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Enantioselective Organocatalytic Mannich Reactions with Autocatalysts and Their Mimics

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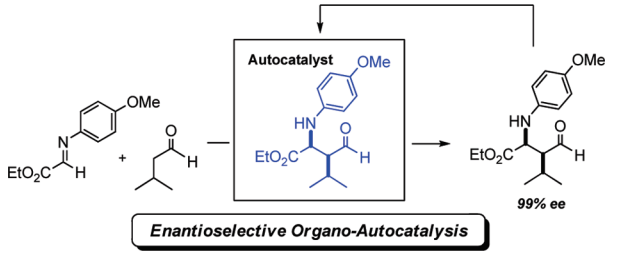
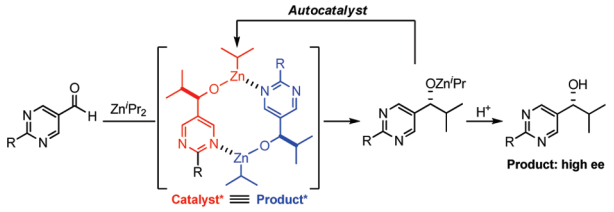


The Mannich reactions previously extensively investigated with organocatalysis of L-proline and other related small molecules were reinvestigated with detailed stereochemical analysis of their autocatalysis pathways, through employment of both the products themselves and their close structural mimics as the catalysts. These organo-autocatalytic processes function as meaningful molecular models toward understanding the origin and maintenance of homochirality under biologically relevant conditions.

Many molecules naturally occurring in the biological world, such as L-amino acids and D-sugars, are chiral, meaning they exist in only one form of the two possible mirror images. But exactly how did one mirror image form start out and come to dominate the other, i.e., the problem of the origin and maintenance of homochirality, remains to be a fundamental challenge yet to be solved. However, several inspirational hypotheses have been advanced,[1] the most appealing one being the autocatalysis concept proposed by Frank in 1953, in which he suggested that reactions whose products themselves act as the catalysts in their formations could in principle amplify a slight enantiomeric excess of one enantiomer into its overwhelming predominance.[2] But experiments supporting this scenario did not arrive until 1995, when Soai and his co-workers described autocatalytic additions of dialkylzincs to pyrimidine carbaldehydes[3] (Scheme 1). Due to the operation of strong positive nonlinear effect, the chirality replication efficiency observed in these reactions is enormously high,[4] and a tiny initial chirality imbalance created by even random chance[5] or carbon isotopes[6] can autocatalytically lead to very high levels of enantiomeric excess. While it is not readily conceivable if such air-sensitive organometallics could possibly function comparably well under prebiotic environment, this landmark accomplishment has inspired us to embark on a search of small organic molecule-based autocatalysis systems that are capable of delivering high enantioselections under more biologically relevant conditions. On a more general perspective, although such organoautocatalytic processes developed at this early stage may not benefit from the nonlinear effect for enantioselective amplification, we believe they would serve as structurally well-defined small-molecule models that should aid our understanding of the stereochemical control modes involved in biological replication events.[7]

SCHEME 1. Remarkable Chiral Catalyst−Product Structural Resemblance in the Soai Organometallic Autocatalysis Reaction



The field of organocatalysis has recorded tremendous progress during the past few years, as witnessed by the discovery and development of an unusually diverse range of small molecules capable of promoting impressive reactivity and stereoselectivity.[8] In spite of these marvelous advancements, surprisingly, enantioselective organoautocatalysis,[9] a process in which a small organic molecule product enantioselectively catalyzes its own formation, has for long represented a completely unexplored area until the pioneering work of Mauksch, Tsogoeva, and co-workers, who reported in 2007 the product catalysis in the reaction of acetone with an imine. Such fully organoautocatalytic reactions, when efficiently developed, not only have

