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A chiral hydrazone derived from D-glyceraldehyde: a convenient starting material for the stereoselective synthesis of α-hydrazino acids

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Abstract: The chiral hydrazone synthesized from 2,3-di-*O*-benzyl-D-glyceraldehyde and benzoic acid hydrazide undergoes addition with methylmagnesium bromide in the presence of cerium trichloride in a diastereoselective manner. The major addition compound can be easily transformed into α-hydrazinopropanoic acid in four steps in 57% overall yield.

There is growing interest in the stereospecific synthesis of α-hydrazino acids because, as a result of their strong resemblance to α-amino acids, they can act as inhibitors of enzymes which metabolise the corresponding α-amino acids.[1] Moreover, they have been found in natural peptide antibiotics[2] and have been used for the synthesis of metabolically-stable peptidomimetics with potential for the treatment of viral infections.[3] In this sense, attempts at introducing hydrazino acids in peptide analogues remains very limited because of the difficulties in obtaining enantiomerically pure hydrazino acids.

The most efficient procedures described for obtaining non-racemic α-hydrazino acids are based on asymmetric electrophilic "hydrazination" of chiral enolates with azodicarboxylate esters,[4] amination of chiral α-amino acids with *N*-alkoxycarbonyl-3-phenyloxaziridines,[5] displacement of the hydroxyl group by Boc-hydrazine in chiral 2-nosyloxy and 2-triflyloxy esters,[6] and most recently catalytic asymmetric hydrogenation of *N*-acylhydrazones derived from α-keto acids,[7] or ring opening of chiral *N*-aminoaziridine derivatives by nucleophiles.[8]

In our recent work, directed towards the synthesis of amino acid surrogates as modifiers of peptide backbones, we were interested in developing a new route to α-hydrazino acids from readily available and cheap starting materials.

We have recently reported that chiral imines derived from 2,3-di-*O*-benzyl-D-glyceraldehyde undergo highly diastereoselective additions of organometallic reagents, a process which constituted a new route to α-hydroxy-β-amino acids[9] and α-amino acids.[10] This synthetic methodology can presumably be applied to the synthesis of the desired hydrazino acids by simply starting from the appropriate hydrazone. Moreover, there are several examples in the literature reporting the diastereoselective addition of organometallic reagents to *N*,*N*-dimethylhydrazones derived from chiral α-alkoxycarbonyl compounds[11] in the synthesis of chiral 1,2-aminoalcohols.

Taking into account these precedents we have studied, as a model, the behaviour of acylhydrazones derived from 2,3-di-*O*-benzyl-D-glyceraldehyde towards organometallic reagents in order to develop a new route to α-hydrazino acids. The *N*-acyl protecting group is necessary to maintain the hydrazino moiety in the final deprotection of this functional group.

Chiral acylhydrazone **1** is readily prepared in 94% yield from 2,3-di-*O*-benzyl-D-glyceraldehyde and benzoic acid hydrazide. Compound **1** was used as the substrate for the addition of methyl organometallic reagents under a variety of conditions in order to optimise the stereochemical course of the reaction (Scheme 1).

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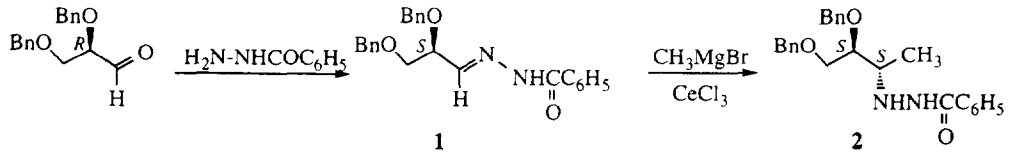


Scheme 1.

