The Direct Catalytic Asymmetric Cross-Mannich Reaction: A Highly Enantioselective Route to 3-Amino Alcohols and α-Amino Acid Derivatives

Armando Córdova*[a]

Abstract: The first proline-catalyzed direct catalytic asymmetric one-pot, three-component cross-Mannich reaction has been developed. The highly chemoselective reactions between two different unmodified aldehydes and one aromatic amine are new routes to 3-amino aldehydes with $dr > 19:1$ and up to $> 99\%$ *ee*. The asymmetric cross-Mannich reactions are highly *syn*-selective and in several cases the two new carbon centers are formed with absolute stereocontrol. The reaction does not display nonlinear effects and therefore only one proline molecule is involved in the transition state. The reaction was also catalyzed with good selectivity by other proline derivatives. The Mannich products were converted into 3-amino alcohols and 2-aminobutane-1,4-diols with up to $> 99\%$ *ee*. The first one-pot, three-component, direct catalytic asymmetric cross-Mannich reactions between unmodified aldehydes, *p*-anisidine, and ethyl glyoxylate have been developed. The novel cross-Mannich reaction furnishes either enantiomer of unnatural α-amino acid derivatives in high yield and up to $> 99\%$ *ee*. The one-pot, three-component, direct catalytic asymmetric reactions were readily scaled up, operationally simple, and conductible in environmentally benign and wet solvents. The mechanism and stereochemistry of the proline-catalyzed, one-pot, three-component, asymmetric cross-Mannich reaction are also discussed.

Keywords: aldehydes · asymmetric synthesis · catalysis · Mannich reaction · proline

Introduction

One of the ultimate goals and challenges in chemistry is to develop stereoselective transformations for the creation of functionalized optically active molecules with structural diversity from simple and easily available starting materials. Hence, during the last two decades, the synthesis of enantiomerically pure or enriched compounds has emerged as one of the most important fields in organic synthesis. Several procedures to generate optically active molecules are known, and among these, asymmetric catalysis is a highly active research field.[1]

The Mannich reaction is a classic method for the preparation of nitrogen-containing compounds and therefore a very important carbon–carbon bond-forming reaction in organic synthesis. The versatility and potential to create both functional and structural diversity through this reaction have long stimulated the creativity of chemists.[2] It has been successfully employed numerous times, for example, as a key step in natural product synthesis and in medicinal chemistry.[3] However, regardless of the immense importance of this reaction only a few catalytic stereoselective Mannich-type reactions have been developed.[4] One major obstacle is the capability to control the roles of the three components of the Mannich reaction: carbonyl donor, amine, and aldehyde acceptor. Failure leads to competing side-reactions and decreases in product yield. Chemists have therefore developed several indirect methods that employ preformed enol equivalents or imines.[5] The first successful examples of catalytic asymmetric additions of enolates to imines were reported by Kobayashi and co-workers, who used chiral zirconium/BINOL complexes as catalysts.[6] Sodeoka et al.[7] and Lectka et al.[8] reported that palladium(II)/BINAP and copper(I)/BINAP complexes, respectively, are excellent catalysts for indirect asymmetric Mannich reactions with α-iminoglyoxylates. However, a disadvantage of these stereoselective Mannich reactions can be the preparation and instability of the preformed enolates used. An important advance for this class of asymmetric reactions would therefore be a catalytic stereoselective version employing unmodified carbonyl compounds.

Recently, Shibasaki and co-workers reported that heterodimetallic complexes are catalysts for the direct asymmetric Mannich reaction.[9] Shibasaki et al.[10] and Trost et al.[11]

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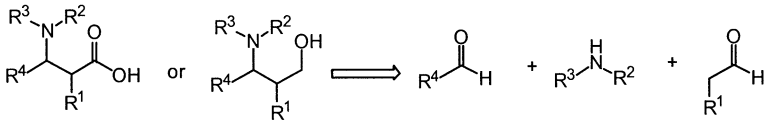
have also developed dinuclear zinc organometallic complexes that catalyze highly enantioselective Mannich-type reactions between hydroxyarylketones and preformed imines. Jørgensen et al. have developed direct asymmetric Mannich reactions involving activated ketones as donors and catalyzed by chiral copper(II) bisoxazoline (BOX) complexes.[12]

Asymmetric reactions catalyzed by metal-free organic catalysts have received increased attention in recent years.[13] Interestingly, after the discovery of amino acid catalyzed stereoselective Robinson annulations in the early 1970s,[14] there was no intensive research on this concept for other C–C bond-forming reactions for several decades, even though the reaction is frequently used in the preparation of building blocks for the total synthesis of natural products.[15] It was not until recently that researchers demonstrated that amino acid derivatives function as catalysts for direct asymmetric intermolecular C–C bond-forming reactions.[16–23] Among these reactions, List et al.,[24] Barbas et al.,[25] and we have developed organocatalytic asymmetric Mannich reactions that involve unmodified ketones as donors.[26] During our initial studies of proline-catalyzed, direct asymmetric cross-aldol reactions, we realized the ability of small organic molecules to activate unmodified aldehydes through an enamine mechanism for asymmetric additions to other electrophiles.[16f] We thus applied this strategy in the first organocatalytic asymmetric Mannich-type reactions with unmodified aldehydes as nucleophiles and preformed α-imino glyoxylate esters as the electrophiles.[27] In addition, Wenzel and Jacobsen have reported indirect organocatalytic asymmetric Mannich-type reactions between silyl enol ethers and preformed imines.[28] However, a more effective and atom-economic process would be a catalytic enantioselective one-pot, three-component cross-Mannich reaction with unmodified aldehydes, which would lead to a new route for the synthesis of β-amino acids and γ-amino alcohols (Scheme 1).[29]

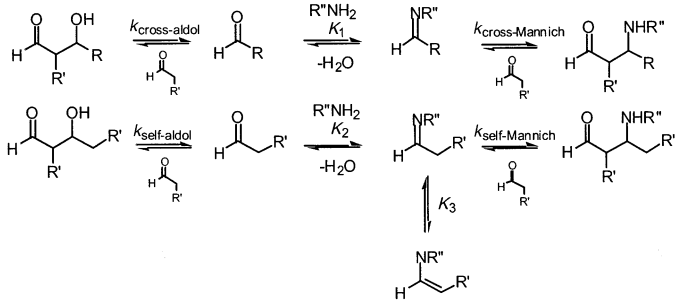


Scheme 1. Catalytic enantioselective one-pot, three-component cross-Mannich reaction with unmodified aldehydes.

We therefore embarked on the quest to develop a novel enamine-catalyzed asymmetric route for the synthesis of nitrogen-containing molecules. We have most recently disclosed the first one-pot, three-component, proline-catalyzed asymmetric cross-Mannich reactions between two different unmodified aldehydes and one amine, which provided Mannich adducts in up to >99% *ee*.[30] In this paper we describe the scope, mechanism, and applications of this novel, highly stereoselective, three-component, carbon–carbon bond-forming reaction.

Results and Discussion

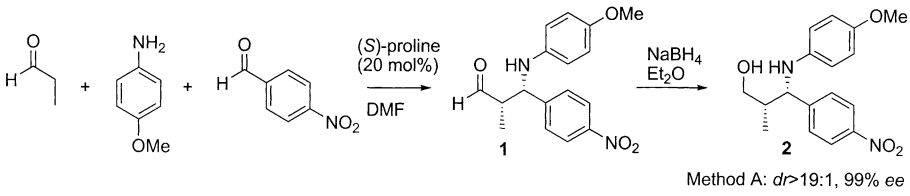
Scheme 2 depicts the different reaction pathways that could occur in a reaction between two different unmodified aldehydes. In order to obtain the desired product, the catalyst



Scheme 2. Potential different reaction pathways occurring in a reaction between two different unmodified aldehydes.

and reaction conditions have to allow and favor specific reaction pathways and equilibria. For example: 1) imine formation has to occur specifically with the acceptor aldehyde $K_1 \gg K_2$, 2) $k_{\text{cross-Mannich}} > k_{\text{self-Mannich}} > k_{\text{cross-aldol}} > k_{\text{self-aldol}}$, and 3) enamine formation (K_3) between the donor aldehyde and the amine component has to be avoided.