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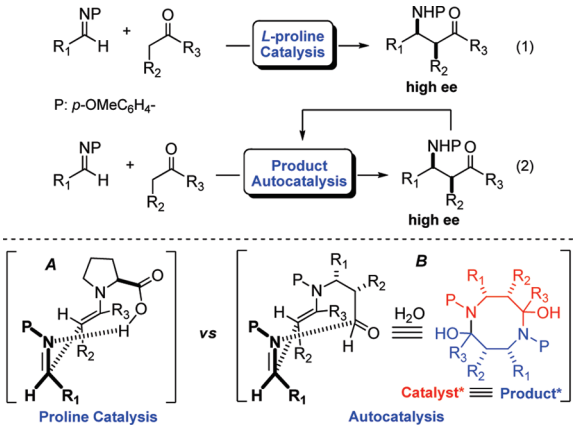
significant practical value, as they eliminate the often troublesome problem of catalyst recovery and product purification, but also possess considerable theoretical merits, as they offer conceptually new models for enantioselective molecular replication, a scenario that should pave the way to the discovery of broadly useful systems for efficient chirality amplification for which the Soai organometallic autocatalysis processes appear up to now to be the only successful examples (Scheme 1).[6] In a new helix electronic theory of molecular chirality and chiral interactions published recently by one of us,[10] it was reasoned that high enantioselectivity would most likely arise from a type of autocatalytic system in which the product not only catalyzes its own formation, but also does so through a corresponding enantioselection-determining step in which the forming product and its catalyst share an identical or closely resembling structure, thereby ensuring a maximum level of stereochemical matching and enantioselection.[10b,d]

In this context, the Soai organometallic autocatalytic addition of Zn^iPr_2 to pyrimidine-5-carbaldehyde reaction (Scheme 1) represents an outstanding example in which the forming product (highlighted in blue) structurally fully mirrors the chiral catalyst (in red) in the transition state elucidated through various mechanistic studies.[11] This unique feature was not yet examined in those limited few systems[9,12] in which the catalysis stereochemical courses were reported to be significantly influenced by their reaction products, and this feature, in conjunction with the strong positive nonlinear effect[13] involved in aminoalcohol-Zn-catalyzed asymmetric alkylation of aldehydes, are responsible for the extremely efficient chirality amplification observed in the Soai systems. Guided by this new conceptual framework, we became interested in exploring the possibility of autocatalysis pathways in the Mannich-type condensation of protected imines and carbonyl compounds (Scheme 2). The reactions were widely studied with L-proline[14] and related catalysts,[15] yielding often *syn*- or *anti*-products in

SCHEME 2. Proline Catalysis and Autocatalysis Mechanistic Scenarios in the Organocatalytic Mannich Reactions between Protected Imines and Carbonyl Compounds



high enantioselectivities. A transition state assembly **A** involving concomitant enamine activation of the carbonyl precursor and hydrogen bonding to electrophilic imine has been elegantly derived from experimental[16] as well as computational[17] investigations.

We envisioned that the amine and carbonyl moieties in the Mannich product may well mimic the roles of the bifunctional proline thus leading to enantioselective autocatalysis. This hypothesis was illustrated through the intermediacy of **B**, it was a remarkable observation that in **B** the catalyst portion (in red) and the forming product (in blue) are likely to share exactly the same structural characters. The feasibility of such an enamine-type carbonyl substrate activation by its Mannich product is supported by the observation of vinyl proton resonance at 5.64 ppm when mixing an aldehyde **2e** (see entry 5, Table 1) with its product mimic catalyst **3e** in d_6-DMSO. Mauksch, Tsogoeva, and their co-workers had reported autocatalysis in the reaction of acetone with imine **1** (Table 1) under various catalyst loadings inducing 29−96% ee;[9] Córdova and his co-workers had communicated that the reaction of propionaldehyde and **1** gave product in merely 1% yield and 40% ee when 30% mol of the product was employed as the catalyst.[18] Due to the indistinguishable catalyst−product structures, in these reports the characterizations on the yields, enantio- and diastereoselectivities of the newly formed autocatalysis products, were indirectly derived on the premise that the catalyst initially added into the reaction mixture remained intact. This, however, was not necessarily the case as the instability of the Mannich products had already been noted by several authors.[14,15] In the present study, we therefore desired to employ the catalyst **3** as an excellent product structure mimic, which was found to differentiate itself from its product in both NMR and chiral HPLC analysis thus ensuring an accurate account of both the reaction reactivity and stereoselectivity in autocatalytic processes. The alkyne moiety in **3** may offer additional benefits in catalyst−product isolation through click chemistry technology.[19] **3** itself could be readily

