Amino Sugars

Asymmetric Synthesis of Selectively Protected Amino Sugars and Derivatives by a Direct Organocatalytic Mannich Reaction**

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In the classic Mannich reaction the corresponding β-aminocarbonyl compounds are formed from formaldehyde, an amine, and an enolizable carbonyl component.[1] These so-called Mannich bases have found broad applications as synthetic building blocks,[2] most importantly in the preparation of natural products and biologically active compounds.[3] The main disadvantage of the classic Mannich reaction has been the lack of stereocontrol and the formation of by-products. As a result, the development of more selective and particularly diastereo- and enantioselective protocols for this important C–C bond-forming reaction has been of substantial interest. In 1985 our research group, in cooperation with Steglich et al., disclosed for the first time a procedure for a stereoselective Mannich reaction, by which enamines together with acyliminoacetates could be transformed into diastereo- and enantiomerically pure α-amino-γ-keto esters.[4] Later on we developed a first practical procedure for the regio- and enantioselective α-aminomethylation of ketones with the assistance of a directing silyl group at the α-position to the carbonyl group.[5]

Interest in catalytic asymmetric variants of the Mannich reaction has grown considerably in recent years. The application of both metal-containing and metal-free catalysts has led to a breakthrough in accomplishing diastereo- and enantioselective Mannich reactions.[6] Although very low loadings of sophisticated chiral metal-based catalysts can be employed and lead to excellent yields as well as diastereo- and enantioselectivities,[7] more generous loadings of readily available metal-free organocatalysts are often preferentially used.

Special notice should be taken of the proline-catalyzed three-component Mannich reaction developed by List et al.[8] In this highly developed organocatalytic method, enolizable aldehydes and ketones are treated with in situ generated imines to afford the corresponding Mannich products with good to excellent stereoselectivities.[9] Barbas and his co-workers independently used this strategy for the direct

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asymmetric synthesis of α-amino acids by employing preformed iminoglyoxylates.[10]

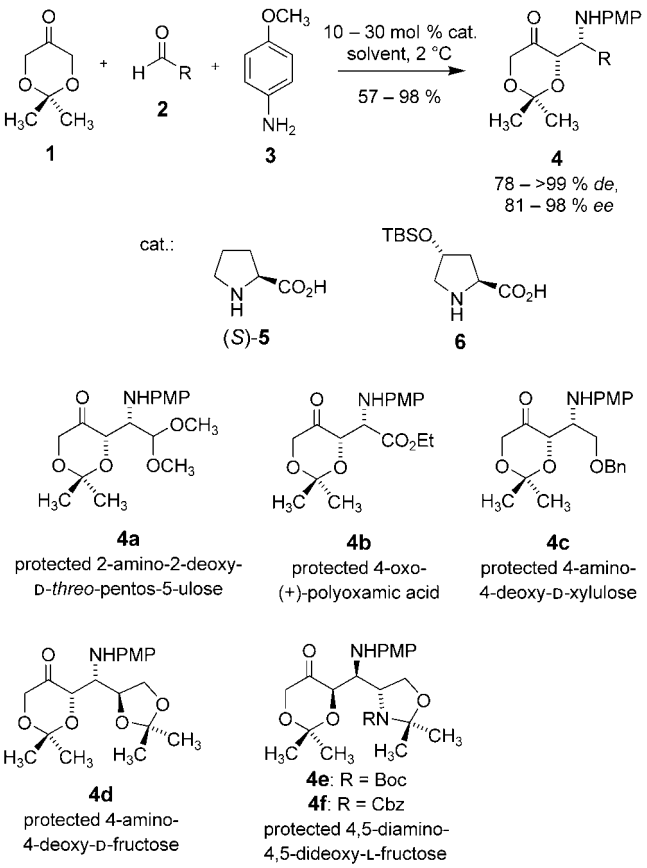
Recently, we reported a direct, organocatalytic de novo synthesis of carbohydrates. Starting from the dihydroxyacetone equivalent 2,2-dimethyl-1,3-dioxan-5-one (**1**),[11] various protected carbohydrates and amino sugars could be assembled in one step by a highly diastereo- and enantioselective proline-catalyzed aldol reaction.[12]

