* **1968**, *23*, 115. (b) Fellows, L. E. *Chem. Br.* **1987**, *23*, 842. (c) Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744. (d) Inouye, S.; Tsuruoka, T.; Ito, A.; Niida, T. *Tetrahedron* **1968**, *24*, 2125. (e) Muller, L. In *Biotechnology*; Rehm, H.-J., Reed, G., Eds.; VCH Verlagsgesellschaft: Weinheim, 1985, Vol. 4, Chapter 18. (f) Sinnott, M. L. In *Enzyme Mechanisms*; Pike, M. I., Williams, A., Eds.; Royal Soc. Chem.: London, 1987; p 259. (g) Lalegerie. P.; Legler, G.; You, J. M. *Biochemie* **1982**, *64*, 977. (h) Bayer, A. G.; Kinast, G.; Schuller, M.; Schroder, T. Ger. Offen. DE 3620645. (i) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539. (j) Yoshikuni, Y.; Ezure, Y.; Aoyagi, Y.; Enomoto, H. *J. Pharmacobio-Dyn.* **1988**, *11*, 356. (k) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229. (l) Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084. (m) Evans, S. V.; Fellows, L. E.; Shing, K. T. M.; Fleet, G. W. *J. Phytochem.* **1985**, *24*, 1953. (n) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.

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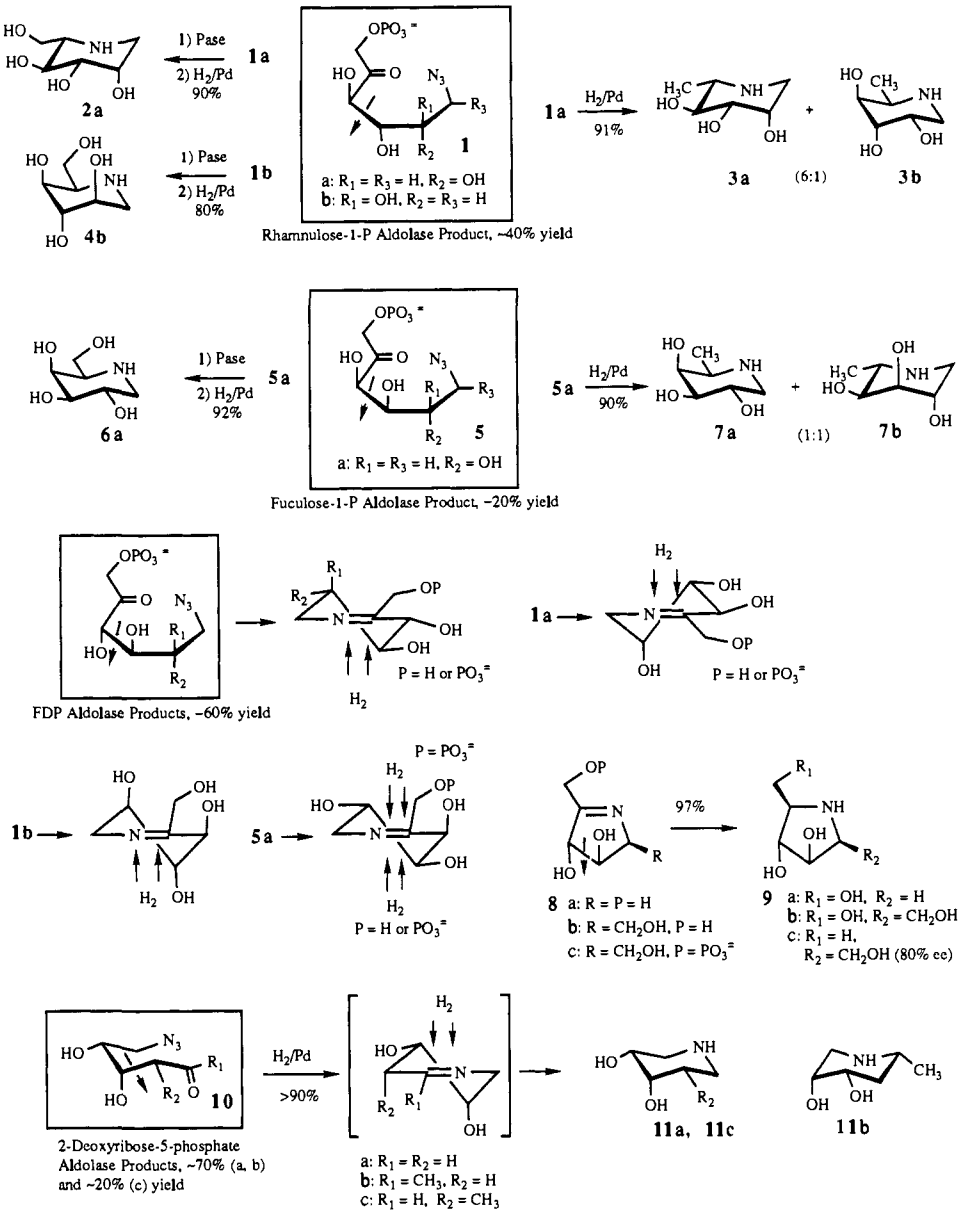
Scheme 1



