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Short α/β-Peptides as Catalysts for Intra- and Intermolecular Aldol Reactions

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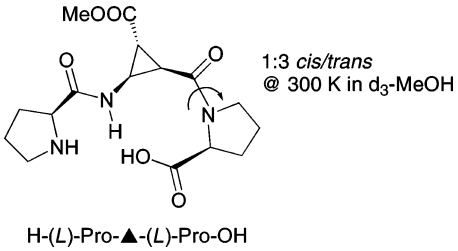


Short α/β-peptides, containing conformationally restricted *cis*-β-aminocyclopropylcarboxylic acid units as turn-inducing elements, have been found to be efficient catalysts for inter- and intramolecular aldol reactions. The tripeptide H−(*L*)-Pro-▲-(*L*)-Pro−OH was identified to perform especially well in homogeneous and heterogeneous aqueous solutions as well as in organic solvents.

The aldol reaction represents one of the most powerful tools available for C−C bond formation. In the last years several efforts have been directed to create metal-free catalysts that would allow high yield and selectivity for this reaction. With the pioneering work of Hajos and Parrish and Eder et al.,[1] it became apparent that (*L*)-proline arguably represents the best example of a naturally available organocatalyst. Its unique mode of action, i.e., both the amino and the carboxylic acid functionality of the catalyst cooperate in activating and arranging the reagents[2] (Figure 1), recalls the biological activity of the enzyme type I aldolase.[3] However, proline does not currently represent the most efficient organocatalyst for this process because of the solvent choice necessary (DMSO) to be an effective catalyst.[4]

β-aminocyclopropane carboxylic acids (β-ACCs) have proved to greatly stabilize secondary structures even in short peptides when combined with natural α-amino acids, which has led to the synthesis of a novel class of foldamers[5] as well as to ligands with high affinity and selectivity for specific neuropeptide Y and integrin receptors.[6] On the basis of these structural properties, we set out to explore if the β-ACCs would also be useful building blocks for peptidic organocatalysts. We would like to disclose here short α,β-peptides containing the unnatural *cis*-β-ACCs ▲ and ▼ (Figure 1 and Scheme 1) that allow inter- and intramolecular aldol reactions to be carried out with high yields and enantioselectivity.

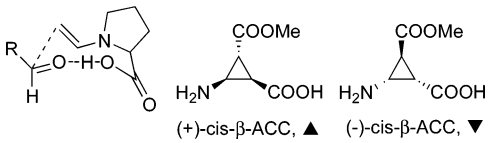
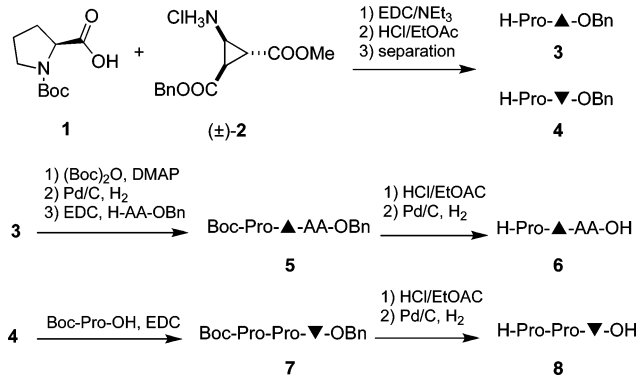


FIGURE 1. Transition-state model for the (*L*)-proline-catalyzed aldol reaction (left) and the *cis*-β-ACC enantiomers ▲ and ▼ used in this study.

SCHEME 1. Standard Reaction Scheme for the Synthesis of Peptides with Central and Terminal β-ACC Units



Taking the excellent results of Wennemers and co-workers[7] into account, who demonstrated the benefits of (*L*)-proline in tripeptide catalysts for the aldol reaction, we concentrated on combinations of at least one of this residue with ▲ or ▼.