Carbohydrates are of great significance because of their diverse biological activities and application as synthetic building blocks and chiral auxiliaries.[13] Amino sugars are a class of carbohydrates, in which one or more hydroxy functions are replaced by amino groups. They are found as parts of glycoproteins, glycolipids, aminoglycosides, and many biologically active secondary metabolites containing free, methylated, or acetylated amino group.[14] The substitution of a hydroxy function by an amino group may alter the properties of the sugar significantly, for example, its hydrogen bonding properties, solubility, and charge. Consequently, amino sugars play important physiological roles in many glycoconjugates and are of interest for the development of new drugs.[15] There are numerous approaches for the synthesis of amino sugars. Most of them are based on naturally occurring carbohydrates and involve several protecting group manipulations as well as oxidation–reduction steps.[16] Alternatively, a linear synthetic sequence is used, but generally many reaction steps are required.[17]

Based on our organocatalytic $[C_3+C_x]$ concept for the direct synthesis of carbohydrates, we report here the successful development of a diastereo- and enantioselective Mannich variant that paves the way to selectively protected amino sugars and their derivatives.[18a] Initially, the (*S*)-proline-catalyzed three-component Mannich reaction of **1** with dimethoxyacetaldehyde (**2a**) and *para*-anisidine (**3**), as the amine component, was achieved. Thus, in the presence of 30 mol% proline in DMF at 2°C we obtained the Mannich product **4a** in 91% yield and excellent stereoselectivities (>99% *de*, 98% *ee* determined by HPLC; see Scheme 1). After recrystallization from heptane/2-propanol (9:1) **4a** could be obtained in practically diastereo- and enantiomerically pure form. Analogous conditions employed for the α-branched aldehydes **2d–g** and aldehyde **2b** also led to very good yields and selectivities; however, in the case of **2g** slightly superior results were obtained when acetonitrile and catalyst **6** were used (see Table 1). In contrast to the results of Barbas et al. aldehyde **2b** could also be used in the three-component reaction without prior isolation of the iminoglyoxylate.[18b]

In the case of linear aldehydes such as **2c** and the aromatic aldehydes **2h** and **2i** the results obtained under the above reaction conditions were not as good. Following extensive optimization of the reaction conditions we were able to verify the following general tendencies for these reactions.

1) The optimal reaction temperature was found to be between 2°C and ambient temperature. Apart from the expected decrease of the reaction rate at lower temperatures, we also observed a decline in the diastereo- and enantioselectivity, which may point to an isoinversion effect.[19]



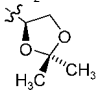
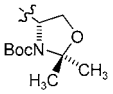
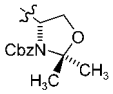
Scheme 1. Organocatalytic asymmetric three-component Mannich reaction of dioxanone **1** with different aldehydes **2** and the amine **3**. R groups are defined in Table 1. PMP = *para*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

2) The addition of 1–10 equivalents of water led to an increase of the stereoselectivity independent of the solvent employed, although depending on the solvent, a decrease in the reaction reate could be observed.
3) The use of catalyst **6** generally led to an enhancement of the reaction rate, due to its superior solubility properties, and also the stereoselectivity subject to the solvent.
4) When catalyst **6** is employed, the addition of water has again a positive effect on the stereoselectivity.

In the case of the (*S*)-proline-catalyzed reaction of **2c**, we found that *N*-methylpyrrolidinone (NMP) accompanied by the addition of 3 equiv of water yielded the best results (94% yield, 60% *de*, 82% *ee*). Substitution of proline and NMP by catalyst **6** and acetonitrile, respectively, accompanied by the addition of 5 equiv of water afforded **4c** in 77% yield and greatly improved the selectivities (88% *de*, 96% *ee*). Similar observations were made in the case of aromatic aldehydes **2h** and **2i**.

In our initial report of the proline-catalyzed aldol reaction of **1**, we were able to show that in the case of NBoc- or NCbz-protected, (*S*)-configured enantiomerically pure Garner aldehydes **2e** and **f** (*S*)-proline is the appropriate catalyst. Analogous investigations of the Mannich reactions showed

Table 1: Catalyzed asymmetric three-component Mannich reaction of dioxanone **1** with the aldehydes **2** and the amine **3** to give the products **4** (see Scheme 1).[a]

