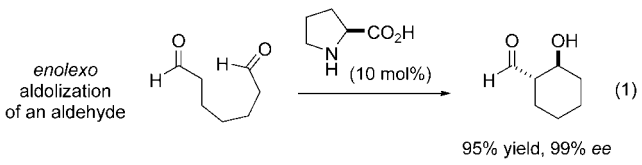
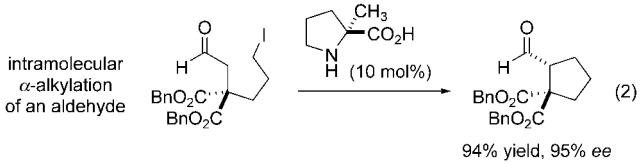
Asymmetric Catalysis

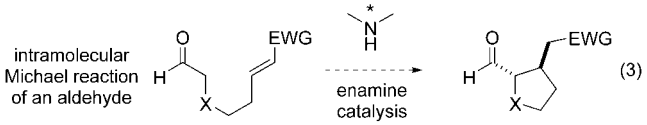
Catalytic Asymmetric Intramolecular Michael Reaction of Aldehydes**

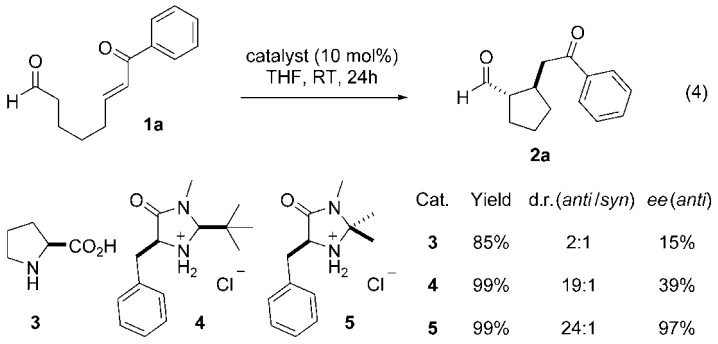
*Maria T. Hechavarria Fonseca and Benjamin List**

Dedicated to Professor Johann Mulzer on the occasion of his 60th birthday









Cat.	Yield	d.r. (*anti*/*syn*)	*ee* (*anti*)
3	85%	2:1	15%
4	99%	19:1	39%
5	99%	24:1	97%

In the last few years the profound efficiency and applicability of asymmetric aminocatalysis in organic synthesis has been firmly established.[1] After discovering the first direct asymmetric enamine catalytic intermolecular aldol,[2] Mannich,[3] Michael,[4] and α-amination reactions,[5] our research group became interested in using this powerful organocatalytic strategy in the design of novel intramolecular reactions in which aldehydes are used as nucleophiles. These efforts led to the first catalytic asymmetric intramolecular *enolexo* aldolization [Eq. (1)][6] and α-alkylation reactions [Eq. (2); Bn = benzyl] of aldehydes.[7] In this context we realized that although there are a number of reports on elegant catalytic enantioselective intermolecular Michael reactions,[8] *intramolecular* catalytic asymmetric Michael reactions of aldehydes are unknown [Eq. (3); EWG = electron-withdrawing group].[9] We felt that such a process would be of great value, particularly if included in strategic reaction sequences, such as the Robinson annulation. Herein we report an efficient enantioselective cyclization of formyl enones in a process that constitutes the first catalytic asymmetric intramolecular Michael reaction of aldehydes.

Remarkable progress has been made recently in the asymmetric catalysis of intermolecular Michael reactions. Both highly effective catalytic enantioselective conjugate addition reactions of stabilized and nonstabilized carbanions[10] and indirect Mukaiyama-type intermolecular Michael reactions have been developed.[11] In addition to these metal-mediated processes, highly enantioselective organocatalytic Michael reactions,[12] including variants based on iminium and enamine catalysis,[13] have been reported. However, intramolecular catalytic asymmetric Michael reactions are extremely rare.[14] We were particularly attracted to the asymmetric aminocatalysis of intramolecular Michael reactions of formyl enones. The ketoaldehydes produced should be good substrates for a subsequent aldol condensation in an overall intramolecular Robinson annulation to yield bicyclic enones of potential use in natural product synthesis. Furthermore, such aminocatalytic Michael cyclizations are mechanistically interesting as they may proceed by either enamine or iminium catalysis, or both simultaneously.

As a model reaction we studied the amine-catalyzed Michael cyclization of formyl enone **1a** to give ketoaldehyde **2a** [Eq. (4)]. This reaction was catalyzed by (*S*)-proline (**3**; 10 mol%, room temperature, DMF (*N*,*N*-dimethylformamide), 3 days), but as expected, both the diastereoselectivity and enantioselectivity were low. Next, we studied the commercial imidazolidinone catalysts **4** and **5** of MacMillan and co-workers.[15] Although these catalysts have not been used previously in enamine catalysis,[16] we found them to catalyze the cyclization reaction effectively. Interestingly, whereas the more reactive catalyst **4** provided the product in very high yield (99%) but with only 39% *ee*, catalyst **5** gave the product in the same yield and with an excellent 97% *ee*. The enantioselectivity and diastereoselectivity were determined by using an assay based on a Horner–Wadsworth–Emmons (HWE) reaction that we had developed earlier for the HPLC analysis of nonchromogenic or sensitive aldehydes.[6]

Fortunately, our results proved quite general; various other formyl enones reacted to give the desired products in excellent yields and with high *ee* values [Eq. (5), Table 1].[17] Thus, both aromatic enones (**1a** and **1b**) and aliphatic enones (**1c** and **1d**) could be used with excellent efficiency and enantioselectivity. Remarkably, even an enal could be