The shelf-stable building block **2** required for the incorporation of β-ACC into peptides is readily accessible from *N*-Boc-pyrrole in either enantiomeric form.[8] Since we could not forsee which β-ACC enantiomer would be more effective in combination with naturally occurring α-amino acids, we wanted to investigate peptides with both ▲ or ▼ being incorporated. Therefore, it was more efficient to synthesize dipeptides using the racemic rather than the enantiomerically pure β-ACCs following the in situ coupling strategy developed by us[9] and separate the resulting diastereomers by column chromatography (Scheme 1). Subsequent deprotection at the C-terminus and coupling with amino acids or peptides cleanly resulted in the corresponding tri- and tetrapeptides.

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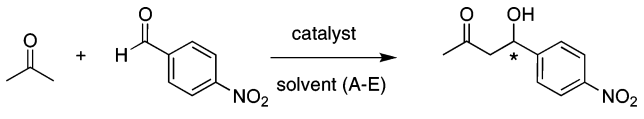
TABLE 1. Aldol Reaction between 9 and 10 Catalyzed by (*L*)-Pro and *β*-ACC-Containing Peptidic Catalysts



9 **10a** **11a**

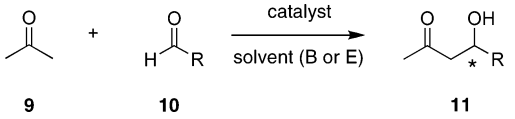
entry	catalyst H−XXX−OH	solvent[a]	yield[b] (%)	ee (%)[b]
1[c]	Pro	DMSO	68	76(*R*)
2	Pro	A	74	53(*R*)
3	Pro	B	98	0
4	Pro	C	95	0
5	Pro	E	68	61(*R*)
6	Pro-▼	A	56	14
7	Pro-▼	C	47	0
8	Pro-▲	A	29	64(*R*)
9	Pro-▲	C	45	65(*R*)
10	Pro-▼-Pro	C	77	6(*R*)
11	Pro-▼-Asp	C	89	13(*R*)
12	Pro-▲-Pro	A	99	70(*R*)
13	Pro-▲-Pro	B	89	78(*R*)
14	Pro-▲-Pro	C	72	74(*R*)
15	Pro-▲-Pro	D	95	71(*R*)
16	Pro-▲-Pro	E	53	29(*R*)
17	Pro-▲-Asp	C	70	62(*R*)
18	Pro-▲-Glu	C	59	73(*R*)
19	Pro-Pro-▲	E	59	64(*S*)
20	Pro-Pro-▲	C	48	0
21	Pro-Pro-▼	E	79	73(*S*)
22	Pro-Pro-▼[d]	E	86	88(*S*)
23	Pro-Pro-▼[d,e]	E	75	83(*S*)
24	Pro-Pro-▼	C	83	57(*S*)
25	Pro-*β*-Ala-Pro	C	96	51(*R*)
26	Pro-*β*-Ala-Pro	E	66	37(*S*)
27	Pro-▲-Pro-▼	C	36	74(*R*)
28	Pro-▼-Pro-Pro	E	76	33(*S*)
29	Pro-▼-Pro-Pro	C	58	0

[a] All reactions were carried out at 25 °C in 24 h, using 0.2 mmol **10a** and 20 mol % of catalyst in 2 mL of solvent unless noted otherwise. A, acetone; B, acetone/water 10:1 (v/v); C, acetone/water 5:1 (v/v); D, acetone/water 3:1 (v/v); E, $CHCl_3$/acetone 2:1 (v/v). [b] Isolated yields, ee determined by chiral HPLC or chiral GC (after converting the product to its corresponding trimetylsilylether). [c] Taken from ref 3. [d] Reaction carried out at 0 °C. [e] With 5 mol % of catalyst.