2/4	R	Cat. (mol%)	Yield [%][b]	Solvent	H_2O [equiv]	*de* [%][c]	*ee* [%][d]
a	$CH(OCH_3)_2$	(*S*)-**5** (30)	91	DMF	4	>99[d]	98
	$CH(OCH_3)_2$	**6** (20)	98	DMF	4	>99[d]	93
b	CO_2Et	(*S*)-**5** (10)	91	DMF	3	≥96	98
	CO_2Et	**6** (20)	94	DMF	–	≥96	95
c	CH_2OBn	(*S*)-**5** (30)	94	NMP	3	60[d]	82
	CH_2OBn	**6** (20)	77	CH_3CN	5	88[d]	96
d		(*S*)-**5** (30)	57	DMF	–	80 (≥96)[e]	≥98[f]
e		(*R*)-**5** (30)	67	DMF	–	≥96	≥96[f]
f		(*R*)-**5** (30)	63	DMF	–	≥96	≥96[f]
g		(*S*)-**5** (30)	83	CH_3CN	–	86	≥96[f]
		6 (20)	85	CH_3CN	–	≥96	≥96[f]
h		(*S*)-**5** (10)	67	NMP	–	≥96	51
		6 (20)	70	NMP	3	≥96	81
i		(*S*)-**5** (30)	75	DMF	2	60[d]	67
		6 (20)	96	CH_3CN	5	78[d]	87

[a] General reaction conditions : 0.77 mmol dioxanone **1**, 0.38 mmol aldehyde **2**, 0.42 mmol *para*-anisidine (**3**), 10–30 mol% catalyst, 1 mL solvent, 2 °C, 2–5 d. [b] Yields of **4** after flash chromatography on silica gel. [c] Determined by ^1H and ^{13}C NMR spectroscopy. [d] Determined by HPLC on chiral stationary phases (Daicel chiralpak AD, Daicel chiralcel OD). [e] After flash chromatography on silica gel. [f] Based on the *ee* value of the corresponding aldehyde **2**.

that when (*S*)-proline is used, only traces of the desired products could be isolated, whereas the (*R*)-proline-catalyzed reaction provided the Mannich products in good yields and virtually stereoisomerically pure (**4e**: 67%, ≤96% *de*, ≤96% *ee*; **4f**: 63%, 96% *de*, 96% *ee*). These results may support the suggestion that the proline-catalyzed Mannich reaction could facilitate kinetic resolutions of **1** with sterically demanding α-substituted aldehydes. Accordingly, (*R*)-proline should be the appropriate catalyst in the case of (*S*)-configurated, α-substituted aldehydes and (*S*)-proline for the application of (*R*)-configurated, α-substituted aldehydes. This was corroborated by the Mannich reaction of **1** with **2d** and **2g** and with (*S*)-proline as the catalyst (Table 1). As is evident from Scheme 1, the Mannich products **4a**–**f** constitute different selectively protected amino sugars and their derivatives, which could either be transformed to the corresponding amino sugars or used as synthetic building blocks, for example, **4a**. This organocatalysis can also be carried out smoothly on a multigram scale without any adverse effects on the yield and stereoselectivity (89% yield, ≤96% *de*, ≤96% *ee*), as exemplified by the reaction of **1** with **2a** and **3** to give **4a**.

The *syn* configuration of the Mannich products **4** was confirmed both by NOE measurements and an X-ray crystal structural analysis[20] on **4a** (Figure 1). These results are consistent with the transition-state model proposed by List et al. for the proline-catalyzed Mannich reaction. The stated absolute configurations are consistent with this model (Figure 2).

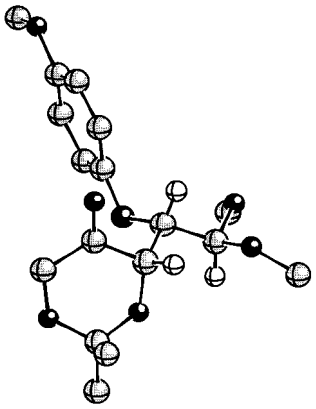


Figure 1. Crystal structure of **4a**.[20]

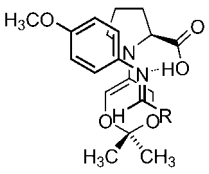
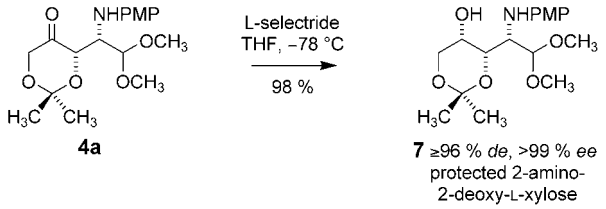


Figure 2. Transition-state model proposed by List et al.

