ACS Catalysis

RESEARCH ARTICLE

pubs.acs.org/acscatalysis

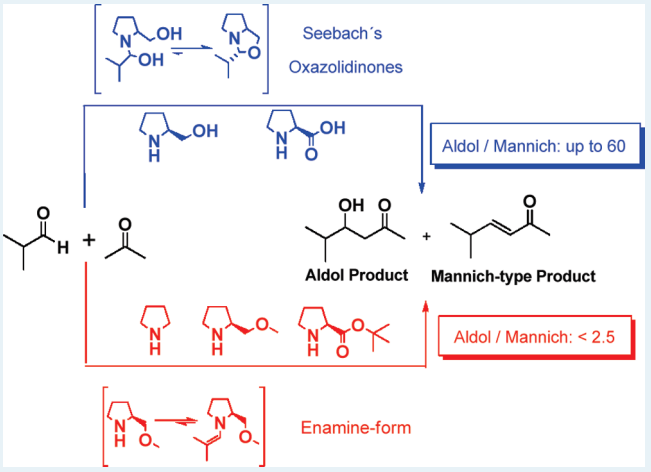
Influence of the Organocatalyst in the Aldol/Mannich-Type Product Selectivities in C−C Bond Forming Reactions

Pablo Domínguez de María,*[,†,‡] Paula Bracco,[†] Luiz Fernando Castelhano,[†] and Gerrald Bargeman[†]

[†]Process and Product Technology Department (CPT), AkzoNobel BV, Velperweg 76, P.O. Box 9300, 6800 SB Arnhem, The Netherlands

Supporting Information

ABSTRACT:



Several organocatalysts were tested in the cross condensation of isobutyraldehyde and acetone. Formation of aldol-type and Mannich-type ("aldol condensation") products was assessed, and Aldol/Mannich proportion studied under several reaction conditions and at different conversions. Organocatalysts able to form Seebach's oxazolidinones, proline and prolinol, led to high Aldol/Mannich relationships (60−10, depending on organocatalyst, reaction conditions, and conversions), whereas organocatalysts unable to form such oxazolidinones (pyrrolidine, *O*-methylprolinol and proline ^{t}butyl ester) yielded much lower Aldol/Mannich relationships in all conditions and conversions studied (<2.8). These results suggest that Seebach's oxazolidinones might act as "controllers" of the reaction, thus partly avoiding the formation of the Mannich-type adducts, by removing activated forms of aldehyde from the catalytic cycle.

KEYWORDS: proline, pyrrolidine, oxazolidinone, aldol, mannich, organocatalysis

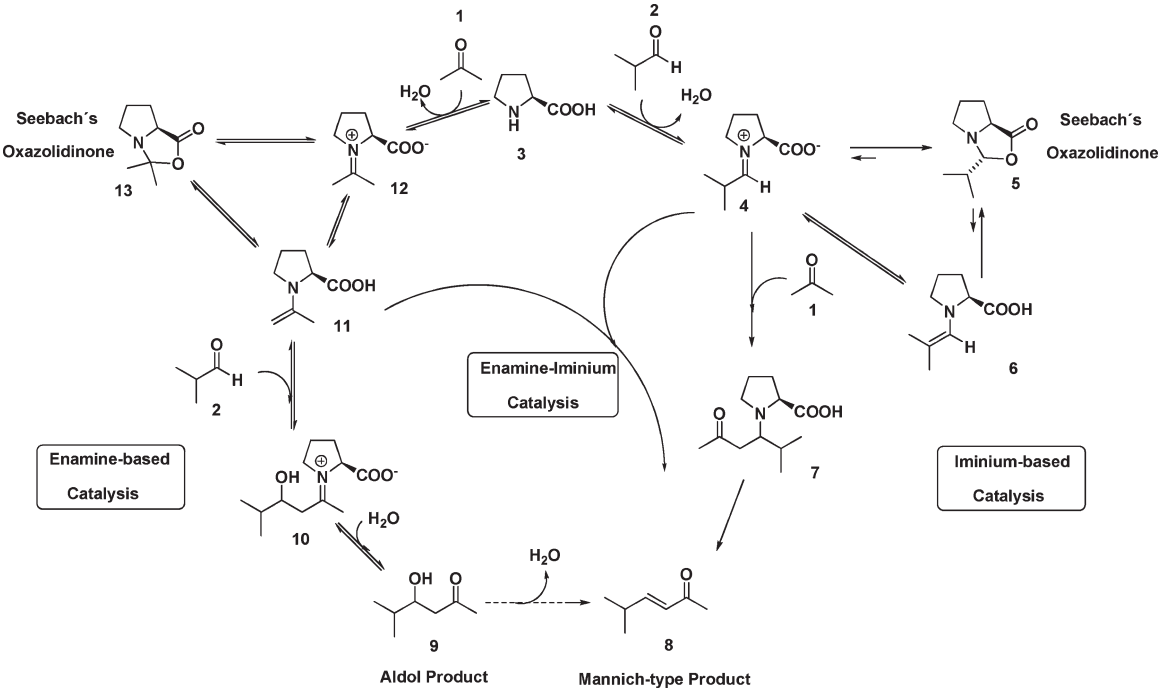
1. INTRODUCTION

A significant number of key synthetic strategies such as aldol reactions, Mannich-type reactions, and Michael additions can be carried out enantio- and regioselectively by means of proline as the organocatalyst.[1−4] Although discovered in the 1970s for *intra*molecular C−C cyclizations,[1−6] proline catalysis has experienced a tremendous renaissance during the past years, triggered by the discovery of proline-catalyzed *inter*molecular aldol reactions.[7] These catalytic concepts have been extended to other amine derivatives, leading to impressive examples of enantioselective and highly concerted processes.[1−7]