During our preliminary investigations of proline-catalyzed stereoselective additions of unmodified aldehydes to preformed imines we realized the potential of a small organic catalyst able to catalyze direct one-pot, three-component, asymmetric cross-Mannich reactions through an enamine mechanism.[30] These studies revealed that (*S*)- and (*R*)-proline were excellent catalysts for cross-Mannich-type reactions, and that a variety of preformed imines could be used as electrophiles. Moreover, we knew from previous Mannich transformations with unmodified ketones that the imine can be generated in situ.[24–26] However, the chemoselectivity of the amine-catalyzed, one-pot, three-component Mannich reactions with unmodified ketones can at times be low, resulting in the formation of significant amounts of aldol products. Furthermore, proline is also a catalyst for cross-aldol and self-aldol reactions and so it is not established whether $k_{\text{cross-Mannich}}$ would be higher than $k_{\text{cross-aldol}}$ and $k_{\text{self-aldol}}$.[16f–i] Nevertheless, we decided to develop a novel one-pot, three-component, direct asymmetric Mannich reaction with unmodified aldehydes. In an initial experiment, *p*-nitrobenzaldehyde (1.0 mmol) and *p*-anisidine (1.1 mmol) were mixed in the presence of a catalytic amount of (*S*)-proline (20 mol%) in DMF at 4°C for 15 minutes. Next, propionaldehyde (3.0 mmol) in cold DMF was slowly added to the reaction mixture by syringe pump over 4 h and the reaction was allowed to run for an additional 16 h at 4°C. The reaction was quenched by extraction and, to our delight, 3-amino aldehyde **1** could be isolated in 81% yield (Scheme 3).[30] The



Scheme 3. In situ reduction of Mannich adduct **1**, providing 3-amino propanol **2**.

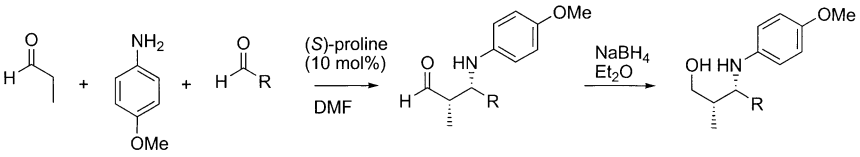
corresponding cross-aldol product was also formed, but in a much lower yield (<10%). Mannich adduct **1** was not significantly stable and decomposed after its isolation. We therefore decided to reduce **1** in situ with excess $NaBH_4$ prior to workup and isolation of the corresponding 3-amino alcohol derivative. Thus, 3-amino propanol **2** was isolated in 75% yield with dr>19:1 and 99% *ee* (Scheme 3, Method A).

In addition, the β-amino aldehydes can be extracted with Et_2O prior to reduction with $NaBH_4$ or another chemical manipulation of the propionaldehyde moiety.

Acceptor aldehyde component: Proline-catalyzed reactions with propionaldehyde as the donor and other aromatic aldehydes as acceptors proceeded readily, affording 3-amino-3-arylpropanols **2–11** with excellent chemo-, diastereo-, and enantioselectivities (Table 1).

Optimization studies of the enantioselectivities of the Mannich reactions with electron-rich aromatic acceptor aldehydes revealed that the use of a syringe pump was not essential at temperatures below 0°C and that the catalyst loading could be reduced. Furthermore, reactions with less polar imines generated in situ could be performed at higher concentrations, since the imines did not precipitate at the set temperature. An alternative method was therefore developed: the acceptor aldehyde (1.0 mmol) and *p*-anisidine (1.1 mmol) were mixed in the presence of a catalytic amount of (*S*)-proline (10 mol%) in DMF at room temperature. After 20–30 minutes the reaction temperature was decreased to below freezing, and propionaldehyde (3.0 mmol) was added in one portion to the reaction mixture, which was stirred for an additional 20 h at below 0°C. Next, the Mannich adduct was reduced in situ with $NaBH_4$ prior to workup and column chromatography (Method B). In addition, decreasing the reaction temperature from 4 to −20°C improved the yields and *ee*s of Mannich adducts derived from transformations with aromatic acceptor aldehydes lacking an electron-withdrawing group. As an example, the *ee* of Mannich adduct **3** was significantly increased from 78% to 93%. Interestingly, proline exhibits a higher selectivity at temperatures below 0°C, and $k_{\text{cross-Mannich}} > k_{\text{cross-aldol}}$ for aromatic acceptor aldehydes. Moreover, pyridinecarbaldehydes and furan-2-carbaldehyde were excellent electrophiles, providing the corresponding 3-aminopropanol adducts **9–11** in good yields with *ee* values of up to >99%, adding valuable new functionalities to the 3-aminopropanol adducts. In general, the yields and enantioselectivities of the Mannich adducts improved with increased reactivity of the acceptor aldehydes (imines formed in situ). The reactions were also readily scaled up to multigram levels without the yield or stereoselectivity being affected. The direct asymmetric cross-Mannich reactions proceeded with excellent chemoselectivity even though proline was able to catalyze the two-component self-Mannich reaction between propionaldehyde and *p*-anisidene to furnish the Mannich adduct **14** in 82% yield, *dr*>10:1, and 94% *ee*. This indicated that proline exhibits a higher $k_{\text{cross-Mannich}} > k_{\text{self-Mannich}}$ and that the equilibrium K_1 favors a stable acceptor imine. However, reactions with aliphatic acceptor aldehydes only afforded trace amounts of the corresponding Mannich adducts. Cyclohexanecarboxaldehyde and isopropylaldehyde, for example, provided a com-

Table 1. One-pot, three-component, direct catalytic asymmetric cross-Mannich reactions.[a]



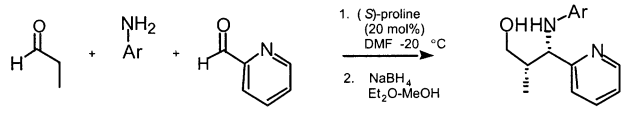
Entry	R	Method	*T* [°C]	Yield[%][b]	*dr*[c]	*ee*[d]	Product[e]
1	*p*-$NO_2C_6H_4$	A	4	75	>19:1	99	**2**
2	*p*-$NO_2C_6H_4$	B	4	41	>19:1	99	**2**
3	*p*-$NO_2C_6H_4$	B	0	46	>19:1	>99	**2**
4	C_6H_5	A	4	62	4:1	75	**3**
5	C_6H_5	B	0	66	10:1	88	**3**
6	C_6H_5	B	−20	80	>10:1	98	**4**
7	*p*-CNC_6H_4	A	0	75	>10:1	98	**4**
8	*p*-CNC_6H_4	B	−20	88	>10:1	>99	**4**
9	*p*-ClC_6H_4	B	−20	88	>10:1	>99	**5**
10	*p*-BrC_6H_4	B	−10	65	>10:1	99	**6**
11	*m*-BrC_6H_4	B	−10	72	>10:1	99	**7**
12	*p*-$MeOC_6H_4$	B	−20	50	>10:1	55	**8**
13	furfuryl	B	−20	80	4:1	84	**9**
14	2-pyridyl	B	−20	86	>10:1	>99	**10**
15	3-pyridyl	B	−20	80	>10:1	>99	**11**
16	cyclohexyl	B	−20	trace	n.d	n.d	**12**
17	isopropyl	B	−20	trace	n.d	n.d	**13**
18	Et	B	−20	82	>10:1	94	**14**

[a] Reaction conditions: Method A or B was used; see the Experimental Section. [b] Isolated yields of the 3-amino alcohol adduct after column chromatography. [c] Determined by NMR spectroscopy. [d] Determined by chiral-phase HPLC. [e] The 3-amino alcohol product.

plex reaction mixture mostly containing the corresponding cross-aldol products and self-aldol products from the donor. Perhaps for these substrates proline preferentially mediates the addition to the carbonyl moiety rather than the imine functionality ($k_{\text{cross-aldol}} > k_{\text{cross-Mannich}}$) and/or the equilibrium (K_1) does not favor a stable imine formation.