fructose-1,6-diphosphate (FDP) alcolase (EC 4.1.2.3) has proven to be a promising approach.[4] We here report that several other aldolases[5] also catalyze stereospecific C–C bond forming reactions with azido aldehydes to form aldol products which, after a Pd-catalyzed reductive amination,[4] can be converted to deoxy aza sugars. Both enzymatic reactions and reductive aminations were conducted in aqueous solution without protection of the functional groups, and isolation of products is very straightforward. The phosphate group can be reductively cleaved in the Pd-mediated process, providing another new method for the synthesis of dideoxy aza sugars.

The aldolases used in this study include FDP aldolase,[6] rhamnulose-1-phosphate (Rham-1-P) aldolase (EC 4.1.2.19),[7] fucu-

(3) For chemical Synthesis: (a) Fleet, G. W. *Chem. Br.* **1989**, *25*, 287 and references cited therein. Fleet, G. W. J.; Witty, D. R. *Tetrahedron* **1990**, *1*, 119. (b) Bernotas, R. G.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 1123. (c) Setoi, H.; Takeno, H.; Hashimoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 2642. (d) Legler, G.; Julich, E. *Carbohydr. Res.* **1984**, *128*, 61. (e) Kinast, G.; Schedel, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 805. (f) Hanesia, S. *Chem. Ind. (London)* **1966**, 2126. (g) Schmidt, R. R.; Michel, J.; Rucker, E. *Justus Liebigs Ann. Chem.* **1989**, *5*, 423. (h) Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1987**, 262. (i) Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res.* **1987**, *167*, 305. (j) Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 699. (k) Fleet, G. W.; Petursson, S.; Campbell, A. L.; Mueller, R. A.; Behling, J. R.; Babiak, K. A.; Ng, J. S.; Scaros, M. G. *J. Chem. Soc., Perkin Trans.* **1989**, 665. (l) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1990**, 854. (m) Fleet, G. W. J.; Smith, P. W.; Nash, R. J.; Fellows, L. E.; Parek, R. B.; Rademacher, T. W. *Chem. Lett.* **1986**, 1051. (n) Chen, S.-H.; Danishefsky, S. J. *Tetrahedron Lett.* **1990**, *31*, 2229. (o) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (p) Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137. (q) Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717. (r) Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1988**, *110*, 312. (s) Jager, V.; Hummer, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1171. (t) Wehner, V.; Jager, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169. (u) Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5494. (v) Boshagen, H.; Heiker, F.-R.; Schuller, A. M. *Carbohydr. Res.* **1987**, *164*, 141. (w) Heiker, F.-R.; Schueller, A. M. *Carbohydr. Res.* **1990**, *203*, 314.

