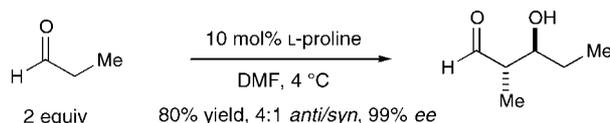


molecular aldol reaction. Almost three decades later, studies by the groups of Barbas<sup>[3a]</sup> and List<sup>[3b]</sup> revealed that proline catalysis could be extended to a variety of transformations, including the direct enantioselective aldol reaction<sup>[4]</sup> between ketones and aldehydes. Recently, our group advanced this proline-catalysis concept to the first example of a direct enantioselective cross-coupling of aldehyde substrates<sup>[5]</sup> (Scheme 1), a powerful yet elusive aldol variant that had previously only been carried out within the realm of enzymatic catalysis.



**Scheme 1.** Proline-catalyzed aldehyde–aldehyde aldol reaction.

As part of an ongoing program to develop organocatalysts of broad utility to chemical synthesis, we recently initiated studies towards the identification of simple amines that mimic aldolase type I enzymes while providing complementary function or stereoselectivity to known enamine catalysts (e.g., proline). Herein we describe a mechanism-based investigation that has established imidazolidinones as efficient catalysts for direct and enantioselective aldehyde–aldehyde aldol reactions. More importantly, we demonstrate a new class of enamine catalyst with selectivity parameters that rival or complement benchmark amino acid catalysts (Scheme 2).

In 2001, Houk and Bahmanyar reported a computational study into the transition-state topographies involved in enamine aldol reactions.<sup>[6]</sup> Besides providing further insight, this study described that secondary enamine additions typically proceed via a late transition state in which the

## Organocatalysis

### The Importance of Iminium Geometry Control in Enamine Catalysis: Identification of a New Catalyst Architecture for Aldehyde–Aldehyde Couplings\*\*

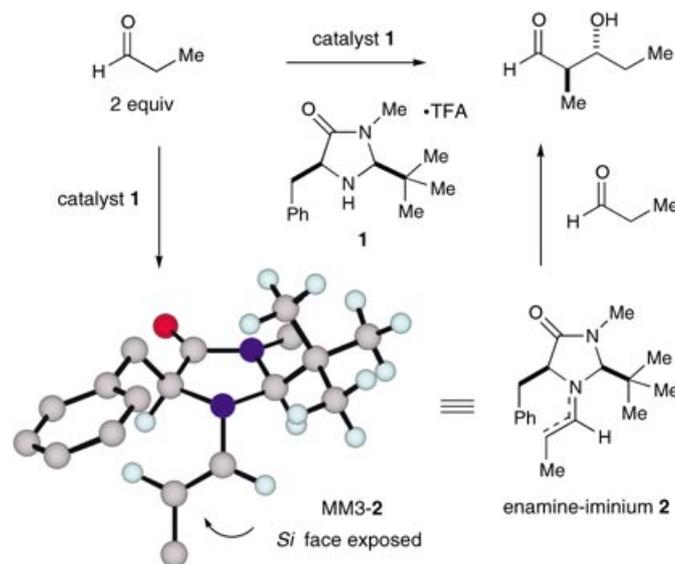
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In 1971, Hajos and Parrish<sup>[1]</sup> and Eder, Sauer, and Wiechert<sup>[2]</sup> independently described the first examples of enantioselective proline-catalyzed reactions in the form of an intra-

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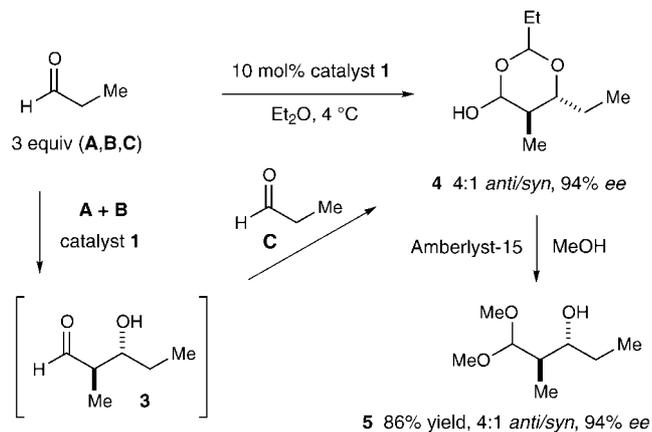
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



**Scheme 2.** Imidazolidinone-catalyzed aldehyde–aldehyde aldol reaction.

development of the iminium  $\pi$  bond precedes the formation of the carbon–carbon bond. On this basis, we hypothesized that enantiofacial discrimination in enamine additions might be governed, in part, by the ability of an amine catalyst to control iminium geometry during the transition state. Given the success of imidazolidinones as asymmetric catalysts that confer iminium activation and geometry control,<sup>[7]</sup> we rationalized that amines of type **1** might readily function as enantioselective enamine-aldol catalysts. This hypothesis was further substantiated by the computational model MM3-2, which predicts  $\pi$ -facial differentiation of enamine-iminiums derived from **1** on the basis of 1) selective formation of the *E* iminium isomer during the transition state to avoid nonbonding interactions with the bulky *tert*-butyl group, and 2) the benzyl group on the catalyst framework which effectively prevents the *Re* face of the enamine from participating in carbonyl addition.