Amine component: The amine component of the asymmetric Mannich reaction can be regarded either as an "ammonia" equivalent or as an additional element of structural diversity, which is highly useful in drug development. The former requires a functional amine that can readily be converted into the free amine through deprotection. For this purpose, *p*-anisidine was used as the amine component, thus introducing a *p*-methoxyphenyl-protected (PMP-protected) amino group into the Mannich adducts. The PMP group is readily removed under oxidative conditions with cerium(IV) ammonium nitrate (CAN) or $PhI(OAc)_2$.[24,26,30a,b] Further introduction of structural diversity into the three-component, direct cross-Mannich reactions was achieved with excellent selectivity by use of proline and different aromatic amines, Mannich adducts **15**–**18** being obtained in high yields and with superb chemo- and enantioselectivities (Table 2). Cross-Mannich reactions with *para*-substituted anilines provided 3-amino alcohol derivatives with slightly

Table 2. One-pot, three-component, direct catalytic asymmetric cross-Mannich reactions with aromatic amines.[a]



Entry	R	Yield [%][b]	*dr*[c]	*ee* [%][d]	Product
1	*p*-$MeOC_6H_4$	85	>19:1	>99	**10**
2	C_6H_5	78	>19:1	>99	**15**
3	*p*-BrC_6H_5	82	>10:1	>99	**16**
4	*m*-BrC_6H_4	56	>10:1	99	**17**
5	*p*-IC_6H_4	65	>10:1	>99	**18**

[a] Reaction conditions: see Method B in the Experimental Section. [b] Isolated yields of the 3-amino alcohol adduct after silica gel column chromatography. [c] Determined by NMR spectroscopy. [d] Determined by chiral-phase HPLC.

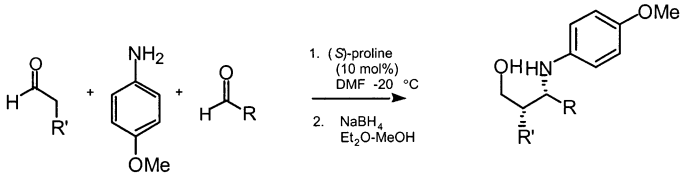
higher yields and *ee*s than those derived from *meta*-substituted anilines. For example, the reaction with *p*-bromoaniline afforded the corresponding 3-amino propanol **16** in 82% yield with $dr > 10{:}1$ and >99% *ee*, while the reaction with *m*-bromoaniline furnished the 3-amino propanol derivative **17** in 56% yield with $dr > 10{:}1$ and 99% *ee*.

Aldehyde donor component: We next investigated the scope of the aldehyde donor component (Table 3). We found that α-unbranched aliphatic aldehydes with a chain length of more than two carbons were excellent nucleophiles for the proline-catalyzed direct asymmetric, one-pot, three-component cross-Mannich reactions, furnishing Mannich adducts **21**–**23** in high yields and with excellent enantioselectivities (Table 3). For example, amino alcohol **23** was isolated in 78% yield with $dr > 19{:}1$ and 99% *ee*. The diastereoselectivity of the reaction varied slightly depending upon the chain length of the nucleophilic aldehyde. Cross-Mannich reactions with *n*-butanal provided a lower *dr* in the 3-amino alcohol adduct than were obtained with *n*-heptanal and propanal. The *ee*s of the Mannich adducts could also slightly decrease with increasing chain length of the aldehyde donor, depending upon the reactivity of the acceptor aldehyde (imine) (Entry 4). Interestingly, acetaldehyde and 2-substituted acetaldehydes only provided trace amounts of the desired cross-Mannich adducts and mainly self-aldol condensation products (entry 1, Table 3). Hence, in this case, $k_{\text{cross-aldol}} > k_{\text{cross-Mannich}}$.

One-pot direct catalytic asymmetric synthesis of either enantiomer of an unnatural amino acid: Up to this point, we had established that reactions with aromatic aldehydes provided excellent results, in contrast to reactions with aliphatic acceptor aldehydes. We were therefore not certain whether α-glyoxylate esters might serve as electrophiles for the one-pot, three-component, direct catalytic cross-Mannich reaction. However, retrosynthetic analysis as depicted in Scheme 1 and previous Mannich-type reactions with *N*-protected iminoglyoxylates had indicated that our synthetic strategy should be applicable to a direct multicomponent route for the synthesis of unnatural amino acid derivatives.[26,27] We thus treated different aldehydes with *p*-anisidine and ethyl glyoxylate in the presence of 10 mol% of either (*S*)- or (*R*)-proline in DMF at 4°C (Table 4).

To our delight, proline was able to catalyze the synthesis of β-formyl-α-amino acid derivatives **24**–**29** in good yield and with excellent chemo- and enantioselectivities. The products were more stable than the aromatic 3-amino aldehydes and subsequent reduction was not required. However, the *dr* values of the aldehyde-functionalized amino acid de-

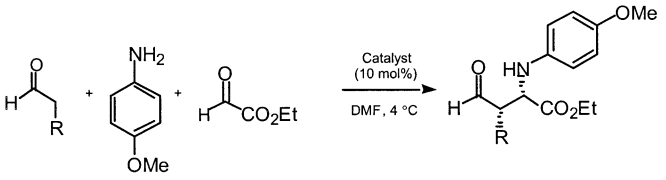
Table 3. One-pot, three-component, direct catalytic asymmetric cross-Mannich reactions with aldehydes.[a]



Entry	R	R′	Yield [%][b]	*dr*[c]	*ee* [%][d]	Product
1	2-pyridyl	H	trace	–	n.d	**19**
2	2-pyridyl	Me	85	>19:1	>99	**10**
3	2-pyridyl	Et	80	2:1	>99	**21**
4	*p*-$NO_2C_6H_4$	*n*-pent	77[e]	>10:1[e]	94[e]	**22**
5	2-pyridyl	*n*-pent	78[e]	>10:1[e]	>99[e]	**23**

[a] Reaction conditions: see Method B in the Experimental Section. [b] Isolated yields of the 3-amino alcohol adduct after silica gel column chromatography. [c] Determined by NMR spectroscopy. [d] Determined by chiral-phase HPLC. [e] Reaction performed with 20 mol% proline and 10 equiv of heptanal.

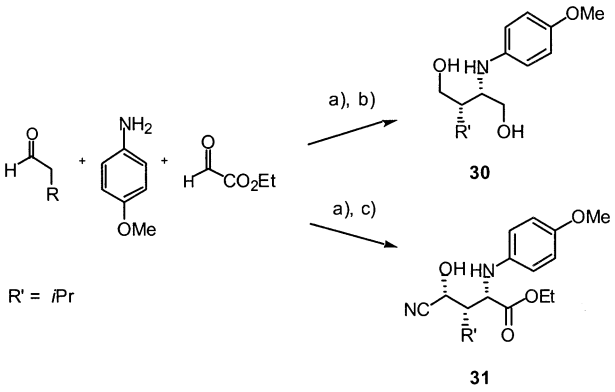
Table 4. One-pot, three-component, direct catalytic asymmetric synthesis of functional α-amino alcohol derivatives.[a]



Entry	Catalyst	R	Yield [%][b]	*dr*[c]	*ee* [%][d]	Product
1	(S)-proline	Me	67	1.5:1	>99	**24**
3	(R)-proline	Bu	80	>10:1	99	*ent-25*
4	(S)-proline	CH_2=$CHCH_2$	77	7:1	99	**26**
5	(S)-proline	pentyl	78	>10:1	>99	**27**
6	(S)-proline	isopropyl	70	>10:1	98	**28**
7	(S)-proline	$CH_3(CH_2)CH$=$CHCH_2$	70	>19:1	>99	**29**

[a] Reaction conditions: see the Experimental Section. [b] Isolated yields after silica gel column chromatography. [c] Determined by NMR spectroscopy. [d] Determined by chiral-phase HPLC.

rivatives decreased slightly during workup and isolation. This is, to the best of our knowledge, the first one-pot, three-component, direct catalytic asymmetric synthesis of either enantiomer of α-amino acid derivatives. The reaction circumvents the preparation of the imine and can readily be coupled with other nucleophilic carbon–carbon bond-forming reactions.[27b,c] We also developed a novel one-pot direct asymmetric synthesis of enantiomerically pure *N*-PMP-protected 2-aminobutane-1,4-diols such as **30**, which are useful precursors for the stereoselective synthesis of substituted 2-aminopyrrolidines (Scheme 4). In addition, β-cyanohydroxy-

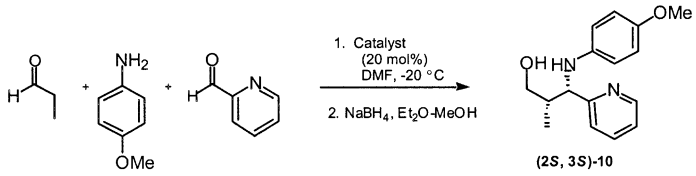


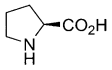
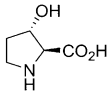
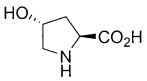
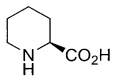
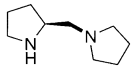
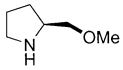
Scheme 4. One-pot direct catalytic asymmetric synthesis of functional α-amino acid derivatives. i: a) Ethyl glyoxylate, 2 equiv isovaleraldehyde, 1.1 equiv *p*-anisidine, 10 mol% (*S*)-proline, 4 °C. ii: either b) LAH, THF, 0 °C, 85% yield two steps, or c) Et_2AlCN, THF, −75 °C, 66% yield two steps.

methyl amino acid derivative **31**, with three contiguous stereocenters, was prepared through a tandem three-component, cross-Mannich cyanation reaction.