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(6) Both rabbit muscle aldolase from Sigma and recombinant *E. coli* aldolase[4c] can be used.

lose-1-phosphate (Fuc-1-P) aldolase (EC 4.1.2.17),[7] and 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4).[8] The first three aldolases use dihydroxyacetone phosphate (DHAP) as donor and a number of aldehydes as acceptors to form two new stereogenic centers with 3*S*,4*R*, 3*R*,4*S*, and 3*R*,4*R* configurations, respectively; DERA expresses relaxed substrate specificity with both donor and acceptor components to form one (when acetaldehyde or acetone is used as donor) or two (when propionaldehyde is used as donor) new stereogenic centers with 3*S* or 2*R*,3*S* configurations.[8] The stereospecificity remains the same in all aldolase reactions with natural and unnatural substrates. Thus, with the use of DHAP[9] and racemic 3-azido-2-hydroxypropanal (3 equiv)[4c] as substrates, compounds **1a** and **5a** were obtained selectively from Rham-1-P aldolase and Fuc-1-P aldolase reactions, respectively (Scheme I). Both Rham-1-P and Fuc-1-P aldolases accept the *S* aldehyde as substrate, whereas FDP aldolase is selective for the *R* enantiomer.[4a,b] Pd-mediated reductive amination of **1a** and **5a** gave **3a** and 1:1 **7a** + **7b**, respectively, each in ~90% yield. Reductive amination of the phosphate-free **1a** and **5a**, however, gave **2a** and **6a**,[3i,w] respectively, also in ~90% yield. Compound **4b** was obtained from the product of Rham-1-P aldolase reaction with (*R*)-3-azido-2-hydroxypropanal.[4c] The reductive aminations are all diastereoselective and consistent with our previous finding[4c] that hydrogens attack the imine intermediate regioselectively to avoid the torsional strain developed during the reduction with the exception of **1b** and **5a**. This study reveals that hydrogens always approach from the side opposite to the axial substituent, and this steric effect seems to override the torsional strain effect. The same situation was observed in the reductive amination of the DERA products **10b** and **10c**.[10] The $A_{1,2}$ strain seems not to affect the stereochemical course of the reduction. Reduction of the five-membered-ring imines **8a**-**8c**[11] prepared via FDP aldolase reactions also gave trans products **9a** and **9b** preferentially in >90% yield. A lower diastereoselectivity (~6:1) was observed for **1a**, **5a**, and **8c** compared to the phosphate-free counterparts, which exhibit >90% diastereoselectivity. The stereochemistry and conformation of each compound were determined with NMR together with NOE, proton-proton decoupling, and coupling. Compounds **2a**, **3a**, **7a**, **9b**,**c**, and **11a**-**c** prepared in this study are new. Compound **9b**, 2(*R*),5(*S*)-bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine, was found to be a competitive inhibitor of brewer's yeast α-glucosidase (K_i = 2.8 μM), almond β-glucosidase (K_i = 19 μM), green coffee bean α-galactosidase (K_i = 50 μM), and jack bean α-mannosidase (K_i = 3.1 mM), but no inhibition (up to 1 mM) of *Escherichia coli* β-galactosidase was observed.[12] Compound **3a** (*rhamnojirimycin*) is structurally related to rhamnose and may be a selective antimicrobial agent or herbicide as rhamnose is often found in microorganisms or plants, but not in humans or animals. Though the enzymes used in this study are not recovered after reactions, they are quite stable and could be immobilized and recovered for reuse.

Supplementary Material Available: Experimental procedures for the synthesis of **1a**, **2a**, **3a**, **4b**, **6a**, **7a**, **9b**, **10a**-**c**, and **11a**-**c** and selected physical data (^{1}H and ^{13}C NMR, HRMS, and rotations) (6 pages). Ordering information is given on any current masthead page.

(7) *E. coli* K40 was used as a source for Rham-1-P aldolase and *E. coli* K58 was used as a source for Fuc-1-P aldolase. The cells were treated with lysozyme (to release the enzyme) and used directly without further purification. For procedure, see: Drueckhammer, D. G.; Durrwachter, J. R.; Pederson, R. L.; Crans, D. C.; Daniels, L.; Wong, C.-H. *J. Org. Chem.* **1989**, *54*, 70. Fuc-1-P aldolase from *E. coli* was cloned and overexpressed (Ozaki, A.; Toone, E. J.; von der Osten, C. H.; Sinskey, A. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 4970.