As a benchmark, we decided to test our peptides as catalysts for the aldol reaction of acetone and *p*-nitrobenzaldehyde (Table 1). From screening a variety of di, tri-, and tetrapeptides, it became apparent that tripeptides with *β*-ACC units appeared to be optimal in length. H−Pro-▲-Pro−OH and H−Pro−Pro-▼−OH were found to be particularly effective, giving rise to **11a** in up to 88% ee (entry 22). It was important to note that both the conformational rigidity as well as the absolute configuration of the *β*-ACCs was a decisive factor. Using *β*-alanine or ▼ as the central or ▲ as the terminal building block in combination with (L)-amino acids gave inferior results; representative examples are shown in Table 1, entries 10−26. Interestingly, the peptide Pro-▲-Pro is an effective asymmetric[10] catalyst[11] in homogeneous aqueous[12] solution without the necessity of employing additives (entry 13−15), contrasting with proline (entries 3 and 4) and comparing well to other organocatalysts that have been investigated in such media for the title reaction.[13]

With H−Pro-▲-Pro−OH in acetone/water and H−Pro−Pro-▼−OH in acetone/chloroform identified as promising catalysts for aldol reactions, their scope was further explored.

TABLE 2. Aldol Reaction between 9 and 10 Catalyzed by (*L*)-Pro and Pro-▲-Pro, Pro-Pro-▼[a]



9 **10** **11**

entry	R	catalyst[a] H−XXX−OH	solvent[b]	yield (%)	ee (%)
1	Ph	Pro-Pro-▼	E	50[c]	79(*S*)
2	Ph	Pro-▲-Pro	B	48	76(*R*)
3	*o*-Cl−Ph	Pro-Pro-▼	E	91[d]	80(*S*)
4	*o*-Cl−Ph	Pro-▲-Pro	B	80	68(*R*)
5	*p*-Cl−Ph	Pro-Pro-▼	E	42[c]	84(*S*)
6	*p*-Cl−Ph	Pro-▲-Pro	B	43	80(*R*)
7	*o*-Br−Ph	Pro-Pro-▼	E	84[d]	82(*S*)
8	*o*-Br−Ph	Pro-▲-Pro	B	86	72(*R*)
9	*o*-NO_2-Ph	Pro-Pro-▼	E	88	88(*S*)
10	*o*-NO_2-Ph	Pro-▲-Pro	B	82	91(*S*)
11	*p*-NO_2-Ph	Pro-Pro-▼	E	86[c]	88(*S*)
12	*p*-NO_2-Ph	Pro-▲-Pro	B	89	78(*R*)
13	*c*-C_6H_{11}	Pro-Pro-▼	E	57	82(*S*)
14	*c*-C_6H_{11}	Pro-▲-Pro	B	57	41(*R*)

[a] Reactions were carried out at 25 °C, for 24 h, using 0.2 mmol **10**, 20 mol % of catalyst in 2 mL of solvent. [b] Cf. Table 1. [c] At 10 °C. [d] At 5 °C.

For aldol reactions with aromatic ketones and acetone, the *β*-ACC-containing peptide catalysts gave generally good yields and selectivities with both catalysts tested, giving rise to the aldol products with opposite absolute stereochemistry. In contrast, for cyclohexylcarbaldehyde, H−Pro−Pro-▼−OH gave considerably better results (Table 2). Conveniently, the peptide catalyst could be recovered quantitatively with excellent purity in all cases by lyophilization after the evaporation of acetone and extraction of **11** with ethyl acetate from the aqueous phase.

The catalyst H−Pro-▲−Pro−OH was subsequently tested in the aldol reaction between aromatic aldehydes and some representative cyclic ketones (Table 3), using either homogeneous water/ketone solutions that had already proved to be effective for this catalyst or heterogeneous water containing mixtures that have been reported in the literature as effective media for this process.[14] Neat ketones have been employed as solvents as well, to investigate the ability of water to enhance the catalytic performance.

High selectivities and good yields have been obtained in the case of cyclic six-membered ketones. A substantial improvement of selectivity for cyclohexanone as substrate was observed by switching from homogeneous to heterogeneous aqueous reaction conditions. However, the reactions proceeded slower in such reaction media to the point that no reaction was observed between *p*-chlorobenzaldehyde and acetone (entry 5). Cyclopentanone proved to be a highly reactive, but less selective substrate.