Catalyst: In our earlier studies of amine-catalyzed direct asymmetric cross-Mannich-type reactions, we discovered that other proline-derived amines are catalysts as well and can switch the diastereoselectivity of the products.[27] We therefore screened different organic amines as potential catalysts for the one-pot, three-component Mannich reactions (Table 5). Of the limited number of catalysts screened, proline provided the highest *ee* of **10**, closely followed by hydroxyproline derivatives, which furnished **10** with >90% *ee*. In addition, all the successful catalysts exhibit *syn* diastereoselectivity for the cross-Mannich reactions, as determined by NMR spectroscopy. Interestingly, picolic acid was not a catalyst for the reaction, establishing the importance of the cyclic five-membered, secondary amine structural motif. A similar observation has also been encountered in amine-catalyzed direct asymmetric aldol reactions.[16c] Furthermore, (*S*)-3-methoxymethylpyrrolidine (SMP) only provided trace amounts of product **2** under the set reaction conditions, due mainly to low imine formation.[27b]

Table 5. Catalyst screen.[a]

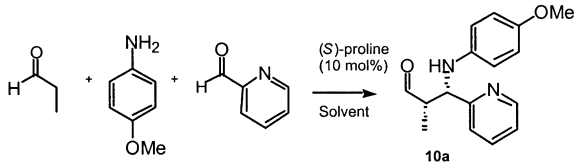


Entry	Catalyst	Yield [%][b]	*dr*[c]	*ee* [%][d]
1		85	>19:1	>99
2		63	>19:1	94
3		66	>19:1	96
4		trace	n.d	n.d
6		20	1:1	<5
7		trace	n.d	n.d

[a] Reaction conditions: see Method B in the Experimental Section. [b] Isolated yields of the 3-amino alcohol adduct after silica gel column chromatography. [c] Determined by NMR spectroscopy. [d] Determined by chiral-phase HPLC.

Solvent screen: We also performed a solvent screen of the one-pot, three-component, proline-catalyzed direct asymmetric cross-Mannich reaction between propionaldehyde, *p*-anisidine, and 2-pyridinecarbaldehyde (Table 6).

Table 6. Solvent screen of the proline-catalyzed, one-pot, three-component cross-Mannich reaction.[a]



Entry	Solvent	T [°C]	Yield [%][b]	*ee* [%][c]
1	dioxane	10	32 (65)[d]	99 (99)[d]
2	ether	−20	<10 (40)[d]	99 (99)[d]
3	THF	−20	39 (50)[d]	>99 (99)[d]
4	DMF	−20	85 (81)[d]	>99 (99)[d]
5	toluene	4	<10 (45)[d]	n.d (99)[d]
6	NMP	−20	88	>99
7	DMA	−20	79 (84)[d]	>99 (99)[d]

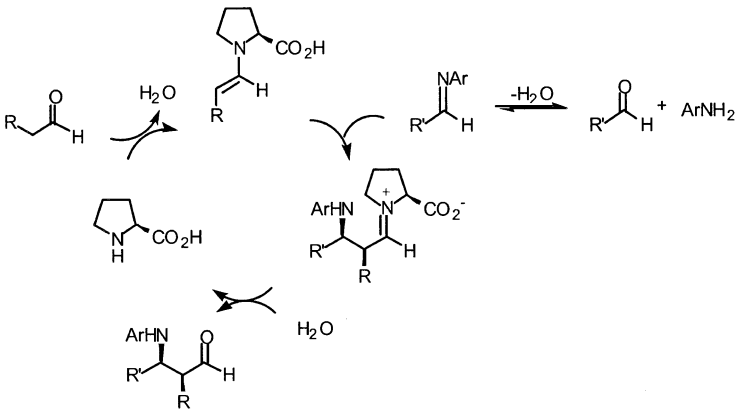
[a] Reaction conditions: see Method B in the Experimental Section. [b] Isolated yields of the corresponding 3-amino alcohol adduct after in situ reduction and silica gel column chromatography. [c] Determined by chiral-phase HPLC of the corresponding amino alcohol **10**. [d] (*S*)-Proline-catalyzed direct asymmetric cross-Mannich-type reactions between propionaldehyde and preformed *N*-PMP-protected *p*-nitrobenzaldimine according to Refs. [30a, b].

The reaction worked well in polar aprotic solvents such as DMF, *N*-methylpyrrolidinone (NMP), and DMA, with DMF and NMP providing the highest yields and *ee*s. The one-pot, three-component, catalytic cross-Mannich transformations in other solvents provided low yields and chemoselectivity. This contrasts with direct asymmetric cross-Mannich-type reactions with *N*-PMP-protected *p*-nitrobenzaldimine, which could be performed in a broader range of solvents.[30a, b] Hence, carbon–carbon bond-formation between the aldehyde and the imine could occur in solvents with smaller dielectric constants, which suggests that the in situ generation/stability of the imine was the predominant limiting factor.

Determination of absolute configuration: Synthesis and comparison with literature data established the absolute stereochemistry of the proline-catalyzed reaction (Scheme 5). Hence, 3-amino alcohol **3** was synthesized according to procedures developed by Viccario et al. and compared to the proline-derived **3**.[31] The amino alcohol adducts were compared by NMR spectroscopy and HPLC analyses; this revealed that (2*S*,3*S*)-**2** was formed by proline catalysis. Furthermore, subsequent deprotection of **3** by CAN afforded the known 3-amino alcohol **3a**.[32] Hence, (*S*)-proline affords (2*S*,3*S*)-3-amino 2-alkyl aldehydes and (*S*)-α-amino acid derivatives with *syn* relative stereochemistry.[33] In addition, NMR analyses revealed that the chemical shift of the doublet corresponding to the RN*H*PMP proton of the 3-amino alcohols and β-formyl amino acid derivatives were between $\delta = 4.52$–4.81 ppm with $J = 3.0$–6.5 Hz and $\delta = 4.18$–4.44 ppm with $J = 6.2$–8.1 Hz for the *syn* and *anti* isomers, respectively.

Scheme 5. Determination of the absolute configuration of amino alcohol adduct **3** and its deprotection. a) i) (*S*)-proline (10 mol%), DMF, −20°C, 20 h, ii) $NaBH_4$, MeOH/Et_2O, 0°C, 10 minutes. b) $LiAlH_4$, THF, 0°C, 3 h. c) CAN, CH_3CN, 0°C, 10 minutes.

Mechanism: The mechanism of the proline-catalyzed Mannich reactions is depicted in Scheme 6. The aldehyde donor reacts with proline, resulting in an enamine. Next, the imine, generated in situ, reacts with the enamine to give (after hydrolysis) the enantiomerically enriched Mannich adduct and the catalytic cycle can be repeated.



Scheme 6. The reaction mechanism for the proline-catalyzed one-pot direct asymmetric cross-Mannich reaction.