Table 1. Selected results for the addition of organometallic reagents to the benzylhydrazone derived from 2,3-di-*O*-benzyl-D-glyceraldehyde

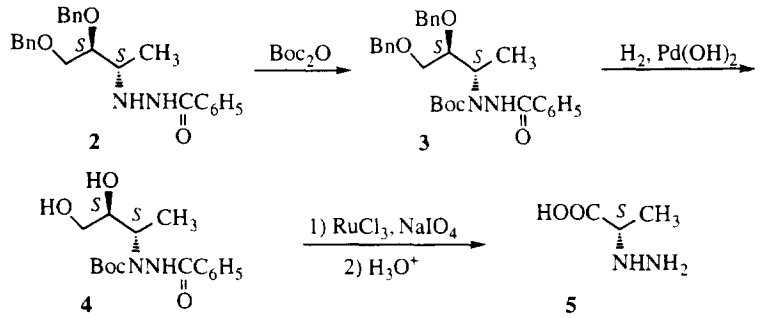
Entry	Organometallic Reagent[a]	Solvent	Temperature	Yield [%]	d.r.[b]
1	CH_3MgBr	ether	r.t.	100	50/50
2	CH_3MgBr	toluene	r.t.	100	50/50
3	CH_3MgBr-$CeCl_3$	ether	r.t.	100	67/33
4	CH_3MgBr-$CeCl_3$	toluene	r.t.	100	67/33
5					
6	CH_3MgBr-$CeCl_3$	ether	- 20	50	78/22

[a]Five equivalents of the organometallic reagent were used to ensure complete consumption of the starting material. [b]The ratios of diastereoisomers were determined by ^{1}H-NMR of crude reaction mixtures.

We initially examined the addition of CH_3Li since it has been described [11a] that the dimethylhydrazone of D-glyceraldehyde acetonide stereoselectively adds CH_3Li both in the absence or presence of a catalytic amount of CuI with excellent yields (95%). However, on using this organometallic reagent we did not obtain the desired compound, even in the presence of $CeCl_3$. No reaction occurred when THF was used as the solvent and only a complex inseparable mixture of compounds was obtained when ether was used as the solvent. The same behaviour was observed with the use of the copper-based organometallic reagent, generated *in situ* from methylmagnesium bromide and copper(I) bromide prior to the addition reaction. In some cases improved yields have been reported[12] for the addition of alkyl copper reagents, complexed with boron trifluoride etherate prior to use, and we also tested these conditions but, unfortunately, the results were similar. Subsequently we tested the addition of CH_3MgBr to chiral hydrazone **1** at room temperature and we observed no reaction when THF was used as the solvent. However, rapid formation (15 min) of an equimolecular mixture of diastereoisomers in nearly quantitative yields was observed when ether or toluene were used as the solvent (Table 1). The same reaction carried out with the cerium-based organometallic reagent prepared from CH_3MgBr and anhydrous $CeCl_3$ afforded a 67/33 mixture of diastereoisomers also in nearly quantitative yields in 15 min. This result is in contrast to that observed by Baker and Condon[11b] who were unable to successfully obtain significant yields in the addition of cerium-based organometallic reagents to chiral *N,N*-dimethylhydrazones.

Encouraged by this result we set out to improve the stereoselectivity of the reaction based on the CH_3MgBr–$CeCl_3$ organometallic reagent and assessed the effect of a decrease in the reaction temperature on the rate and stereoselectivity of the reaction. Three hours were required for complete conversion to the product at 0°C and the diastereoselectivity improved from 67/33 to 78/22. The same stereochemical behaviour was observed at −20°C but we observed only a 50% conversion in 24 h. Although diastereoselectivity at 0°C was only moderate, both diastereoisomers can be easily separated by flash chromatography eluting with hexane/ethyl acetate (1/1) and the pure major diastereoisomer was isolated in acceptable yields (72%).