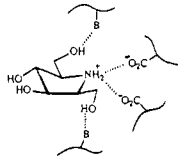
(8) Prepared according to Barbas et al.: Barbas, C. F., III; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1990**, *112*, 2013.

(9) Pederson, R. L.; Esker, J.; Wong, C.-H. *Tetrahedron* **1991**, *47*, 2643.

(10) Compounds **10a**-**c** were selectively obtained from DERA-catalyzed reactions with racemic 3-azido-2-hydroxypropanal. Three equivalents of the aldehyde were used.

(11) Compound **8b** is an imine intermediate obtained in the FDP aldolase reaction with racemic 2-azido-3-hydroxypropanal followed by the reductive amination. The *S* aldehyde was preferentially converted to the aldol product, in a thermodynamically controlled process.

(12) The high potency may be due to the half-chair-like envelope conformation binding to the active site.



Formation of Organozinc Cations and Anions from Diorganozinc Compounds

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Some coordinating agents cause organomagnesium compounds to disproportionate to magnesiate anions and coordinated organomagnesium cations.[1-4] With a favorable cryptand (2,1,1-cryptand)[1,2] or crown ether (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane = 14N4)[3] and benzene as the solvent, conversion of dialkyl- and diarylmagnesium compounds to the ions shown in eq 1 (C = a cryptand or crown ether) can be essentially quantitative. Discrete NMR absorptions are seen for $RMgC^+$

$$2R_2Mg + C \rightleftarrows RMgC^+ + R_3Mg^- \quad (1)$$

and R_3Mg^-; some systems are homogeneous, but others have a second, dense phase, which contains most of the ions.

A similar disproportionation of R_2Zn (eq 2) would form interesting ions. To our knowledge, no RZn^+ ion has been characterized in solution.[5] Solutions having the composition R_3ZnM (M = alkali metal) have been prepared.[6] These solutions, however, may contain species in which M is partially bonded to the α-carbons of the R groups[7] rather than free organozincate ions, such as R_3Zn^-.[8]

$$2R_2Zn + C \rightleftarrows RZnC^+ + R_3Zn^- \quad (2)$$

Addition of cryptands to benzene solutions of diorganozinc compounds provides no evidence for disproportionation to ions.[9]

(1) Squiller, E. P.; Whittle, R. R.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 432.

(2) Kushlan, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2510. Kushlan, D. M., The Pennsylvania State University, unpublished observations.

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(5) However, a solid of composition $MeZnBH_4$ that contains $MeZn^+$ ions somewhat "coupled" to BH_4^- ions has been studied (Nibler, J. W.; Cook, T. H. *J. Chem. Phys.* **1973**, *58*, 1596).

(6) For a review, see: Nützel, K. *Methoden Org. Chem.* (*Houben-Weyl*), *4th Ed.* **1973**, *13*, (Part 2a), 553.

(7) Powder diffraction studies of solid lithium tetramethylzincate (Weiss, E.; Wolfrum, R. *Chem. Ber.* **1968**, *101*, 35) and potassium tetraethynylzincate (Weiss, E.; Plass, H. *J. Organomet. Chem.* **1968**, *14*, 21) show significant bonding of the alkali metals to the α-carbons of the alkyl groups.

(8) Zincate ions prepared from R_2Zn and salts have been studied. KH: Kubas, G. J.; Shriver, D. F. *J. Am. Chem. Soc.* **1970**, *92*, 1949. Kubas, G. J.; Shriver, D. F. *Inorg. Chem.* **1970**, *9*, 1951. Shriver, D. F.; Kubas, G. J.; Marshall, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 5076. Ashby, E. C.; Beach, R. G. *Inorg. Chem.* **1971**, *10*, 2486. Ashby, E. C.; Watkins, J. J. *Inorg. Chem.* **1973**, *12*, 2493. KOR': Fabicon, R. M.; Parvez, M.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 1412. Salts of composition $Pr_4N^+RZnX_2^-$ have been prepared by electrolysis of RX in a $Pr_4N^+X^-$ solution (Habeeb, J. J.; Osman, A.; Tuck, D. G. *J. Organomet. Chem.* **1980**, *185*, 117).

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