PROLINE-CATALYZED DIRECT ASYMMETRIC ALDOL AND MANNICH REACTIONS

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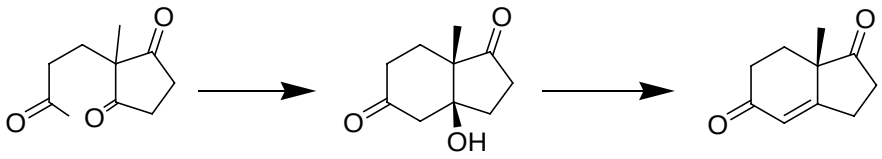
Introduction

Throughout the development of catalytic asymmetric organic synthetic methods, researchers have focused primarily on metal-mediated catalysis. Metal complexes have been shown to catalyze a wide variety of transformations stereoselectively; however, many catalytic metal complexes are difficult to remove from products, highly toxic, and expensive.[1] Thus, as interest in the asymmetric synthesis of chiral molecules continues to grow, there are opportunities for the development of alternative approaches. Over the last decade, organocatalysis has become an area of active interest, and something as simple as proline has been shown to be effective as a catalyst. This amino acid has been lauded as the "simplest enzyme" due to its ability to catalyze reactions with high stereoselectivity.[2] In the last 5 years, proline has been investigated in the catalysis of reduction, oxidation, electrophilic α-fluorination and amination, and carbon-carbon bond forming reactions.[3,4] Two carbon-carbon bond forming reactions that have received attention are the direct asymmetric Mannich and aldol reactions. Efforts toward the elucidation of the mechanism and the scope of both of these reactions are reviewed below.

BACKGROUND

Historical significance

Scheme 1. L-proline catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction



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Proline was first investigated as a small molecule catalyst in the Hajos-Parrish-Eder-Sauer-Wiechert reaction. In the early 1970's, L-proline-catalyzed intramolecular aldol cyclizations were explored in the synthesis of optically pure starting materials for the CD rings of steroids.[5] Hajos and Parrish isolated the hydrindane dione **3** in an early proline-catalyzed intramolecular aldol cyclization. Experiments using 3 mole percent L-proline in DMF gave 96.5:3.5 enantiomeric ratio (er) of aldol product **2** after 20 hours.[6] Despite these encouraging results, which were reported in 1974, the field did not expand, and it was not until the 1990's that a serious

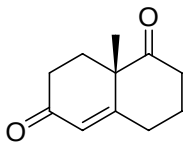

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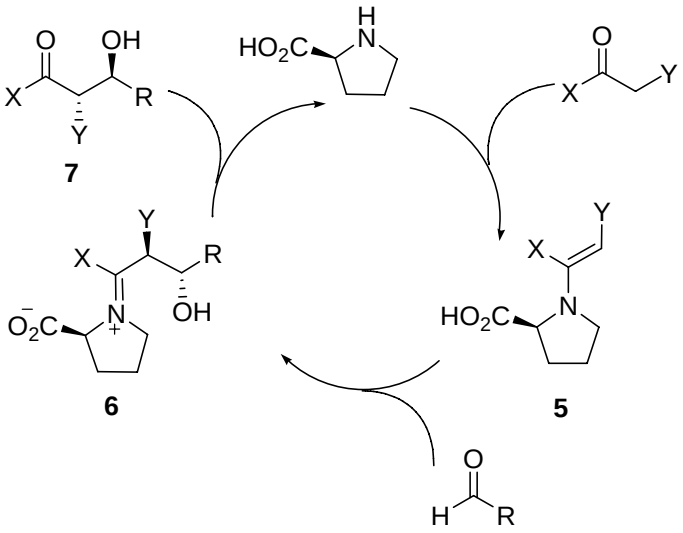
Figure 0. Wieland-Miescher Ketone

Scheme 2. Proline-catalyzed direct aldol reaction



interest in proline as a catalyst was rekindled. Barbas and co-workers were interested in catalyzed intramolecular Robinson annulations when they started studying past syntheses of the Wieland-Miescher ketone (**4**).[7] In 2000, they described the first intermolecular direct asymmetric aldol reaction catalyzed with proline.[8] This sparked intense interest from several groups in further investigating proline-catalyzed direct asymmetric aldol and Mannich reactions.