The synthetic utility of this reaction requires the conversion of addition product **2** into the free hydrazino acid **5** without any degree of racemisation (Scheme 2). As the carboxylic group is generated through oxidative cleavage of the diol moiety that can also break the NH–NH bond it is necessary to prevent this undesired process. For this reason we transformed compound **2** into the corresponding *N*-Boc derivative **3** in 80% yield by treatment with excess di-*tert*-butyldicarbonate in the presence of diisopropylethylamine. Debenzylation of compound **3** was performed by hydrogenolysis in the presence of palladium hydroxide to afford compound **4** in 92% yield. Finally, the free hydrazino acid **5** was obtained by oxidative cleavage of the diol moiety by treatment with excess sodium periodate in the presence of ruthenium trichloride and subsequent hydrolysis using 3 N hydrochloric acid. Elution of the crude hydrazino acid hydrochloride salt through an ion exchange chromatography column yielded enantiomerically pure (*S*)-α-hydrazinopropanoic acid whose specific rotation value {$[\alpha]^{25}_D$=−28 (c=1 in 6 N HCl), lit[7] $[\alpha]^{20}_D$=−28.5 (c=1 in 6 N HCl)} allowed us to determine the absolute configuration of the stereogenic centre created on the addition reaction and confirm the enantiomeric purity of the final hydrazino acid.



Scheme 2.

In conclusion, this synthetic reaction provides a practical method for the preparation of hydrazino alanine **5**. This method can be extended to include the synthesis of a wide variety of hydrazino acids from a common precursor, commercially available D-mannitol, by simply changing the organometallic reagent used.

Experimental

Apparatus

Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin–Elmer 241-C polarimeter with a thermally-jacketed 10 cm cell at 25°C. IR spectra were obtained on a Perkin–Elmer 1600 FTIR infrared spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform or deuterated water and referenced with respect to the residual solvent signal on a Varian Unity 300 or a Bruker AMX300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants (J) are measured in Hertz. The ^1H NMR and ^{13}C NMR spectra of *N*-Boc protected compounds were not conclusive at room temperature due to the presence of a

dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen–carbon bond of the amide group. In order to overcome this problem NMR spectra of these compounds were run at 55°C. Elemental analyses were performed on a Perkin–Elmer 200 C,H,N,S elemental analyser. Mass spectra under electron impact conditions (EI) were determined on a high resolution VG-Autospec spectrometer. The spectra are presented as m/z (% relative intensity).

Chemicals

All reactions were carried out under argon with magnetic stirring. Solvents were dried prior to use. All reagents were obtained from commercial sources and were of analytical grade. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was undertaken on silica gel (Kiesegel 60).

*(2S)-2,3-Di-*O*-benzylglyceraldehyde* N*-benzoylhydrazone*[13] ***1***

A solution of (2*R*)-2,3-di-*O*-benzyl-D-glyceraldehyde (1.35 g, 5 mmol) in dry THF (20 ml) was added to a stirred solution of benzoic acid hydrazide (816 mg, 6 mmol) in dry THF (20 ml) and the mixture was stirred at 80°C for 6 h. The solvent was evaporated *in vacuo* to afford the crude hydrazone which was purified by flash chromatography (ether) yielding 1.8 g (94% yield) of pure (2*S*)-2,3-di-*O*-benzylglyceraldehyde *N*-benzoylhydrazone **1** as a white solid. M.p.=105°C; $[\alpha]^{25}_D$=+28.8 (c, 1 in chloroform); IR (Nujol) 3205, 1665, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65–3.80 (m, 2H), 4.32–4.40 (m, 1H), 4.52 (s, 2H), 4.53 (d, 1H, J=12), 4.61 (d, 1H, J=12), 7.20–7.60 (m, 14H), 7.76–7.82 (m, 2H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.3, 71.5, 73.5, 77.7, 127.3, 127.7, 127.8, 128.3, 128.5, 128.6, 132.1, 132.7, 137.8, 149.6, 164.2. Anal. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.08; H, 6.47; N, 7.05.