We did not observe any nonlinear effect in the proline-catalyzed reaction (Figure 1).[34] Thus, a single proline molecule is involved in the transition state and mechanism, acting as a molecular robot/enzyme. Furthermore, NMR analysis revealed that almost complete imine formation between PMP and aromatic acceptor aldehydes had taken place within five minutes at room temperature. The process was mediated by proline, since no significant amount of imine was formed in DMF in the absence of the catalyst. Importantly, only trace amounts of the cross-aldol products were observed at −20°C for the (*S*)-proline-catalyzed direct catalytic cross-Mannich reactions with aromatic acceptor aldehydes (imines). Hence, proline exhibited a much higher $k_{\text{cross-Mannich}}$ than $k_{\text{cross-aldol}}$ for these substrates under the set reaction conditions. In contrast, significant amounts of cross-aldol products were formed when aliphatic aldehydes were treated

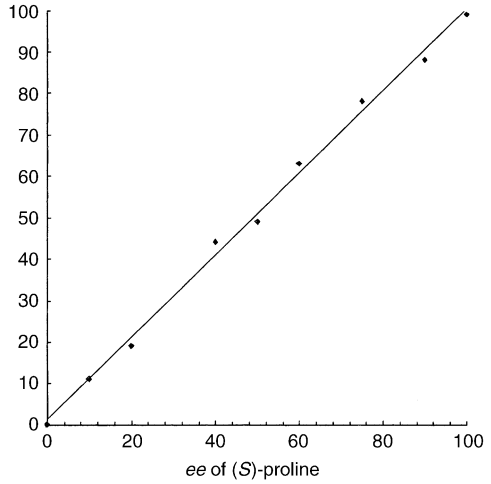


Figure 1. Linear effect in the (*S*)-proline-catalyzed cross-Mannich reaction of propionaldehyde with *p*-anisidine and 2-pyridylcarbaldehyde in DMF ($y = 0.99x + 1.02$, $R^2 = 0.996$).

with propionaldehyde under our reaction conditions, indicating that proline exhibits a higher $k_{\text{cross-aldol}}$ for aliphatic acceptor aldehydes than for the aromatic acceptor aldehydes.

The stereochemical outcome of the (*S*)-proline-catalyzed direct asymmetric Mannich reactions was explained in terms of a *si*-facial attack on the imine with a *trans* configuration by the *si*-face of the enamine (Figure 2, **I**). The six-membered metal-free Zimmermann–Traxler transition state is stabilized by hydrogen bonding between the nitrogen atom of the imine and the carboxylic group of proline. A switch of the facial selectivity is disfavored due to steric repulsion between the PMP group of the imine and the pyrrolidine moiety of the enamine. Interestingly, this is the opposite of what is observed in similar proline-catalyzed direct asymmetric cross-aldol reactions in which a *re*-facial attack occurs on the carbonyl from the *si*-face of the enamine (Figure 2, **II**).[16g–i] Hence, (*S*)-proline affords β-amino aldehydes with *syn* configurations and β-hydroxy aldehydes with *anti* sterochemistry. This switch of selectivity has also been observed in Mannich reactions with unmodified ketones and has been explained by density functional theory calculations of the respective transition states.[24,26,35]

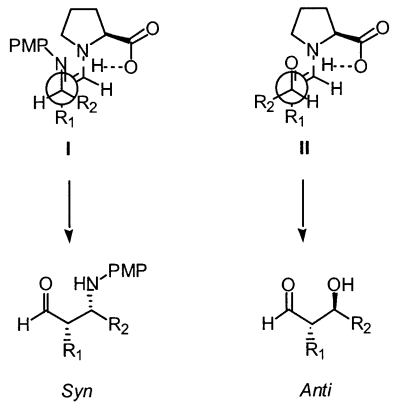


Figure 2. Postulated transition states of the cross-Mannich (**I**) and cross-aldol (**II**) reactions.

Conclusion

The first one-pot, three-component, direct catalytic asymmetric cross-Mannich reactions have been described. The highly chemoselective, proline-catalyzed reactions between two different unmodified aldehydes and one aromatic amine are new routes to β-amino aldehydes with *dr* values of >19:1 and up to >99% *ee*s. The asymmetric cross-Mannich reactions are highly *syn*-selective and in several cases the two new carbon centers are formed with almost absolute stereocontrol. The aldehyde moiety of the Mannich products is readily exploitable in other reactions in one-pot fashion. Furthermore, the β-amino aldehyde adducts are readily convertible into 1,3-amino alcohol derivatives and 2-aminobutane-1,4-diols with up to >99% *ee*s in one-pot operations. In addition, the first one-pot, three-component, direct catalytic asymmetric syntheses of unnatural amino acid derivatives have been developed. The novel cross-Mannich reactions between unmodified aldehydes, *p*-anisidine, and ethyl glyoxylate can furnish either enantiomer of unnatural α-amino acid derivatives in high yield and with up to >99% *ee*s. The one-pot, three-component, direct catalytic asymmetric reactions were readily scaled up, operationally simple, and did not require an inert atmosphere. In addition, the reactions could be conducted in environmentally benign and wet solvents. The reaction was also catalyzed with good selectivity by other proline derivatives. The reaction does not display nonlinear effects, and so only one proline molecule was involved in the transition state. In addition, proline activates aldimines preferentially to aldehydes at low reaction temperatures. The mechanisms and transition-state model have been discussed on the basis of the stereochemistry of the Mannich adducts. Taken as a whole, the reported transformation should be an inexpensive and useful route for the synthesis of optically active nitrogen-containing molecules.

Experimental Section

General methods: Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica-gel plates (Merck 60 F254) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL), followed by heating. Flash chromatography was performed on silica gel (Merck 60, particle size 0.040–0.063 mm), ^1H NMR and ^{13}C MR spectra were recorded on a Varian AS 400 instrument. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ or CD_3OD as solvents at room temperature, TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR. HPLC was carried out with a Hitachi organizer consisting of a D-2500 Chromato-Integrator, an L-4000 UV-Detector, an L-6200A Intelligent Pump, and a Waters 2690 Millennium with photodiode array detec-

tor. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter ($\lambda = 589$ nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB matrix.

Typical one-pot, three-component experimental procedure for the catalytic asymmetric cross-Mannich reaction of aldehydes and *p*-anisidine

Method A: A mixture of the acceptor aldehyde (1.0 mmol) and *p*-anisidine (1.1 mmol) in DMF (8.0 mL) was stirred for 15 min in the presence of a catalytic amount of proline (20 mol%) at 4°C. Next, a cold solution of the corresponding donor aldehyde (3.0 mmol) in DMF (2.0 mL) was slowly added by syringe pump over 4–5 h at 4°C. After an additional 15–16 h reaction time, the temperature was decreased to 0°C, followed by dilution with anhydrous Et_2O or MeOH (2.0 mL) and careful addition of excess $NaBH_4$ (0.4 g). The reaction was quenched after 10 minutes by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and 1 M aqueous HCl. The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis on chiral stationary phases.

Method B: A mixture of the acceptor aldehyde (1.0 mmol) and *p*-anisidine (1.1 mmol) in DMF (1.0 mL) was stirred for 20–30 minutes in the presence of a catalytic amount of proline (10 mol%) at room temperature. Next, the temperature of the reaction mixture was decreased to −20°C, and the donor aldehyde (3.0 mmol) was added to the reaction mixture in one portion. After 20 h vigorous stirring at −20°C, the solution was diluted with Et_2O (2.0 mL) and MeOH (2.0 mL), followed by the addition of excess $NaBH_4$ (0.4 g), and the reaction temperature was increased to 0°C. The reaction was quenched after 10 minutes by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and 1 M aqueous HCl. The organic layer was separated, and the aqueous phase was extracted thoroughly with ethyl acetate.[36] The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis on chiral stationary phases.