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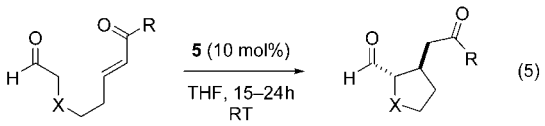
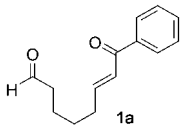
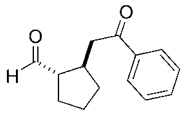
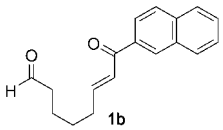
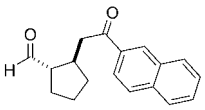
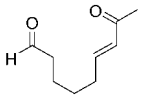
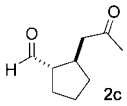
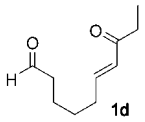
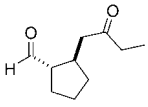
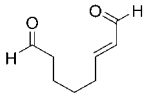
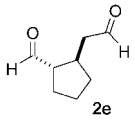
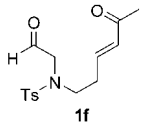
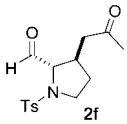


(5)

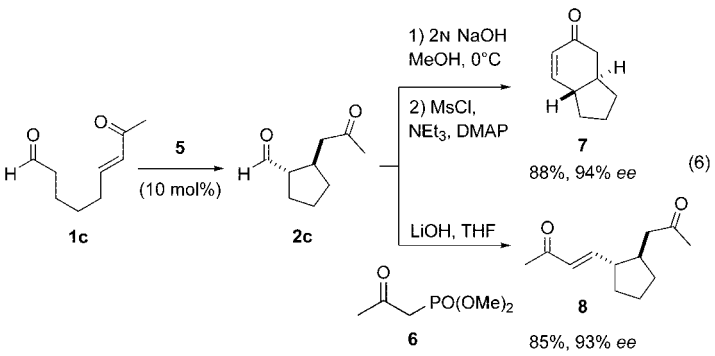
Table 1: Catalytic asymmetric intramolecular Michael reaction of aldehydes.

Starting material[a]	Yield [%]	Product	*ee* [%]	*anti*/*syn*
 1a	99	 2a	97	24:1
 1b	99	 2b	97	17:1
 1c	99	 2c	93	20:1
 1d	99	 2d	94	21:1
 1e	85	 2e	80	49:1
 1f	90	 2f	93	8:1

[a] Ts = *p*-toluenesulfonyl.

employed as the Michael acceptor to furnish a dialdehyde (**1e**→**2e**), although in somewhat reduced yield and enantioselectivity. To our delight, we were able to extend our asymmetric intramolecular Michael reaction to the synthesis of heterocyclic products. Thus, the reaction of aldehyde **1f** gave the corresponding pyrrolidine **2f** with excellent enantioselectivity and in good yield.

Having established an efficient process for the synthesis of ketoaldehydes **2**, we next investigated their application in two tandem sequences. Thus, the treatment of formyl enone **1c** with catalyst **5** and subjection of the product **2c** to an in situ intramolecular aldolization or HWE reaction with dimethyl (2-oxopropyl)phosphonate (**6**) gave enones **7** and **8**, respectively, in high yields and enantiomeric purity [Eq. (6); DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl]. Hydrindenone **7** has been described previously as the racemate, but this is the first enantioselective synthesis of **7**.[18] Both the bicyclic enone **7** and diketone **8** should be useful



(6)

additions to the chiral pool and valuable precursors in natural product synthesis.

We assume the Michael reaction described herein to proceed through an enamine mechanism. However, the observation that only enones react to give the desired products with very high enantioselectivity may be interpreted as evidence for an intriguing dual-activation mechanism involving both enamine and iminium catalysis. Furthermore, an inverse-electron-demand hetero-Diels–Alder mechanism, reminiscent of the intramolecular enamine/enal cycloaddition of Schreiber et al.[19] and the organocatalytic hetero-Diels–Alder reaction of Juhl and Jørgensen,[20] should be considered.

In summary, we have disclosed the first catalytic asymmetric intramolecular Michael reaction of aldehydes. Our process furnishes cyclic ketoaldehydes in excellent yields, with high enantioselectivities, and under very mild and convenient reaction conditions. This reaction is therefore expected to find use in organic synthesis. Further studies towards expanding the scope of this reaction and developing a more detailed mechanistic understanding are well underway in our laboratory.

Experimental Section

Typical procedure: Ketoaldehyde **1c** (123 mg, 0.8 mmol) was dissolved in dry THF (8 mL) and treated with **5** (20.4 mg, 0.08 mmol, 10%). The resulting mixture was stirred under argon at room temperature until the starting material had disappeared (15 h). The solution was then concentrated and filtered through silica. The product **2c** was dissolved in methanol (4 mL), cooled to 0°C, and treated with NaOH (2N, 4 mL).[21] After 5 min, TLC analysis indicated completion of the reaction. The mixture was poured into saturated aqueous ammonium chloride solution, the resulting mixture was extracted with ether, and the extracts were dried, filtered, and concentrated to give the crude aldol product. This material was dissolved in CH_2Cl_2 (5.2 mL) and stirred with methanesulfonyl chloride (0.16 mL), DMAP (35.6 mg), and triethylamine (0.39 mL) under argon for 30 min. After an aqueous workup and purification by chromatography on silica gel (20% ether/pentane), enone **7** was obtained as a colorless oil (95.2 mg, 0.7 mmol, 88%).[22]

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