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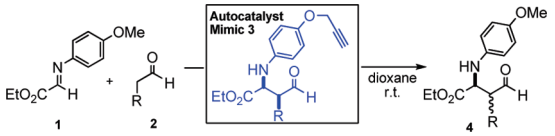
TABLE 1. Enantioselective Aldehyde Mannich Reactions Promoted by Autocatalyst Mimic 3[d]



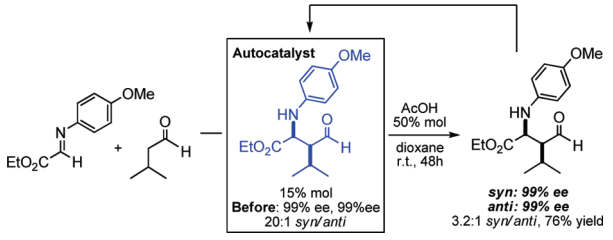
				catalyst **3** before reaction[b]			catalyst **3** after reaction			autocatalysis product **4**			
entry[a]	R	cat., %	AcOH	dr	ee^{syn}, %	ee^{anti}, %	dr	ee^{syn}, %	ee^{anti}, %	dr	ee^{syn}, %	ee^{anti}, %	yield, %
1	Me	15	0	3:1	99	20	3:1	98	44	1:1.4	99	26	15
2	^{n}Pr	15	0	11:1	99	99	6:1	99	75	1:9	55	15	27
3	^{n}Pent	15	0	11:1	95	99	6:1	93	99	1.3:1	52	99	37
4	Dec[c]	15	0	20:1	99	93	2:3	4	91	1:2.2	77	91	87
5	^{i}Pr	15	0	20:1	99	99	16:1	99	99	1:1	99	90	31
6	^{i}Pr	5	0	2.3:1	99	99	4:3	96	90	1:10	64	99	29
7	^{i}Pr	10	0	2.3:1	99	99	4:3	95	87	1:10	3	99	41
8	^{i}Pr	30	0	2.3:1	99	99	3:2	98	96	1:8	77	99	45
9	^{i}Pr	15	15	2.3:1	99	99	2:3	78	96	1:11	26	99	43
10	^{i}Pr	15	30	2.3:1	99	99	1:2	89	93	1:8	33	99	37
11	^{i}Pr	15	50	2.3:1	99	99	3:2	99	70	5:1	99	99	65
12	^{i}Pr	15	100	2.3:1	99	99	1:4	45	88	1:6	47	99	33

[a]In all entries, enantiomeric excesses were determined by HPLC analysis on a Daicel ChiralPak AS-H column, and diastereomeric ratios (dr = *syn*/*anti*) were measured by ^{1}H NMR integrations of the formyl hydrogen signals of the crude reaction mixture. [b]**3** was prepared following published procedure.[14] [c]The substrate is 4-decenal. [d]Reaction conditions: Imine **1**, 0.5 mmol; aldehyde **2**, 0.75 mmol; autocatalyst mimic **3**, 0.15 equiv; anhydrous dioxane, 5 mL; room temperature, 48 h.

prepared through L-proline-catalyzed Mannich reactions, generally in high enantio- and diastereoselectivities (up to 99% ee for both *syn*- and *anti*-isomers).[14] **3** is labile for isomerization at its α-aldehyde position, even at neat storage or on brief exposure to silica gel, thus its inseparable diastereomers were purified via silica gel flash chromatography and used directly as the catalyst. Prior to each use, the mixture was analyzed by NMR (via integration of the formyl hydrogen signals) to ascertain its current diastereomeric ratio. The results on **3**-catalyzed Mannich reactions of **1** and various aldehydes **2** at room temperature were compiled in Table 1. The reaction diastereomeric ratios were determined by NMR analysis of the original crude mixture, and the enantiopurities of the autocatalysis product and the recovered catalyst were determined by chiral HPLC analysis of their chromatographically purified mixture.