Typical one-pot, two-component catalytic asymmetric self-Mannich reaction: A mixture of the aldehyde (3.0 mmol) and *p*-anisidine (1.1 mmol) in DMF (1.0 mL) was stirred for 20 h in the presence of a catalytic amount of proline (10 mol%) at −20°C. Next, the solution was diluted with Et_2O or MeOH (2.0 mL), followed by addition of excess $NaBH_4$ (0.4 g), and the reaction temperature was increased to 0°C. The reaction was quenched after 10 minutes by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and 1 M aqueous HCl. The organic layer was separated, and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis on chiral stationary phases.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-nitrophenyl)propan-1-ol (2): $[\alpha]_D = -65.2$ ($c = 0.2$ in MeOH); ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (d, $J = 7.0$ Hz, 3H), 2.21 (m, 1H), 3.64 (m, 2H), 3.67 (s, 3H; OMe), 4.65 (d, $J = 4.0$ Hz, 1H), 6.42 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.8$ Hz, 2H), 8.17 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR: $\delta = 11.9$, 41.6, 56.0, 60.8, 66.0, 115.0, 115.1, 123.9, 128.3, 141.0, 147.3, 150.6, 152.6 ppm; HR-MS: *m*/*z* calcd for $C_{17}H_{20}N_2O_4$: 317.1496;found: 317.1496 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 36.10$ min; minor isomer: $t_R = 21.49$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol (3): $[\alpha]_D = -6.2$ ($c = 1$ in MeOH); ^{1}H NMR (CD_3OD): $\delta = 0.95$ (d, J = 7.0 Hz, 3H), 2.05 (m, 1H), 3.38 (dd, 1H), 3.56 (dd, 1H), 3.62 (s, 3H; OMe), 4.43 (d, J = 4.0 Hz, 1H), 6.38 (d, J = 8.8 Hz, 2H), 6.50 (d, J = 8.8 Hz, 2H), 7.12 (m, 1H), 7.24 (m, 2H), 7.31 ppm (d, J = 7.7 Hz, 2H); ^{13}C NMR: $\delta = 12.8$, 43.7, 56.3, 61.4, 66.0; 115.7, 116.0, 127.7, 128.6, 129.3, 143.9, 144.6, 151.9, 153.1, 157.7 ppm; HR-MS: *m*/*z* calcd for $C_{17}H_{21}NO_2$: 272.1645;found: 272.1647 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 14.02$ min; minor isomer: $t_R = 12.18$.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-cyanophenyl)propan-1-ol (4): $[\alpha]_D = -63.7$ ($c = 0.1$ in $CHCl_3$); ^{1}H NMR (CD_3OD): $\delta = 0.85$ (d, $J = 7.0$ Hz, 3H), 1.98 (m, 1H), 3.32 (dd, 1H), 3.45 (dd, 1H), 3.67 (s, 3H; OMe), 4.47 (d, $J = 4.0$ Hz, 1H), 6.38 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.54 ppm (d, $J = 8.0$ Hz, 2H); ^{13}C NMR: $\delta = 12.3$, 43.4, 56.1, 60.7, 65.5; 115.6, 115.7, 129.5, 133.1, 143.2, 151.3, 153.1 ppm; HR-MS: *m*/*z* calcd for $C_{18}H_{20}N_2O_2$: 297.1583; found: 297.1597 ($[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 28.86$ min; minor isomer: $t_R = 19.31$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-chlorophenyl)propan-1-ol (5): $[\alpha]_D = -29.6$ ($c = 1.9$ in CD_3OD); ^{1}H NMR (CD_3OD): $\delta = 0.93$ (d, $J = 7.0$ Hz, 3H), 2.02 (m, 1H), 3.38 (m, 1H), 3.53 (m, 1H), 3.67 (s, 3H; OMe), 4.45 (d, $J = 4.8$ Hz, 1H), 6.47 (d, $J = 8.4$ Hz, 2H), 6.62 (d, $J = 9.2$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.31 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 12.7$, 43.6, 56.3, 60.7, 65.8, 115.7, 115.9, 129.3, 130.2, 133.3, 143.6, 153.1 ppm; HR-MS: *m*/*z* calcd for $C_{17}H_{20}ClNO_2$: 305.1182; found: 305.1173 $[M]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 15.15$ min; minor isomer: $t_R = 10.84$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-bromophenyl)propan-1-ol (6): $[\alpha]_D = -38.9$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (CD_3OD): $\delta = 0.94$ (d, $J = 7.3$ Hz, 3H), 2.03 (m, 1H), 3.37 (dd, 1H), 3.55 (dd, 1H), 3.62 (s, 3H; OMe), 4.43 (d, $J = 5.1$ Hz, 1H), 6.47 (d, $J = 9.2$ Hz, 2H), 6.61 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.40 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 12.7$, 43.6, 56.3, 60.8, 65.8, 115.7, 115.9, 130.6, 132.3, 143.7, 144.1, 153.2 ppm; HR-MS: *m*/*z* calcd for $C_{17}H_{20}BrNO_2$: 350.0753; found: 350.0753 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 14.00$ min; minor isomer: $t_R = 10.14$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(3-bromophenyl)propan-1-ol (7): $[\alpha]_D = -28.6$ ($c = 1.7$ in MeOH); ^{1}H NMR (CD_3OD): $\delta = 0.85$ (d, $J = 7.0$ Hz, 3H), 1.98 (m, 1H), 3.32 (dd, 1H), 3.45 (dd, 1H), 3.54 (s, 3H; OMe), 4.35 (d, $J = 5.9$ Hz, 1H), 6.39 (d, $J = 9.2$ Hz, 2H), 6.52 (d, $J = 9.2$ Hz, 2H), 7.15 (dd, $J = 8.1$ Hz, $J = 7.5$ Hz, 2H), 7.21 (m, 2H), 7.42 ppm (br s, 1H); ^{13}C NMR: $\delta = 12.5$, 43.5, 56.2, 60.6, 65.7, 115.6, 115.7, 127.3, 130.6, 130.8, 131.6, 147.0, 147.6, 153.0 ppm; HR-MS: *m*/*z* calcd for $C_{17}H_{20}BrNO_2$: 350.0753; found: 350.0753 $[M+H]^+$; HPLC (Daicel Chiralpak OD-H, hexanes/*i*PrOH = 99.5:0.5, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 24.90$ min; minor isomer: $t_R = 21.71$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-methoxyphenyl)propan-1-ol (8): $[\alpha]_D = -6.6$ ($c = 2.7$ in MeOH); ^{1}H NMR ($CDCl_3$): $\delta = 0.92$ (d, $J = 7.0$ Hz, 3H), 2.15 (m, 1H), 3.64 (d, $J = 6.4$ Hz, 2H), 3.69 (s, 3H; OMe), 3.78 (s, 3H; OMe), 4.45 (d, $J = 4.4$ Hz, 1H), 6.54 (d, $J = 8.8$ Hz, 2H), 6.69 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.24 ppm (d, $J = 8.8$ Hz, 2H); ^{13}C NMR: $\delta = 12.6$, 41.6, 55.4, 56.0, 66.4, 114.0, 114.2, 114.9, 115.7, 128.4, 128.5, 133.6, 158.8 ppm; HR-MS: *m*/*z* calcd for $C_{18}H_{23}NO_3$: 302.3968; found: 302.3969 $[M+H]^+$; HPLC (Daicel Chiralpak OD-H, hexanes/*i*PrOH = 99.5:0.5, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 14.90$ min; minor isomer: $t_R = 11.71$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(2-pyridinyl)propan-1-ol (10): $[\alpha]_D = -28.9$ ($c = 1.2$ in MeOH); ^{1}H NMR (CD_3OD): $\delta = 0.85$ (d, $J = 7.0$ Hz, 3H), 2.11 (m, 1H), 3.32 (dd, 1H), 3.45 (dd, 1H), 3.54 (s, 3H; OMe), 4.53 (d, $J = 5.9$ Hz, 1H), 6.51 (d, $J = 9.2$ Hz, 2H), 6.63 (d, $J = 9.2$ Hz, 2H), 7.21 (m, 1H), 7.42 (m, 1H), 7.70 (m, 1H), 8.48 ppm (m, 1H); ^{13}C NMR: $\delta = 12.7$, 42.7, 56.3, 62.8, 66.0, 115.7, 116.0, 123.5, 123.8, 138.5, 143.6, 149.7, 153.4, 164.3 ppm; HR-MS: *m*/*z* calcd for $C_{16}H_{20}N_2O_2Na$: 295.3321; found: 295.3307 $[M+Na]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 90:10, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 42.57$ min; minor isomer: $t_R = 36.85$ min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(3-pyridinyl)propan-1-ol (11): $[\alpha]_D = -33.7$ ($c = 1.2$ in MeOH); ^{1}H NMR (CD_3OD): $\delta = 0.97$ (d, $J = 7.0$ Hz, 3H), 2.09 (m, 1H), 3.39 (dd, 1H), 3.56 (dd, 1H), 3.58 (s, 3H; OMe), 4.57 (d, $J = 5.9$ Hz, 1H), 6.51 (d, $J = 9.2$ Hz, 2H), 6.61 (d, $J = 9.2$ Hz, 2H), 7.26 (m, 1H), 7.78 (m, 1H), 8.31 (m, 1H), 8.51 ppm (m, 1H); ^{13}C NMR: $\delta = 12.8$, 43.5, 56.4, 59.1, 65.6, 115.9, 116.2, 125.1, 137.5, 137.7 143.3, 148.4, 149.8, 153.4 ppm; HR-MS: *m*/*z* calcd for $C_{16}H_{20}N_2O_2Na$: 295.3321; found: 295.3320 $[M+Na]^+$; HPLC (Daicel

Chiralpak AD, hexanes/*i*PrOH = 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 43.56 min; minor isomer: t_R = 37.88 min.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-pentan-1-ol (14): $[\alpha]_D$ = + 8.5 (c = 1 in MeOH); ^{1}H NMR (CD_3OD): δ = 0.92 (t, J = 6.9 Hz, 3H), 0.95 (d, J = 7.7 Hz, 3H), 1.52 (m, 2H), 1.87 (m, 1H), 3.50 (dd, 1H), 3.66 (dd, 1H), 3.68 (s, 3H; OMe), 6.70 (d, J = 8.8 Hz, 2H), 6.81 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR: δ = 11.9, 12.3, 26.7, 40.0, 56.4, 58.8, 66.3, 115.9, 116.0, 145.3, 153.0 ppm; HR-MS: m/z calcd for $C_{13}H_{21}NO_2$: 224.1645; found: 224.1645 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, λ = 254 nm): major isomer: t_R = 8.09 min; minor isomer: t_R = 12.18 min.