Mechanism of aldol and Mannich reactions

In aldol reactions, proline effects reaction through enamine catalysis, as shown in Scheme 2. Enamine **5** is formed from the pyrrolidine nitrogen and the carbonyl donor. Iminium ion **6**, created by attack of the enamine on the *re*-face of the aldehyde, is subsequently hydrolyzed to afford chiral β-hydroxyketone **7**.[9] Proposed transition state **8** illustrates that in the aldol reaction, enamine attack occurs on the *re*-face of the aldehyde. This facial selectivity of attack by the enamine (**8**) is dictated by minimizing steric interactions between the aldehyde substituent and the enamine substituent; thus, attack of the enamine on the *si*-face of the aldehyde leads to the unfavorable transition state **9**, shown in Figure 2. Stereochemistry is also controlled by hydrogen transfer between the carboxylate on proline and the oxygen of the aldehyde, thus controlling the enantioselectivity by limiting which face of the enamine attacks the aldehyde.[10] One of the most attractive features of proline catalysis for the aldol reaction is that both

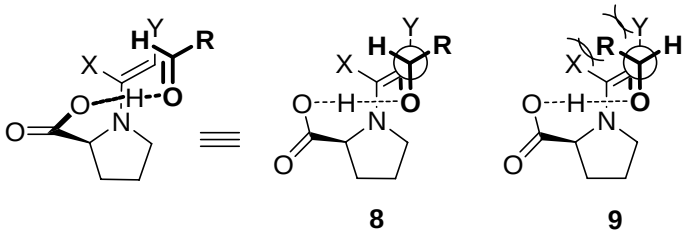
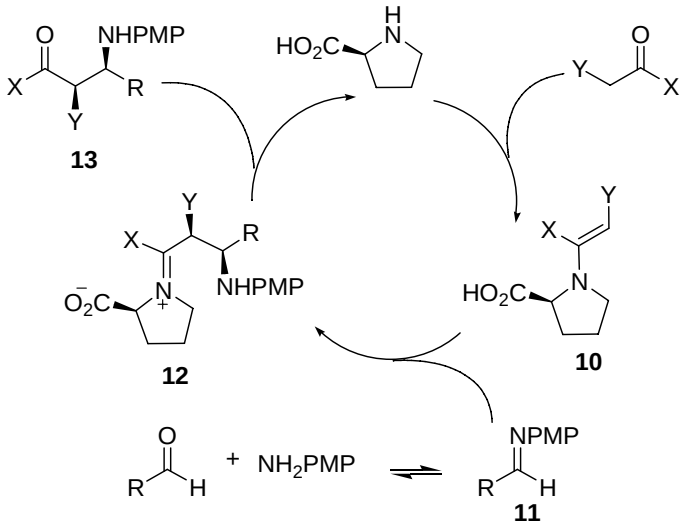


Figure 2. Aldol transition states

Scheme 3. Proline-catalyzed Mannich reaction



D- and L-proline are readily available, so both enantiomers can accessed.

The mechanism of proline-catalyzed direct Mannich reactions (Scheme 3) is analogous to the mechanism of proline-catalyzed direct aldol reactions. Enamine **10** is first formed from proline and an aldehyde or ketone. Preformed imine **11** is then added to the reaction mixture. Alternatively, a primary amine, generally a *p*-methoxyphenyl (PMP) protected amine, and an aldehyde can form the imine *in situ*. The imine formed from PMP-protected amines is observed to be an (*E*)-aldimine, which is important for the explanation of the preferred diastereo- and enantioselectivities of this Mannich reaction.[3] The imine is attacked by the enamine to form new stereocenters in iminium product **12**, which is then hydrolyzed to give Mannich product **13** stereoselectively.[3] The stereoselectivity is controlled through transition state **14**, shown in Figure 3. The (*E*)-aldimine is attacked by the enamine on its *si*-face to give the *syn* product with at least one new stereocenter. Because of the E geometry of the aldimine, the *re*-face is blocked by steric interactions between the aromatic ring of the *p*-methoxyphenyl group and the ring of proline. A transition state that has these two rings overlapping on the *re*-face gives the anti product.[10] Interestingly, the diastereoselectivity of the reaction is opposite that of the aldol reaction because the PMP-protected amine completely defines the diastereoselectivity in the Mannich reaction. In parallel with the aldol reaction, enantioselectivity is controlled through hydrogen transfer that selects the attacking face of the enamine and is reversed by using D-proline.