As is evident from the data in Table 1, the enantiomeric and diastereomeric purities of the catalysts could undergo fairly significant changes during the reaction courses, for example, in entry 4, while the catalyst initially had 99% ee in *syn*-isomer, 93% ee in *anti*-isomer, and a high diastereomeric ratio of 20:1, after the reaction these numbers degraded to 4% ee, 91% ee, and 2:3, respectively. The reactions generally went to completion within 48 h of stirring at rt, the yields of the autocatalysis products showed a high level of substrate dependence and were comparable to those found in proline-catalyzed processes. In all of the cases except entries 3 and 11, while the catalysts are mainly *syn*-enantiomers, in their corresponding products *anti*-enantiomers predominated with various ratios (1:1.4 to 1:11). This observation may be accommodated by isomerization and/or by the possibility that the formation of *anti*-products via *Z*/*E* enamine geometry equilibrium may characterize a relatively faster catalysis channel. Also in all of the cases except entry 2, *syn*- or *anti*-products **4** were formed in high enantiopurities (>90% ee), demonstrating a high level of chirality induction. Particularly notable is the autocatalytic reaction involving isovaleraldehyde (entry 11), in which both isomers were obtained in 99% ee and 65% yield. The use of acetic acid as a potential imine-activating additive at various loadings was also examined with the isovaleraldehyde substrate, and was found to lead to higher product yields via suppressing the Aldol reactions of **2** but impose limited effect on reaction stereoselectivities.

SCHEME 3. Enantioselective Organoautocatalytic Mannich Reaction of Imine 1 and Isovaleraldehyde



It should be emphasized that without employing these close structural mimics **3** as the autocatalysts, it is simply impossible to probe the stereochemical changes that might have been associated with these labile species during the reactions. Equally significant is that autocatalysis with the products themselves reproduced the results in Table 1. For example, stirring isovaleraldehyde and imine **1** with 15% mol of the autocatalyst (99% ee in both *syn*- and *anti*-isomers, 20:1 *syn*/*anti* diastereomeric ratio) and 50% mol of AcOH in dioxane for 2 days at rt gave the product in 76%, i.e., a net 61% yield and 3.2:1 *syn*/*anti* diastereomeric ratio, and the enantiomeric excess of both isomers was 99% ee (Scheme 3).

The three-component Mannich reactions[20] involving ketone **5**, aldehyde **6**, and amine **7** were next investigated (Table 2). Regardless of the loading of the autocatalyst mimic **8**, the product **9** was consistently obtained in >99% ee in both its *syn*- and *anti*-enantiomers. Importantly, while in the aldehyde

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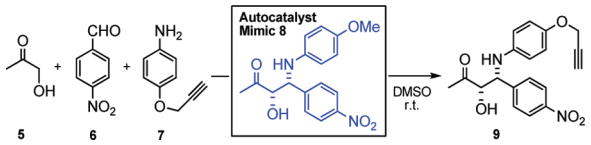
TABLE 2. Enantioselective Ketone Mannich Reactions Promoted by Autocatalyst Mimic 8[c]



			catalyst 8 before reaction[b]			catalyst 8 after reaction			autocatalysis product 9			
entry[a]	cat., %	AcOH	dr	ee^{syn}, %	ee^{anti}, %	dr	ee^{syn}, %	ee^{anti}, %	dr	ee^{syn}, %	ee^{anti}, %	yield, %
1	10	0	24:1	97	–	>30:1	>99	–	3.6:1	>99	>99	28
2	20	0	24:1	97	–	>30:1	>99	–	4.3:1	>99	>99	30
3	30	0	24:1	97	–	>30:1	99	–	3.7:1	>99	>99	36

[a]In all entries enantiomeric excesses and diastereomeric ratios (dr = *syn*/*anti*) were both determined by HPCL analysis on a Daicel ChiralPak AD-H column. [b]**8** was prepared following a published procedure.[14] [c]Reaction conditions: Ketone **5**, 1 mL (in excess); aldehyde **6**, 0.5 mmol; aniline **7**, 0.55 mmol; autocatalyst mimic **8**, 0.1−0.3 equiv based on the amount of **6**; DMSO solvent, 5 mL; room temperature, 50 h.

Mannich systems (Table 1) both the diastereomeric ratios and enantiopurities of the autocatalyst **3** were generally eroded in the reactions, those of **8** in the three-component Mannich reactions were, however, found to be improved, and the products were predominantly *syn*-enantiomers.