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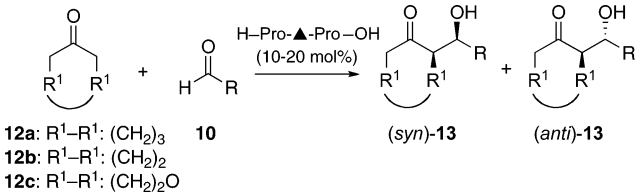
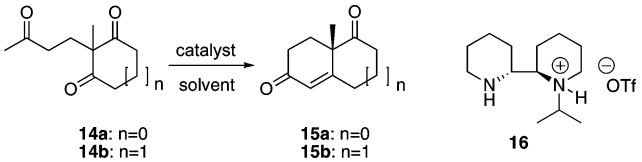
TABLE 3. Reaction between Aromatic aldehydes and Cyclic Ketones



entry	12	R	ketone/water (v/v)[a]	yield (%)[b]	d.r. anti/syn[c]	ee (%) anti[c]	ee (%) syn[c]
1	**12a**	*p*-NO_2	neat	76	3/1	66	10
2	**12a**	*p*-NO_2	20:1	96	2/1	87	73
3	**12a**	*p*-NO_2	10:1[d]	75[e]	6/1	95	99
4	**12a**	*p*-Cl	20:1	50	9/1	91	66
5	**12a**	*p*-Cl	10:1[d]	[e]			
6	**12a**	*o*-Br	20:1	72	40/1	93	
7	**12a**	*o*-Br	10:1[d]	60[e]	90/1	95	
8	**12a**	*o*-Cl	20:1	63	45/1	90	
9	**12a**	*o*-Cl	10:1[d]	40[e]	70/1	98	
10[f]	**12b**	*p*-NO_2	neat	46	1/2	46	
11[f]	**12b**	*p*-NO_2	20:1	99	1/3	56	49
12[f]	**12b**	*p*-NO_2	10:1	90	1/3	61	37
13[f]	**12b**	*p*-NO_2	5:1[d]	70	1/2	68	40
14	**12c**	*p*-NO_2	20:1	71	1/2	83	87
15	**12c**	*p*-NO_2	3:1	80	3/2	91	76

[a] Reactions were carried out at 25 °C, for 24 h, using 0.15 mmol of aldehyde, 20 mol % of catalyst in 0.4 mL of ketone, and the proportional amount of water. [b] Isolated after column chromatography. [c] Determined through chiral GC (after converting the product to its corresponding trimetylsilylether). [d] Heterogeneous reaction mixture. [e] Reaction in 48 h. [f] With 10 mol % catalyst.

TABLE 4. Intramolecular Aldol Reactions of 14[a]



entry	14	catalyst	solvent	yield (%)	ee (%)	time (days)
1	**a**	Pro-▲-Pro	$CHCl_3$	95	83	5
2[b]	**b**	**16**[c]	MeCN[d]	82	95	4
3	**b**	Pro-▲-Pro	$CHCl_3$	88	92	1
4	**b**	Pro-▲-Pro	THF/H_2O 10:1	49	92	1
5	**b**	Pro-Pro-▼	$CHCl_3$	10	38	1
6	**b**	Pro-▼-Pro	$CHCl_3$	11	37	1

[a] All reactions were run at room temperature with 10 mol % of catalyst unless otherwise noted. [b] Taken from reference 17a. [c] With 20 mol %. [d] Reaction run at 82 °C.