(2*S*,3*S*)-2-Methyl-3-(phenylamino)-3-(2-pyridinyl)propan-1-ol (15): $[\alpha]_D$ = −34.1 (c = 1.6 in MeOH); ^{1}H NMR (CD_3OD): δ = 0.96 (d, J = 7.0 Hz, 3H), 2.21 (m, 1H), 3.41 (dd, 1H), 3.59 (dd, 1H), 4.60 (d, J = 5.9 Hz, 1H), 6.54 (m, 2H), 7.18 (d, 2H), 7.42 (m, 1H), 7.63 (m, 1H), 8.47 ppm (m, 1H); ^{13}C NMR: δ = 12.8, 42.7, 61.9, 65.9, 114.6, 118.2, 123.6, 130.0, 138.6, 143.6, 149.4, 149.7, 164.3 ppm; HR-MS: m/z calcd for $C_{15}H_{18}N_2O$: 243.1497; found: 243.1495 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 28.87 min; minor isomer: t_R = 25.34 min;.

(2*S*,3*S*)-2-Methyl-3-(4-bromophenylamino)-3-(2-pyridinyl)propan-1-ol (16): $[\alpha]_D$ = −29.1 (c = 2.1 in MeOH); ^{1}H NMR (CD_3OD): δ = 0.97 (d, J = 7.0 Hz, 3H), 2.19 (m, 1H), 3.40 (m, 1H), 3.53 (m, 1H), 4.61 (d, J = 5.9 Hz, 1H), 6.49 (m, 2H), 7.10 (m, 2H), 7.21 (m, 1H), 7.42 (m, 1H), 7.67 (m, 1H), 8.48 ppm (m, 1H); ^{13}C NMR: δ = 12.7, 42.7, 61.9, 65.7, 114.6, 118.1, 123.5, 123.7, 130.0, 138.5, 149.7, 149.7 d, 164.3 ppm; HR-MS: m/z calcd for $C_{15}H_{17}BrN_2O$: 321.0602; found: 321.060 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 29.59 min; minor isomer: t_R = 39.57 min.

(2*S*,3*S*)-2-Methyl-3-(4-iodophenylamino)-3-(2-pyridinyl)propan-1-ol (18): $[\alpha]_D$ = −31.2 (c = 0.6 in MeOH); ^{1}H NMR (CD_3OD): δ = 0.99 (d, J = 7.0 Hz, 3H), 2.21 (m, 1H), 3.41–3.59 (m, 2H), 4.58 (d, J = 5.1 Hz, 1H), 6.40 (m, 2H), 7.26 (m, 3H), 7.45 (m, 1H), 7.75 (m, 1H), 8.52 ppm (m, 1H); ^{13}C NMR: δ = 9.9, 39.8, 58.8, 62.8, 114.0, 120.7, 120.8, 135.7, 135.8, 146.4, 146.8, 147.0 ppm; HR-MS: m/z calcd for $C_{15}H_{17}IN_2O$: 350.0753; found: 350.0751 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 38.22 min; minor isomer: t_R = 29.18 min.

(1*S*,2*S*)-1-(4-Methoxyphenylamino)-1-(2-pyridyl)-2-hydroxymethylbutane (21): ≈2:1 mixture of diastereoisomers, * denotes the *anti* diastereomer; ^{1}H NMR (CD_3OD): δ = 0.88 (t, J = 7.0 Hz, 1.5H*), 0.90 (t, J = 7.0 Hz, 3H), 1.39–1.61 (m, 2H, 1H*), 1.85–1.98 (m, 1H, 1H*), 3.51 (dd, 1H*), 3.53 (dd, 2H), 3.61 (s, 3H, 1.5H*; OMe), 4.34 (d, J = 7.0 Hz, 1H*), 4.59 (d, J = 4.0 Hz, 1H), 6.48 (dd, 2H, 1H*), 6.61 (dd, 2H, 1H*), 7.19 (m, 1H, 0.5H*), 7.42 (m, 1H, 0.5H*), 7.67 (m, 1H, 0.5H*), 8.47 ppm (m, 1H, 0.5H*); ^{13}C NMR: δ = 12.2, 12.4, 20.4, 22.4, 49.8, 56.3, 62.4, 63.0, 115.5, 115.8, 115.9, 116.0, 116.1, 123.5, 123.6, 124.0, 124.1, 138.4, 138.5, 143.6, 149.7, 153.5, 164.2, 164.5 ppm; HR-MS: m/z calcd for $C_{17}H_{22}N_2O_2$: 272.1645; found: 2721645 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 98:2, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 59.35 min; minor isomer: t_R = 46.47 min; major isomer*: t_R = 61.17 min; minor isomer*: t_R = 59.35 min.

(1*S*,2*S*)-1-(4-Methoxyphenylamino)-1-(4-nitrophenyl)-2-hydroxymethylheptane (22): $[\alpha]_D$ = −24.7 (c = 0.2 in MeOH); ^{1}H NMR (CD_3OD): δ = 0.83 (t, J = 7.0 Hz, 3H), 1.22–1.55 (m, 8H), 2.08 (m, 1H), 3.54 (d, J = 3.3 Hz, 1H), 3.68 (s, 3H; OMe), 3.73 (d, J = 3.3 Hz, 1H), 4.71 (d, J = 3.3 Hz, 1H), 6.48 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 8.17 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR: δ = 14.4, 22.9, 27.8, 29.7, 46.4, 56.1, 63.9, 96.6, 115.3, 124.1, 128.7, 147.5 ppm; HR-MS: m/z calcd for $C_{21}H_{28}N_2O_4$: 373.2122; found: 373.2120 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): major isomer: t_R = 17.79 min; minor isomer: t_R = 7.43 min.

(1*S*,2*S*)-1-(4-Methoxyphenylamino)-1-(2-pyridyl)-2-hydroxymethylheptane (23): $[\alpha]_D$ = −33.9 (c = 0.3 in MeOH); ^{1}H NMR (CD_3OD): δ = 0.82 (t, J = 7.0 Hz, 3H), 1.22–1.55 (m, 8H), 2.08 (m, 1H), 3.54 (d, J = 3.3 Hz, 1H), 3.59 (d, J = 3.3 Hz, 1H), 3.59 (s, 3H; OMe), 4.64 (d, J = 3.3 Hz, 1H), 6.51 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H) 7.16 (m, 1H), 7.41 (m, 1H), 7.65 (m, 1H), 8.46 ppm (m, 1H); ^{13}C NMR: δ = 14.6, 23.7, 27.3, 28.5, 33.2, 48.8, 56.3, 62.5, 63.5, 123.5, 124.1, 138.4, 143.6, 149.7, 153.4, 164.2 ppm; HR-MS: m/z calcd for $C_{20}H_{28}N_2O_4$: 373.2122; found: 373.2120 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 98:2, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 154.7 min; minor isomer: t_R = 94.3 min.