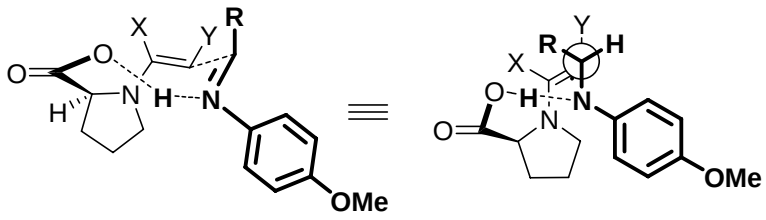


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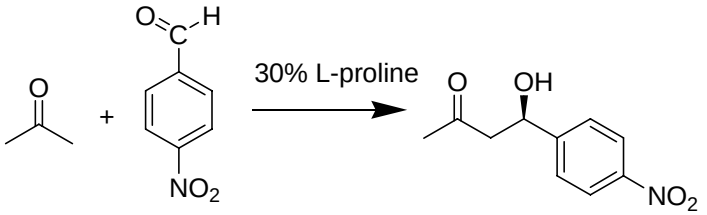
Figure 3. Transition state of *syn* Mannich reaction

ALDOL REACTION

Beginnings

It was an aldol reaction that was first investigated in the renaissance of proline catalysis started by Barbas.[8] The first aldol reaction performed was between acetone and 4-nitrobenzaldehyde, using 30 mole percent L-proline, conditions that gave the aldol product in 68% yield with 88:12 er (Scheme 4). A screen of commercially available proline derivatives revealed no appreciably better catalysts. Direct proline catalysis was considered to be particularly favorable because, as the authors noted, the reactions have several advantages over normal enolate

Scheme 4. First proline catalyzed direct asymmetric aldol



chemistry: proline is inexpensive, it exists in both enantiomersic forms, reactions can normally be done at ambient temperature, and ketones and aldehydes can be used without prior modification. Barbas noted that unbranched aldehyde acceptors do not give cross-aldol product but instead tend towards aldehyde self-aldolization and aldol condensation products.[8] The potential of this reaction was investigated further by a small group of chemists.

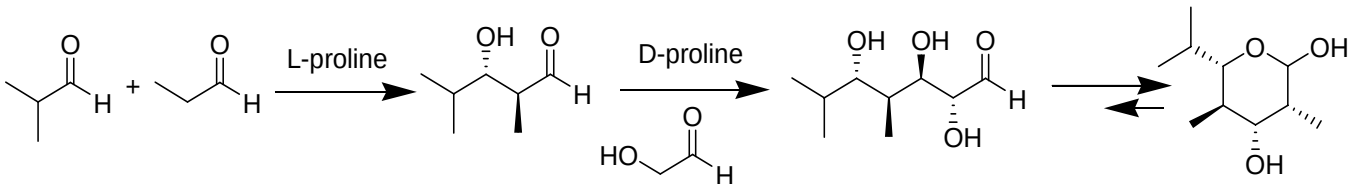
Scope of the proline-catalyzed aldol reaction

Anti-1,2-diols were easily obtained from hydroxyacetone and various α-substituted ketones as donors. All the aldehyde acceptors but one used were branched at the α position, and no linear aldehyde acceptors were reported (Table 1, **15, 16**).[11] List reported that cross-aldol reaction with linear aldehydes as acceptors was dependent on solvent. Use of either 20% v/v acetone in chloroform or pure acetone as solvent suppressed aldehyde self-aldolization under the long reaction times of 3 to 7 days (Table 1, **17, 18**). The aldol condensation product from dehydration of the β-hydroxyketone could not be avoided, so the yields of the β-hydroxyketone and α,β-unsaturated ketone were generally equivalent, although er's were rather modest.[12] Cross-aldol reactions between aldehydes afford β-hydroxyaldehydes. MacMillan performed aldehyde cross-aldol reactions with 10 mole percent L-proline in DMF, and he obtained *anti* cross-aldol products with good er's (Table 1, **19, 20**).[13] α-Keto esters and fluoroacetone compounds as enamine acceptors have also been investigated (Table 1, **21**).[14] Interestingly, it was found that α-branched aldehydes are not good enolate donors, because these would lead to a β-hydroxyaldehyde with a quaternary α carbon (Table 1, **22**).[15]

Aldehyde cross-aldol reactions also have been shown to be effective in ionic liquid solvents thereby allowing catalyst recycling. Córdova has reported reusing L-proline in [bmim]PF_6 four times without significant reduction in yield or stereoselectivity (Table 1, **23, 24**).[16] Water has also been used as a solvent for cross aldol reactions, but yields and stereochemistry suffer.[17] In an effort to improve stereoselectivity and yield of aqueous proline-catalyzed aldol reactions, D-camphorsulfonic acid was added in ten mole percent. The result was higher yields and enantioselectivity (Table 1, **25**, **26**).