(2S,3S)-1,2-Di-benzyloxy-3-(2-benzoylhydrazino)butane ***2***

A flask fitted with septum and gas inlet was charged with anhydrous $CeCl_3$ (4.93 g, 20 mmol), vented to dry argon, and ether was added *via* syringe. This slurry was stirred for 1 h at room temperature. To this white suspension was added methylmagnesium bromide (3 M solution in dibutyl ether, 6.66 ml, 20 mmol) slowly *via* syringe, and the reaction mixture was stirred for 1 h and cooled to 0°C. A solution of (2*S*)-2,3-di-*O*-benzylglyceraldehyde *N*-benzoylhydrazone **1** (1.55 g, 4 mmol) in ether/dichloromethane 1/1 (30 ml) was added slowly *via* syringe. After being stirred for 3 h at room temperature, the reaction mixture was poured into water (100 ml), and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford a 78/22 mixture of diastereoisomers in nearly quantitative yield. Purification of the residue by flash chromatography (hexane/ethyl acetate 1:1) afforded 1.16 g (72% yield) of diastereomerically pure (2*S*,3*S*)-1,2-di-benzyloxy-3-(2-benzoylhydrazino)butane **2** as a colourless oil. $[\alpha]^{25}_D$=−33.2 (c, 1 in chloroform); IR (Nujol) 3285, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.14 (d, 3H, J=6.9), 2.93 (dq, 1H, J=6.9, J=6.3), 3.66–3.80 (m, 3H), 4.53 (d, 1H, J=12.0), 4.57 (d, 1H, J=12.0), 4.66 (d, 1H, J=11.7), 4.75 (d, 1H, J=11.7), 7.20–7.45 (m, 14H), 7.45–7.60 (m, 2H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 58.0, 70.4, 72.4, 73.5, 82.5, 126.7, 127.7, 128.0, 128.4, 128.5, 131.4, 132.8, 138.0, 138.4, 165.9. Anal. Calcd. for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.51; H, 6.87; N, 6.81.

*(2S,3S)-1,2-Di-benzyloxy-3-(2-benzoyl-1-*tert*-butoxycarbonylhydrazino)butane* ***3***

Di-*tert*-butyl dicarbonate (1.25 g, 5.75 mmol) was added to a stirred solution of (2*S*,3*S*)-1,2-di-benzyloxy-3-(2-benzoylhydrazino)butane **2** (1 g, 2.5 mmol) and diisopropylethylamine (33 mg, 0.25 mmol) in dioxane (10 ml). After being stirred for 15 h at 50°C, the reaction mixture was treated with ether, washed with 1 M aqueous $KHSO_4$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexane/ethyl acetate 1/3) afforded 1.0 g (80%) of (2*S*,3*S*)-1,2-di-benzyloxy-3-(2-benzoyl-1-*tert*-butoxycarbonylhydrazino)butane **3** as a colourless oil. $[\alpha]^{25}_D$=21.1 (c, 1 in chloroform); IR (Nujol) 3306, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.25

(d, 3H, J=6.8), 1.44 (s, 9H), 3.65–3.74 (m, 3H), 4.50 (d, 1H, J=11.7), 4.51 (d, 1H, J=11.4), 4.55 (d, 1H, J=11.7), 4.72 (d, 1H, J=11.4), 7.25–7.50 (m, 15H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.4, 28.2, 55.1, 71.4, 73.0, 73.9, 81.0, 81.1, 127.0, 127.7, 127.8, 127.9, 128.4, 131.4, 133.0, 137.8, 138.4, 154.3, 166.5. Anal. Calcd. for $C_{30}H_{36}N_2O_5$: C, 71.41; H, 7.19; N, 5.55. Found: C, 71.68; H, 7.08; N, 5.42.