Finally, we also tested our catalysts for intramolecular aldol reactions of **14** (Table 4). While there is little need for improvement on the cyclization of **14a**, which proceeds with only 3 mol % of proline with 93% ee,[1a] **14b** has proved to be a more challenging substrate for small molecules serving as organocatalysts. Proline or other α-amino acids are less efficient,[15] but notably the *β*-amino acid *cis*-pentacin furnished **15b** in 86% ee.[16] Recently, the bismorpholine **16** was discovered, which allows the synthesis of **15b** in up to 95% ee,[17]

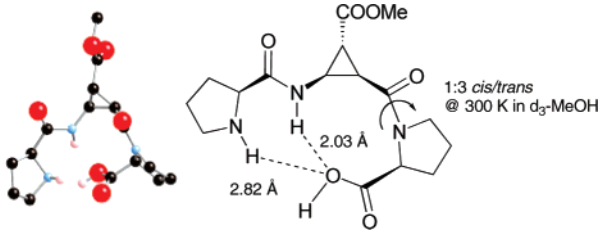


FIGURE 2. Low-energy structure of H−Pro-▲-Pro−OH having a *cis*-amide bond at the C-terminal proline.

rivaling the use of catalytic antibodies with respect to selectivity.[18] From the *β*-ACC-containing peptides, again the tripeptides and particularly H−Pro-▲-Pro−OH proved to be the most effective catalysts.

The cyclization of **14b** was achieved with 92% ee (Table 4, entry 3), coming close to the level that is reached with **16** (entry 2), but notably, high yields were already reached with 10 mol % catalyst within 1 day at room temperature. Good enantioselectivites were also observed in aqueous solvents (entry 4); however, the rate was considerably diminished, while in DMF, DMSO, or acetonitrile the reaction did not proceed at all.

The remarkable catalytic properties of the peptide H−Pro-▲-Pro−OH suggested the existence of privileged conformations in which the C- and N-termini are close to each other. Indeed, this is supported by NMR studies in methanol-d_3, which revealed the presence of two rotamers around the C-terminal proline amide bond in a ratio of 3:1. On the basis of the analysis of NOE signals[19] and ^{13}C shifts[20] of the *β*- and *γ*-carbons of proline, the minor, but nevertheless significantly[21] populated rotamer was assigned to have a *cis*-proline bond being in agreement with the low-energy, turn-like structure calculated by molecular modeling with the *Spartan* program package[22] (Figure 2).

In conclusion, novel peptide catalysts based on conformationally highly restricted *β*-aminocyclopropanecarboxylic acids were identified. Noteworthy, H−Pro-▲-Pro−OH is effective in inter- and intramolecular aldol reactions either in organic or in homogeneous aqueous solvents.

Experimental Section

Representative Procedures for Aldol Reactions. a. Water-Free Conditions. Portions of 0.01−0.04 mmol (5−20% catalyst) of the selected catalyst were added to 0.2 mmol of aldehyde and dissolved under N_2 atmosphere in 2 mL of dry acetone or $CHCl_3$/acetone mixture in a 10 mL vial. The reaction was stirred for the time indicated; subsequently, the solvent was evaporated and 5 mL of EtOAc and 2 mL of water were added to the crude material.

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(22) http://www.wavefun.com.

The organic phases were extracted again with 1 mL of water, dried (Na_2SO_4), concentrated, and purified on silica (3:1 hexanes/EtOAc) to yield the desired aldol product.

b. Homogeneous Acetone/Water Mixture. *p*-Nitrobenzaldehyde (38 mg, 0.25 mmol) and catalyst (H−Pro-▲-Pro−OH) (17.7 mg, 0.05 mmol) were dissolved in 0.75 mL of a 3:1 acetone/water (molar ratio 1:30:42 aldehyde/acetone/water), and the reaction mixture was stirred for 6 h at room temperature. Acetone was evaporated under reduced pressure, and EtOAc (5 mL) and water (2 mL) were added to the resulting suspension. The organic layers were separated, extracted with water (1 mL), dried (Na_2SO_4), and evaporated. The residue was purified on silica (3:1 hexanes/EtOAc) to yield **11a** (50 mg, 95% yield, 71% ee).

Catalyst Recovery. The combined aqueous layers were extracted with Et_2O (2 mL) and frozen at −20 °C. Lyophilization allowed recovery of the catalyst (90−95%), which could be reused without any loss in performance.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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