Proline catalysis has been applied to the synthesis of carbohydrates. The vision is a two-step

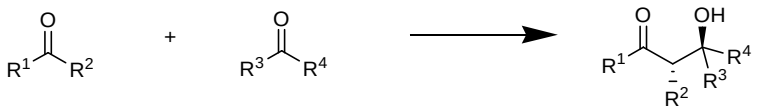
Scheme 5. Córdova's hexose synthesis



route to carbohydrates using sequential aldol reactions. MacMillian and workers believed it is essential to understand the nature of α-substituted aldehydes in order to control the regio- and stereoselectivity of

the proline-catalyzed direct aldol reaction. They found that protected α-oxyaldehydes act as both donors and acceptors in the aldol reaction: α-alkylaldehydes with α-methylene protons act as donors in reaction with protected α-oxyaldehydes, and alkylaldehydes without α-methylene protons act as acceptors in reactions with protected α-oxyaldehydes (Table 1, **27, 28**).[18] MacMillan, however, was not the first to make carbohydrates by complete proline catalysis. It was Córdova who synthesized a hexose in a two-step sequence that proceeded in 29% overall yield and 99.5:0.5 er and involved the use of both L and D-proline, as shown in Scheme 5.[19]

Table 1. Scope of proline-catalyzed direct aldol reaction



Entry	Donor		Acceptor		Solvent	dr[a]	er[b]	Yield
	R1	R2	R3	R4				(%)
15[11]	CH_3	CH_2OH	H	$CH(OH)CH_2OH$	DMSO	2:1	98.5:1.5	40
16[11]	CH_3	CH_2OH	H	$CH(CH_3)_2$	DMSO	>20:1	>99.5:0.5	62
17[12]	CH_3	CH_3	H	$(CH_2)_3CH_3$	$CHCl_3$[c]	-	85:15	29
18[12]	CH_3	CH_3	H	$CH_2CH(CH_3)_2$	$CHCl_3$[c]	-	68:32	22
19[13]	H	CH_2CH_3	H	$CH(CH_3)_2$	DMF	24:1	>99.5:0.5	82
20[13]	H	CH_2CH_3	H	$CH_2CH(CH_3)_2$	DMF	3:1	98.5:1.5	88
21[14]	H	$(CH_2)_2CHCH_2$	CO_2Et	CO_2Et	CH_2Cl_2	1.1:1	93:7	66
22[15]	H	$CH(CH_3)_2$	H	*p*-$NO_2(C_6H_4)$	DMSO	-	90:10	34
23[16]	H	CH_2CH_3	H	$CH_2CH(CH_3)_2$	[d]	>19:1	>99.5:0.5	76
24[16e]	H	CH_2CH_3	H	$CH_2CH(CH_3)_2$	[d]	>19:1	>99.5:0.5	75
25[17]	CH_3	CH_3	H	*p*-$NO_2(C_6H_4)$	H_2O	-	67:33	47
26[17f]	CH_3	CH_3	H	*p*-$NO_2(C_6H_4)$	H_2O	-	80.5:19.5	74
27[18]	H	CH_2CH_3	H	CH_2OTIPS	DMF	4:1	99.5:0.5	75
28[18]	H	CH_2OTIPS	H	$CH(CH_3)_2$	DMF	8:1	99.5:0.5	43