The Mannich products **4** described here could be transformed into the corresponding β-amino alcohols by reduction of the keto function, which was successfully demonstrated in the

case of **4a**. Thus, the reduction of **4a** with L-selectride proceeded at −78 °C with high stereocontrol to yield the all-*syn*-configured β-amino alcohol **7**, which in its protected form belongs to the class of the biologically very important 2-amino-2-deoxy sugars (Scheme 2).[17c,21] Furthermore, the polyoxamic acids are directly available from **4b** by reduction of the keto function.[22] They are integral parts of the polyoxines and also occur in isolated form in nature, and have attracted interest due to their biological activity.[23]



Scheme 2. Diastereoselective reduction of **4a** to **7** with L-selectride.

The efficient asymmetric catalytic method we have described here starting from simple and commercially available compounds provides a viable alternative to the conventional, relatively elaborate, and less flexible methods for the synthesis of amino sugars. Our protocol facilitates the synthesis of different amino pentoses and hexoses with high diversity in only one to two steps.

Experimental Section

Unless otherwise stated, all chemicals are commercially available and were used without further purification with the exception of aldehyde **2g**[24] and catalyst **6**.[25] All new compounds were fully characterized (IR, NMR, MS, elemental analysis, optical rotation, melting point).

4a: In a 100-mL round-bottomed flask a 60 % aqueous solution of **2a** (2.6 g, 15 mmol) was dissolved together with **3** (2.04 g, 16.5 mmol) and (*S*)-proline (519 mg, 4.5 mmol) in DMF (55 mL) at 2 °C. The solution was stirred for 30 min before **1** (2 g, 15 mmol) was added, and the mixture was stored for 5 days at 2 °C. The reaction was quenched with pH 7 buffer (50 mL) and the mixture stirred for 15 min at ambient temperature. After extraction of the aqueous phase with ethyl acetate (3 × 75 mL), the combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography using silica gel (diethyl ether/pentane, 1:2). The product **4a** (4.53 g, 89 %) was obtained as a pale yellow solid, which was recrystallized from heptane/2-propanol (9:1) to afford colorless crystals. M.p. 78–80 °C. $[\alpha]_D^{23} = -83.3$ ($c = 0.98$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3375$ (w), 2990 (m), 2938 (m), 2833 (m), 1748 (s), 1617 (s), 1515 (s), 1462 (m), 1378 (m), 1232 (s), 1123 (m), 1094 (m), 1040 (m), 977 (m), 889 (m), 824 (m), 757 (s), 527 cm^{-1} (s); ^1H NMR (400 MHz, C_6D_6): $\delta = 1.27$ (s, 3H, CCH_3), 1.29 (s, 3H, CCH_3), 3.02 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.76 (d, $J = 16.4$ Hz, 1H, CH_2), 3.94 (dd, $J = 16.4$ Hz, $J = 1.4$ Hz, 1H, CH_2), 4.38 (dd, $J = 6.6$ Hz, $J = 1.6$ Hz, 1H, *CH*) 4.44 (d, $J = 6.6$ Hz, 1H, $CH(OCH_3)_2$), 4.68 (br, 1H, *CH*), 6.75 ppm (*app*-s, 4H, Ar); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 23.0$ (CH_3), 24.3 (CH_3), 53.3 (OCH_3), 54.5 (OCH_3), 54.9 (OCH_3), 56.3 (*CH*), 66.9 (CH_2), 75.1 (*CH*), 100.1 ($C(CH_3)_2$), 104.4 ($CH(OCH_3)_2$), 114.6 (*CH*), 115.9 (*CH*), 141.7 (*C*), 152.8 (*C*), 207.2 ppm (*CO*); MS (EI, 70 eV): *m*/*z* (%): 338.8 (11) [M^+], 263.9 (10) [$M^+ - C_3H_7O_2$], 217.9 (100) [$M^+ - C_7H_7NO$], 209.9 (16) [$M^+ - C_6H_9O_3$], 177.9 (68) [$C_{10}H_{12}NO_2^+$], 135.9 (17) [$C_8H_9NO^+$], 74.9 (31) [$C_6H_4^+$]; HPLC (Daicel OD, heptane/iPrOH 95/5, flow rate 0.8 mL min^{-1}, major isomer: $t_R =$ 11.86 min; minor isomer: $t_R = 8.78$ min; elemental analysis (%): calcd for $C_{17}H_{25}NO_6$: C 60.16, H 7.42, N 4.13; found: C 60.04, H 7.61, N 4.05.

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[20] CCDC 265324 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[22] We will report shortly in detail on the synthesis of the polyoxamic acids.

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