General procedure for the direct catalytic synthesis of β-formyl amino acid derivatives

Ethyl (2*S*,3*S*)-3-formyl-2-(4-methoxyphenylamino)butanoate (24): Ethyl glyoxylate (2.5 mmol) and *p*-anisidine (2.8 mmol) were stirred in the presence of a catalytic amount of (*S*)-proline (10 mol %) in DMF (2.5 mL) for 30 minutes at room temperature. Next, the temperature was decreased to 4 °C, followed by addition of the propanal (5 mmol). After stirring for 20–24 h, the reaction was quenched by addition of aqueous NH_4Cl solution, followed by extraction with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash column chromatography (pentanes/ethyl acetate = 5:1) afforded the corresponding β-formyl amino acid derivative **24** (0.38 g, 65 %): ≈1.5:1 mixture of diastereoisomers, * denotes the *anti* diastereomer. ^{1}H NMR ($CDCl_3$): δ = 1.10–1.40 (m, 12H), 2.87 (m, 2H), 3.73 (brs, 3H, 3H*; OMe), 3.91 (d, 1H, 1H*), 4.16 (m, 2H, 2H*), 4.38 (d, J = 6.6 Hz, 1H*), 4.49 (d, J = 3.4 Hz, 1H), 6.67 (m, 2H, 2H*), 6.77 (m, 2H, 2H*), 9.72 ppm (brs, 1H, 1H*); ^{13}C NMR: δ = 9.0, 9.8, 14.1, 14.1, 48.1, 48.4, 55.5, 55.6, 58.4, 58.6, 61.5, 61.6, 114.7, 114.8, 115.6, 116.3, 140.1, 140.4, 153.1, 153.4, 171.7, 172.3, 201.7, 201.8 ppm; HR-MS: m/z calcd for $C_{14}H_{19}NO_4Na$: 265.1309; found: 265.1316 $[M+Na]^+$; HPLC (Daicel Chiralpak AS, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, λ = 254 nm): major isomer: t_R = 18.82 min, major isomer*: t_R = 20.12 min, minor isomer: t_R = 23.11 min, minor isomer: t_R = 27.01 min.

(2*S*,3*S*)-3-Hydroxymethyl-2-(4-methoxyphenylamino)-4-methylpentan-1-ol (30): Ethyl glyoxylate (2.5 mmol) and *p*-anisidine (2.8 mmol) were stirred in the presence of a catalytic amount of (*S*)-proline (10 mol %) in DMF (2.5 mL) for 30 minutes at room temperature. Next, the temperature was decreased to 4 °C, followed by addition of isovaleraldehyde (5 mmol). After stirring for 20 h, the reaction mixture was diluted with THF (30 mL), and $LiAlH_4$ (50 mL, 1 M solution in THF) was added. The reaction mixture was allowed to reach room temperature and stirred for 1 h. The mixture was cooled and quenched by careful addition of aqueous NH_4Cl solution, followed by 3 M HCl, and extraction with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes/ethyl acetate 1:5) afforded diol **30** as a pale yellow oil (0.7 g, 85 %): ^{1}H NMR ($CDCl_3$): δ = 0.93 (d, J = 7.9 Hz, 3H), 1.02 (d, J = 7.9 Hz, 3H), 1.55 (m, 1H), 1.92 (m, 1H), 3.55 (m, 1H), 3.63 (m, 1H), 3.71–3.3.83 (m, 6H), 6.58 (d, J = 8.8 Hz, 2H), 6.76 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR: 20.1, 21.3, 25.9, 47.5, 55.2, 55.7, 59.1, 60.8, 115.0, 115.2, 141.1, 152.1 ppm; HR-MS: m/z calcd for $C_{14}H_{32}NO_3$: 254.1751; found: 254.1752 $[M+H]^+$; HPLC (Daicel Chiralpak AS, hexane/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 23.12 min; t_R (minor) = 26.64 min.

Ethyl (2*S*,3*S*)-3-[(*R*)-cyanohydroxymethyl)-2-(4-methoxyphenylamino]-4-methylpentanoate (31): Ethyl glyoxylate (2.5 mmol) and *p*-anisidine (2.8 mmol) were stirred in the presence of a catalytic amount of (*S*)-proline (10 mol %) in DMF (2.5 mL) for 30 minutes at room temperature. Next, the temperature was decreased to 4 °C, followed by addition of isovaleraldehyde (5 mmol). After stirring for 20 h, the reaction mixture was diluted with THF (7.5 mL) and the temperature was decreased to −75 °C. Next, Et_2AlCN (1 M solution in toluene, 10 mmol) was added, and the solution was stirred for 2.5 h. The mixture was quenched by addition of 1 M $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by flash column chromatography (pentanes/ethyl acetate = 4:1) afforded cyanohydrin **31** as a clear oil (0.52 g, 66 %): $[\alpha]_D$ = −13.3 (c = 2.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ = 1.10 (d, J = 5.5 Hz, 3H), 1.16 (d, J = 5.5 Hz, 3H), 1.28 (t, 3H), 2.18 (brs, 2H), 3.74 (s, 3H; OMe), 4.22 (q, 2H), 4.39 (d, J = 6.3 Hz, 1H), 4.87 (brs, 1H), 6.70 (d, J = 8.8 Hz, 2H), 6.79 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR: 13.9, 20.7, 21.4, 26.3, 50.7, 55.6, 57.8, 61.2, 61.6, 114.8, 116.4, 119.2, 139.9, 153.4, 173.4 ppm; HR-MS: m/z calcd for $C_{14}H_{32}NO_3$: 321.1809; found: 321.1811 $[M+H]^+$; HPLC (Daicel Chiralcel OD-H, hexane/*i*PrOH 98:2, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R (major) = 8.32 min; t_R (minor) = 12.59 min.

Synthesis of (2*S*,3*S*)-2-methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol and (2*R*,3*S*)-2-methyl-3-(4-methoxyphenylamino)-3-phenylpropan-1-ol: A diastereomeric mixture (*syn*/*anti* 0.9:1) of methyl (3*S*)-2-

methyl-3-(4-methoxyphenylamino)-3-phenylpropanoate (0.1 mmol) in THF (5 mL), synthesized according to ref. [31], was reduced by addition of $LiAlH_4$ (1 mmol) at 0 °C. After 4 h at this temperature the reaction mixture was allowed to reach room temperature and quenched by addition of $Na_2SO_4{\cdot}10H_2O$ and filtered through Celite. Next, the filtrate was diluted with ether and washed with brine. The organic layer was separated, and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford β-amino alcohol **3** as an inseparable mixture of diastereomers (dr = 0.9:1, *syn*/*anti*) in 72% yield. ^{1}H NMR (CD_3OD): (* denotes the *anti* diastereomer) $\delta = 0.79$ (d, $J = 7.0$ Hz, 3H*), 0.95 (d, $J = 7.0$ Hz, 3H), 2.05 (m, 1H, 1H*), 3.38 (dd, 1H), 3.56 (dd, 1H), 3.61 (d, $J = 5.9$ Hz, 2H*), 3.62 (s, 3H, 3H*; OMe), 4.27 (d, $J = 7.0$ Hz, 1H*), 4.43 (d, $J = 4.0$ Hz, 1H), 6.50 (dd, 2H, 2H*), 6.61 (dd, 2H, 2H*), 7.12 (m, 1H, 1H*), 7.24 (m, 2H, 2H*), 7.31 ppm (m, 2H, 2H*); ^{13}C NMR: $\delta = 12.8$, 14.6, 42.8, 43.6, 56.2, 56.3, 61.4, 66.0, 66.3, 115.6, 115.7, 116.0, 116.5, 127.7, 127.9, 128.6, 129.2, 129.3, 143.9, 144.4, 153.2, 153.4 ppm; HR-MS: *m*/*z* calcd for $C_{17}H_{21}NO_2$: 272.1645; found: 272.1647 $[M+H]^+$; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH = 99:1, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_R = 14.02$ min; minor isomer: $t_R = 12.18$ min; major isomer*: $t_R = 15.55$ min; minor isomer*: $t_R = 13.55$ min.

(2*S*,3*S*)-3-Amino-2-methyl-3-phenylpropan-1-ol (3a): CAN (386 mg) in H_2O (1.74 mL) was added to a solution of β-amino alcohol **3** (87.5 mg) in acetonitrile (5.7 mL) at −15 °C. After 15 min the reaction mixture was directly purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford **3a** in 65% yield (35 mg). ^{1}H NMR (CD_3OD): $\delta = 1.10$ (d, J = 4.4 Hz, 3H), 2.35 (m, 1H), 3.44 (d, $J = 5.14$ Hz, 1H), 3.48 (d, $J = 6.6$ Hz, 1H), 4.35 (d, $J = 6.6$ Hz, 1H), 7.54 ppm (m, 5H); ^{13}C NMR: $\delta = 12.0$, 40.9, 59.1, 66.2, 126.9, 127.1, 128.2, 143.9 ppm. Comparison of the NMR data with those previously reported for 3-amino-2-methyl-3-phenylpropan-1-ol revealed a *syn* relationship of the substituents.[32]

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