*(2S,3S)-3-(2-Benzoyl-1-*tert*-butoxycarbonylhydrazino)-1,2-butanediol* **4**

A solution of (2*S*,3*S*)-1,2-di-benzyloxy-3-(2-benzoyl-1-*tert*-butoxycarbonylhydrazino)butane **3** (756 mg, 1.5 mmol) in methanol (10 ml) was hydrogenated with $Pd(OH)_2$ (200 mg) as catalyst at room temperature for 12 h. When the reaction was complete the catalyst was removed by filtration and the filtrate evaporated to dryness to afford 447 mg (92% yield) of (2*S*,3*S*)-3-(2-benzoyl-1-*tert*-butoxycarbonylhydrazino)-1,2-butanediol **4** as a white solid. M.p.=117°C; $[\alpha]^{25}_D$=−34.0 (c, 0.8 in chloroform), IR (Nujol) 3205, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (d, 3H, J=6.9), 1.39 (s, 9H), 3.52–4.00 (m, 3H), 4.10–4.35 (m, 1H), 7.63–7.54 (m, 3H), 7.66–7.90 (m, 2H), 8.42 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.4, 28.2, 56.0, 63.3, 74.0, 82.2, 127.4, 128.7, 132.2, 132.5, 155.1, 168.5. Anal. Calcd. for $C_{16}H_{24}N_2O_5$: C, 59.25; H, 7.46; N, 8.64. Found: C, 59.09; H, 7.61; N, 8.72.

(S)-α-Hydrazinopropanoic acid **5**

Small portions of $NaIO_4$ (850 mg, 4 mmol) were added to a stirred solution of (2*S*,3*S*)-3-(2-benzoyl-1-*tert*-butoxycarbonylhydrazino)-1,2-butanediol **4** (324 mg, 1 mmol) in 2:2:3 acetonitrile–carbon tetrachloride–water (20 ml). After being vigorously stirred for 5 min following completion of the addition the mixture was treated with $RuCl_3 \cdot H_2O$ (8 mg, 0.04 mmol) and stirring was continued for 2 h. Dichloromethane (40 ml) was added and the mixture was extracted with 1 M aqueous $NaHCO_3$. The aqueous solution was washed with ethyl acetate, carefully acidified with 1 M aqueous $KHSO_4$ solution and extracted with dichloromethane (3×30 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was hydrolysed by refluxing for 5 h with 3 N hydrochloric acid (15 ml). After filtration the aqueous solution was washed with ether and evaporated *in vacuo* to give the crude product, which was purified by ion exchange chromatography (Dowex 50x8) to afford 81 mg (78% yield) of (*S*)-α-hydrazinopropanoic acid. $[\alpha]^{25}_D$=−28.0 (c, 1 in 6 N HCl), lit.[7] $[\alpha]^{20}_D$=−28.5 (c, 1 in 6 N HCl); ^{1}H NMR (D_2O, 300 MHz): δ 1.30 (d, 3H, J=7.2), 3.59 (q, 1H, J=7.2); ^{13}C NMR (D_2O, 75 MHz): δ 12.4, 58.8, 173.8. Anal. Calcd. for $C_3H_8N_2O_2$: C, 34.61; H, 7.75; N, 26.91. Found: C, 34.49; H, 7.92; N, 27.03; MS (EI) 105 (10, MH^+), 77 (7), 59 (100).