Initial investigations revealed that the (2*S*,5*S*)-5-benzyl-2-*tert*-butylimidazolidinone catalyst **1** (10 mol%) does, indeed, promote the aldol self-coupling of propionaldehyde to provide the putative aldol adduct **3** in  $\geq 86\%$  yield with 94% *ee* (Scheme 3). Unexpectedly, the initial aldol dimeriza-



**Scheme 3.** Imidazolidinone-catalyzed aldol reaction: initial results.

tion adduct **3** undergoes rapid formation to the hemiacetal system **4**, a self-termination step that fortuitously protects the product from participation in further aldol processes. To our delight, methanolysis of this aldol hemiacetal product in situ allows direct access to the bench-stable  $\beta$ -hydroxy dimethoxyacetal **5** without loss in enantiopurity or diastereocontrol. Notably, the observed sense of asymmetric induction is in accord with the calculated enamine-iminium model MM3-2. In contrast to the proline variant, this enantioselective aldehyde coupling is readily accomplished in a wide variety of solvents,<sup>[8]</sup> with low dielectric media (e.g., hexane: 90% *ee*; dioxane: 94% *ee*) being generally most efficient. The superior levels of asymmetric induction and efficiency exhibited by the amine salt **1** in  $Et_2O$  to afford the dimethoxy-protected aldehyde (2*R*)-**5** in 86% yield with 94% *ee* in one chemical process prompted us to select these catalytic conditions for further exploration.

The ability of imidazolidinone **1** to catalyze enantioselective cross-aldol reactions between non-equivalent aldehydes was examined next. As highlighted in Table 1, addition of  $\alpha$ -methylaldehyde donors by means of a syringe pump to a

**Table 1:** Imidazolidinone-catalyzed direct aldol condensation: reaction scope.

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield [%] <sup>[a]</sup>	<i>anti/syn</i> <sup>[b]</sup>	<i>ee</i> [%] <sup>[c,d]</sup>
1	Me	Me		86	4:1	94
2	Me	<i>i</i> Pr		90	5:1	95
3	Me	<i>c</i> -C <sub>6</sub> H <sub>11</sub>		81	5:1	97
4	Me	Ph		61	4:1	93
5	<i>n</i> Bu	<i>i</i> Pr		72	6:1	91
6	Bn	<i>i</i> Pr		80	5:1	91
7	Me	OPiv		58	4:1	90
8	OBn	OBn		64	4:1	92
9	SBn	SBn		84	11:1	97
10 <sup>[e]</sup>	OTIPS	OTIPS		84	1:4	92

[a] Absolute and relative stereochemistry assigned by chemical correlation. [b] Determined by chiral GLC or Mosher ester analysis. [c] Enantiomeric excess of major diastereomer. [d] Performed in dioxane. [e]  $Et_2NH/SiO_2$  in place of  $MeOH/Amberlyst-15$ . TIPS = triisopropylsilyl, Piv = pivaloyl.

variety of formyl acceptors effectively prevents homodimerization while providing the desired cross-aldol products in excellent yields (Table 1, entries 1–10, 58–90% yield). Significant electronic and structural modification in the acceptor component can be realized to incorporate  $\alpha$ -alkyl,  $\alpha$ -aromatic, and  $\alpha$ -oxy functionality (Table 1, entries 1–7, 90–97% *ee*).

Whereas it has been documented that  $\alpha$ -acyloxy-substituted aldehydes are inert to proline catalysis,<sup>[9]</sup> we have found that these substrates readily participate as electrophilic aldol partners in the presence of amine **1** (Table 1, entry 7, 58% yield, 90% *ee*).

We next examined the capacity of imidazolidinone **1** to catalyze the homodimerization of  $\alpha$ -heterosubstituted aldehydes (Table 1). It has been established that proline catalysis in this venue provides erythrose architecture in one step,<sup>[9]</sup> a transformation that enables the selective production of mannose, glucose, or allose in only two chemical reactions.<sup>[10]</sup> As shown in Table 1, entries 8 and 9, exposure of catalyst **1** to  $\alpha$ -benzyloxy or  $\alpha$ -benzylsulfide aldehydes also provides the erythrose aldol adduct with high levels of enantiocontrol (92–97% *ee*). In contrast,  $\alpha$ -silyloxy aldehydes provide the corresponding threose aldehyde product upon hydrolysis of the corresponding hemiacetal over silica gel (Table 1, entry 10, 4:1 *syn/anti*, 92% *ee*). As such, we anticipate that the imidazolidinone catalyst will be valuable in the production of hexose carbohydrates that are not available through proline catalysis (e.g. idose, gulose, galactose).<sup>[11]</sup> More importantly, this result demonstrates the capacity for orthogonal enamine selectivities as a function of amine catalyst architecture.

In summary, we have documented the first asymmetric organocatalytic aldol reaction in the presence of imidazolidinone catalysts. This method allows enantioselective access to  $\beta$ -hydroxy dimethoxyacetals, bench-stable adducts that functionally complement the  $\beta$ -hydroxyaldehyde adducts derived from proline-catalyzed aldol reactions.

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