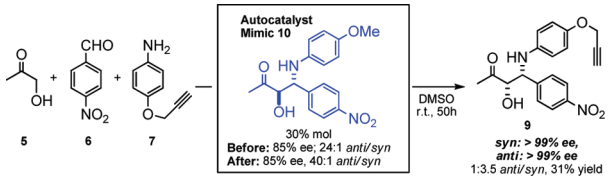
Employment of an *anti*-autocatalyst mimic **10** prepared via L-tryptophan catalysis (85% ee in *anti*-isomer, 24:1 *anti*/*syn* diastereomeric ratio)[21] was also found to yield both *syn*- and *anti*-product **9** in >99% ee, but again with *syn*-**9** as the major isomer (Scheme 4). These inherent *syn*-stereochemical preferences uncovered with both **8** and **10** should have an origin in the *E*-enamine geometry generated from **5**.

In summary, with detailed stereochemical analysis of both the catalysts and the products, we presented herein an accurate account of the autocatalytic Mannich reactions previously extensively investigated with L-proline and other chiral organocatalysts. These organoautocatalytic processes offer striking advantages in such critical issues as new enantiocontrol strategy and catalyst−product isolation, thus representing an exciting new area of endeavors. In addition to these practical merits, organoautocatalysis also provides conceptually novel and structurally well-defined small-molecule models in which chirality can be replicated with useful efficiency and under biologically relevant conditions. Our results on the design and development of other highly enantioselective organoautocatalysis reactions will be communicated in due course.

Experimental Section

General Procedure for the Enantioselective Mannich-Reaction between *N*-PMP-Protected Imine 1 and Aldehyde Donors 2. In a typical experiment, *N*-PMP-protected imine **1** (0.5 mmol) was dissolved in anhydrous dioxane (5 mL) and then to the solution was added the corresponding aldehyde donor **2** (0.75 mmol), followed by addition of the autocatalyst mimic **3** (15 mol %) that was separately prepared following literature procedure. After being stirred for 48 h at room temperature in a closed system, the reaction mixture was worked up by addition of half-saturated NH_4Cl solution and extraction with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuum, then the residue was analyzed by ^1H NMR to determine the diastereomeric ratios of both the autocatalyst mimic and the reaction product. The residue was then purified via silica gel flash column chromatography (note that silica gel exposure here may cause partial compound isomerization, but this generally will not affect the subsequent enantiopurity measurement), and the enantiomeric excesses of the autocatalyst and the reaction product were determined through chiral HPLC analysis.

SCHEME 4. Enantioselective Ketone *anti*-Mannich Reaction Promoted by Autocatalyst Mimic 10



General Procedure for the Enantioselective Ketone Three-Component Mannich Reaction. To a solution of 4-nitrobenzaldehyde (**6**, 75 mg, 0.5 mmol), 4-(prop-2-ynyloxy)aniline (**7**, 81 mg, 0.55 mmol), and 1-hydroxypropan-2-one (**5**, 1 mL, in large excess) in DMSO (5 mL) was added (3*S*,4*R*)-3-hydroxy-4-(4-methoxyphenylamino)-4-(4-nitrophenyl)butan-2-one (**8**, 10 mmol %, 20 mmol %, or 30 mmol % as noted in the text and based on the aldehyde). The mixture was stirred for 50 h at room temperature. The reaction was worked up by addition of phosphate-buffered saline (PBS) solution (pH 7.4) and extraction with ethyl acetate. The organic layer was dried with Na_2SO_4, and concentrated in vacuum to give the crude Mannich product, which was used directly for HPLC analysis. Characterization data for compound **9**: ^1H NMR (500 MHz, $CDCl_3$) 8.17 (d, 2H, J = 8.6 Hz), 7.56 (d, 2H, J = 8.6 Hz), 6.69 (d, 2H, J = 8.8 Hz), 6.47 (d, 2H, J = 8.8 Hz), 5.03 (s, 1H), 4.45 (d, 1H, J = 1.9 Hz), 3.94 (b, 1H), 3.68 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 206.4, 152.9, 147.4, 139.3, 128.1, 123.7, 115.2, 115.0, 79.9, 60.3, 58.8, 55.6, 24.9, 14.1. Anal. Calcd for $C_{19}H_{19}N_2O_5$: 355.1296. Found: 355.1301.

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Supporting Information Available: Experimental procedures, compound characterizations, and chiral HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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