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References

1. See for example: (a) Lam, L. K. P., Arnold, L. D., Kalantar, T. H., Kelland, J. G., Lane-Bell, P. M., Palcic, M. M., Pickard, M. A., Vederas, J. C., *J. Biol. Chem.*, **1988**, *263*, 11814. (b) Scamen, C. H., Palcic, M. M., McPhalen, C., Gore, M. P., Lam. L. K. P., Vederas, J. C., *J. Biol. Chem.*, **1991**, *266*, 5525.
2. (a) Kasahara, K., Iida, H., Kibayashi, C., *J. Org. Chem.*, **1989**, *54*, 225. (b) Schmidt, U., Riedl, B., *J. Chem. Soc., Chem. Commun.*, **1992**, 1186.
3. (a) Morley, J. S., Payne, J. W., Hennessey, T. D., *J. Gen. Microbiol.*, **1983**, *129*, 3701. (b) Chen, S., Crusciel, R. A., Nakanishi, H., Raktabutr, A., Johnson, M. E., Sato, A., Weiner, D., Hoxie, J., Saragibi, H. U., Greene, M. I., Kahn, M., *Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 5872. (c) Aubry, A., Bayeul, D., Mangeot, J. P., Vidal, J., Sterin, S., Collet, A., Lecoq, A., Marraud, M., *Biopolymers*, **1991**, *31*, 793. (d) Aubry, A., Mangeot, J. P., Vidal, J., Collet, A., Zerkout, S., Marraud, M., *Int. J. Pept. Prot. Res.*, **1994**, *43*, 305. (e) Zerkout, S., Dupont, V., Aubry, A., Vidal, J., Collet, A., Vicherat, A., Marraud, M., *Int. J. Pept. Prot. Res.*, **1994**, *44*, 378.

4. (a) Genari, C., Colombo, L., Bertolini, G., *J. Am. Chem. Soc.*, **1986**, *108*, 6394. (b) Evans, D. A., Britton, T. C., Dorrow, R. L., Dellaria, J. F., *J. Am. Chem. Soc.*, **1986**, *108*, 6395. (c) Trimble, L. A., Vederas, J. C., *J. Am. Chem. Soc.*, **1986**, *108*, 6397. (d) Oppolzer, W., Moreti, R., *Helv. Chim. Acta*, **1986**, *69*, 1923. (e) Evans, D. A., Britton, T. C., Dorrow, R. L., Dellaria, J. F., *Tetrahedron*, **1988**, *44*, 5525. (f) Oppolzer, W., Moreti, R., *Tetrahedron*, **1988**, *44*, 5541. (g) Guanti, G., Banfi, L., Narisano, E., *Tetrahedron*, **1988**, *44*, 5553. (h) Greck, C., Bischoff, L., Ferreira, F., Pinel, C., Pireteau, E., Genet, J. P., *Synlett*, **1993**, 475.
5. (a) Viret, J., Garbar, J., Collet, A., *Tetrahedron*, **1987**, *43*, 891. (b) Vidal, J., Drouin, J., Collet, A., *J. Chem. Soc., Chem. Commun.*, **1991**, 435. (c) Niederer, D. A., Kapron, J. T., Vederas, J. C., *Tetrahedron Lett.*, **1993**, *34*, 6859.
6. Hoffman, R. V., Kim, K. O., *Tetrahedron Lett.*, **1990**, *31*, 2953.
7. Burk, M. J., Martinez, J. P., Feaster, J. E., Cosford, N., *Tetrahedron*, **1994**, *50*, 4399.
8. Kapron, J. T., Santarsiero, B. D., Vederas, J. C., *J. Chem. Soc., Chem. Commun.*, **1993**, 1074.
9. Cativiela, C., Diaz-de-Villegas, M. D., Galvéz, J. A., *Tetrahedron: Asymmetry*, **1996**, *7*, 529.
10. Badorrey, R., Cativiela, C., Diaz-de-Villegas, M. D., Galvéz, J. A., *Tetrahedron*, **1997**, *53*, 1411.
11. (a) Claremon, D. A., Lumma, P. K., Phillips, B. T., *J. Am. Chem. Soc.*, **1986**, *108*, 8265. (b) Baker, W. R., Condon, S. L., *J. Org. Chem.*, **1993**, *58*, 3277. (c) Remuzon, P., Dussy, C., Jacquet, J. P., Roty, P., Bouzard, D., *Tetrahedron: Asymmetry*, **1996**, *7*, 1181.
12. Wada, M., Sakurai, Y., Akiba, K. Y., *Tetrahedron Lett.*, **1984**, *25*, 1079.
13. Notice that *S*-benzoylhydrazone arise from *R*-glyceraldehyde according to Canh–Ingold–Prelog priority rules.

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