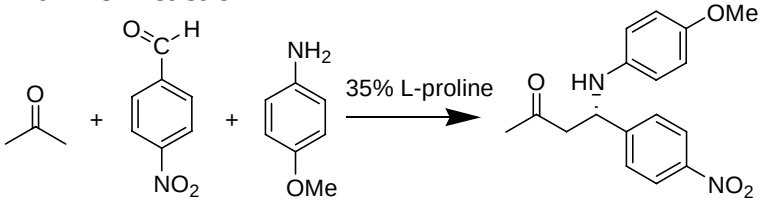
[a]Diastereomer ratio *anti*:*syn*. [b]With L-proline, major enantiomer is as shown. [c]Acetone was used as cosolvent. [d]A mixture of $[bmim]PF_6$ and DMF in 1.5 to 1 ratio was used as solvent. [e]Catalyst was used from entry 25. [f]D-Camphorsulfonic acid added in 10 mole percent

THE MANNICH REACTION

Beginnings

In 2000, List reported the first direct catalytic asymmetric Mannich reaction.[18] These first published results are illustrated in Scheme 6. L-proline in a substoiciometric amount, acetone, *p*-anisidine, and *p*-nitrobenzaldehyde gave the Mannich product in 50% yield and 97:3 er after 12 hours. The amine used was PMP protected for two reasons: anilines readily form aldimines, and PMP deprotection of the amine in the Mannich proeduct can be effected through mild oxidative cleavage. In addition to acetone, methoxyacetone was investigated as an enolate donor (Table 2, **29**).[20]

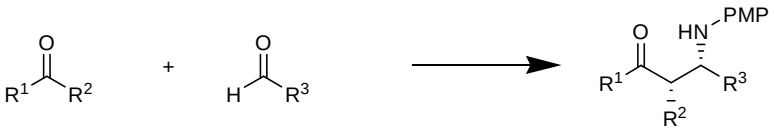
Scheme 6. First proline-catalyzed direct asymmetric Mannich reaction



Scope

Following these initial studies of the Mannich reaction, Barbas and coworkers further explored the scope of this reaction. They found that a cross-Mannich reaction with aldehyde donors affords the syn diastereomers (Table 2, **30-32**). The enantioselectivity is independent of existing stereocenters, and wet solvents can be tolerated.[21] Barbas and workers synthesized syn amino alcohols and γ-oxo-α-amino

Table 2. Scope of proline-catalyzed direct Mannich reaction

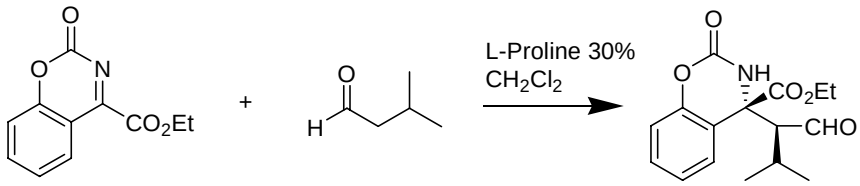


Entry	Donor		Acceptor	solvent	dr[a]	er[b]	Yield
	R^1	R^2	R^3				(%)
29[20]	H	CH_2OMe	*p*-$NO_2(C_6H_4)$		>20:1	99:1	93
30[21]	H	$(CH_2)_5CH_3$	CO_2Et	DMSO	32:1	>99.5:0.5[c]	88
31[21]	H	$(CH_2)_5CH_3$	CO_2Et	DMSO	19:1	>99.5:0.5[d,e]	73
32[21]	H	CH_2CH_3	CO_2Et	dioxane	1.1:1	99.5:0.5	72
33[22]	CH_3	CH_2OH	CO_2Et	DMSO	>19:1	99.5:0.5	62
34[22]	CH_3	CH_2OH	$(CH_2)_4CH_3$	DMSO	>20:1	97:3	46
35[22]	CH_3	CH_2OH	naphthyl	DMSO	2.6:1	95:5	83
36[24]	H	$CH(CH_3)$*p*-t-Bu-C_6H_4	CO_2Et	DMSO	1.5:1	99.5:0.5	80
37[24]	H	cyclohexyl	CO_2Et	DMSO	-	77.5:22.5	85
38[26]	CH_2OH	CH_2OH	CO_2Et	TFE	32:1	99.5:0.5	72
39[26]	CH_2OH	CH_2OH	CO_2Et	TFE[f]	9:1	97:3	72

[a]Diasteriomer ratio *syn*:*anti.* [b]Major enantiomer as shown above. [c]Major enantiomer (S, S). [d]Major enantiomer (R, R). [e]Reaction catalyzed with D-proline. [f]Reaction heated with microwave radiation for 10 minutes.

acids using hydroxyacetone as the enamine carbonyl donor and either-hydrocarbon substituted aldehydes or PMP-protected α-imino ethyl glyoxylate as the acceptor (Table 2, **33-35**).[22] Amino alcohols and γ-oxo-α-amino acids have been easily converted to products with three contiguous stereocenters through reduction.[23] The synthesis of quaternary amino acid derivatives **36** and **37** was proline catalyzed; however, the diastereoselectivity and enantioselectivity are reduced.[24] In addition to using aldehydes as the acceptor, Jørgensen and coworkers have used ketimines, as shown in Scheme 7.[25] The nitrogen was tethered to the α-aryl imine substituent (**40**) in order to increase reactivity through ring strain. Mannich product **41** was produced in 84% yield with 8:1 diastereoselectivity and 91:9 er.

Scheme 7. Ketimines in proline-catalyzed Mannich reaction



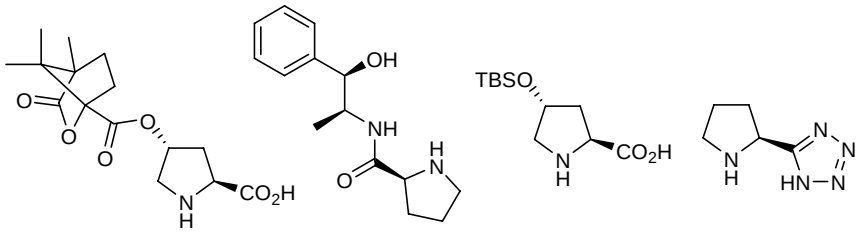
40 **41**

Reaction times for proline-catalyzed direct Mannich reactions range from 3 to 48 hours. Fortunately, the rate of reaction may be increased by microwave irradiation. Protected dihyroxyacetone and preformed PMP-protected α-imino ethyl glyoxylate in 2,2,2-trifluoroethanol with 30 mole percent L–proline gave protected amino alcohol **39** after only 10 minutes with microwave heating. Under these conditions, however, diastereoselectivity and enantioselectivity are lower than with the thermal reaction.[26]

PROLINE DERIVATIVES

Several proline derivatives or analogs that catalyze the aldol and Mannich reactions have been reported in the literature. A few will be presented here briefly.

Scheme 8. Proline derivatives for aldol and Mannich reactions



42 **43** **44** **45**

Proline derivatives for catalysis of the aldol reaction have been synthesized with bulky groups to control the stereoselectivity through steric control. Thus, both proline derivatives **42** and **43** have catalyzed aldol reactions with similar yields to proline. For the reaction of acetone with *p*-nitrobenzaldehyde, catalyst **42** produced the aldol adduct in 90:10 er, whereas L-proline catalysis resulted in 84.5:15.5 er.[27] In a similar reaction, the aldol reaction of acetone and benzaldehyde was catalyzed with **43** to give products with 80:20 er.[28] In addition to these homogeneous derivatives, proline has been attached to polyethylene glycol to provide a system in which the active catalyst can be recovered without sacrificing stereoselectivity, but with diminishing yields.[29] Similarly, peptide-supported proline catalysts have been reported.[30]

Proline derivatives having improved solubility have been explored as catalysis of the Mannich reaction Catalyst **44** increased the yield of the Mannich reaction between benzaldehyde, acetone, and PMP-protected anisidine from less than five percent to 63 percent.[31] Similar results were found with catalyst **45**. No reaction was seen with L-proline; however, the proline tetrazole analog **45** afforded the β-aminoketone in 65 percent yield with 19 to 1 dr and 99.5 to 0.5 ee.[32] The improved yields are presumed to be due to its improved solubility.

CONCLUSION

Proline has been shown to be a powerful catalyst in *syn*-selective Mannich reactions and *anti*-selective aldol reactions. It has many advantages over metal catalysts: both enantiomers can easily be accessed by using the D or L enantiomers of proline: proline is readily available, and it is

environmentally benign. In addition, it has activity comparable to metal catalysts, but high catalyst loadings are required. Despite the synthetic utility of this method, two significant problems remain with proline-catalyzed direct aldol and Mannich reactions: the inability to obtain products with the opposite diastereoselectivity and poor catalyst solubility in organic solvents.[8] Nevertheless, proline-catalyzed direct Mannich and aldol reactions can be a useful addition to the synthetic chemists toolbox.

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