The actual mechanism(s) for proline-catalyzed C−C bond formations have been discussed by several research groups (Scheme 1).[8−17] For the aldol reaction between acetone (2-propanone, **1**) and isobutyraldehyde (2-methylpropanal, **2**) the enamine-based route (via **11**) is followed, whereas the iminium intermediate **4** can trigger a Mannich-type condensation-elimination reaction, finally affording **8**. Furthermore, the formation of oxazolidinones **5** and **13** was reported years ago.[18,19] These molecules have traditionally been considered as "parasitic species", not displaying any productive role in the catalysis, but rather removing catalytic loading from the actual reaction.[11] However, that statement has been challenged by different groups, suggesting a more active behavior for these molecules in the proline-catalyzed reactions, even being actual organocatalysts.[20−22] Apart from the enamine and iminium catalytic routes (Scheme 1), a dual enamine-iminium **4** and **11** reaction has also been proposed.

Received: November 14, 2010
Revised: December 14, 2010
Published: January 7, 2011

Scheme 1. Proposed Mechanism(s) for Proline-Catalyzed C−C Bond Formation, Involving Enamine, Iminium, and Enamine-Iminium Pathways[a]



[a] Acetone **1** and isobutyraldehyde **2** are the substrates studied herein. The direct hydration of Mannich-type product **8** to afford the aldol product **9** is insignificant, supported by low formation of **9** (0.2−0.3% in 24 h, r.t.) from pure **8** in the presence of organocatalysts and excess of water.

Herein two activated substrates are involved, eventually leading to the Mannich-type product **8**. Interestingly, it was demonstrated that processes were first-order at low catalyst loadings, and second-order at higher amounts of catalyst.[23,24]

For proline-catalyzed type reactions the modulation of the contributions from enamine (aldol) and iminium (Mannich-type) may be crucial from a practical viewpoint. In this respect, a recent example described the control of a (reversible) aldol reaction in aqueous environments (by combining proline with some polymeric supports), to enhance selectivity toward the (irreversible) Mannich-type product.[25] Yet, despite the importance of modulating these reactivities, to our knowledge there are not many studies aiming to understand this aldol/Mannich ratio in organocatalytic C−C bond forming reactions. We report herein experiments in that direction.

2. RESULTS AND DISCUSSION

We studied with a model reaction (isobutyraldehyde and acetone as substrates) how the formation of aldol product **9** and Mannich-type adduct **8** may be (catalytically) influenced by the different reaction conditions applied. At temperatures >40 °C, a severe dehydration of **9** to yield **8** was observed (data not shown). At room temperature, however, aldol product **9** remained stable during at least 60 h. Therefore, under those very mild reaction conditions, all Mannich-type adducts are catalytically formed, and not via dehydration of **9** (aldol condensation) (Scheme 1). This stability of **9** at room temperature has been reported by others as well.[26,27]

At first step, the reaction was examined with different organocatalysts at different catalyst loadings. Results are summarized in Table 1.

Organocatalysts able to form oxazolidinones (Proline **3** and Prolinol **14**, entries 1−2) lead to moderate-to-high selectivities for the aldol performance. Prolinol **14** displayed moderate-to-high selectivities for aldol reaction as well. Low catalyst loadings initially led to high aldol selectivities (A/M ca. 60), followed by a decrease in the selectivity (A/M) with progression of the reaction, albeit a high aldol bias remained in all cases (until full conversion). This implies that regardless of the proportion between isobutyraldehyde-acetone, which necessarily changes during the reaction, a high A/M bias (>10) is always observed (Figure 1).

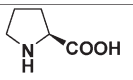
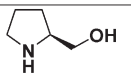
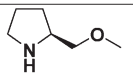
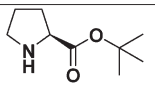
On the other hand, organocatalysts that cannot form oxazolidinones afforded completely different results (Table 1, entries 3−6). Pyrrolidine-catalyzed (**17**) reactions proceeded extremely fast (full conversion in ca. 4 h in all cases), with a high preference toward Mannich-type products. Also in this case, a slightly higher A/M ratio was observed at low catalyst loadings (Figure 2), suggesting that kinetically a first-order or a second-order reaction may proceed depending on the catalyst loading.[23,24] Remarkably, aldol product was stable for longer reaction times (24 h), leading to the conclusion that the Mannich-type adduct **8** is only catalytically produced.

Likewise, these results indicate that for pyrrolidine the aldol reaction cannot be reversible. Otherwise, since pyrrolidine-catalyzed reactions proceed fast (∼ 4 h for full conversion), at longer reaction times only Mannich-type adduct **8** (irreversible) should have been observed. This finding is intriguing, as the proline-catalyzed aldol reaction has been reported as reversible by several groups.[3,4,26,27]

Final A/M ratios (>4 h, full conversions) are constant, and slightly dependent on catalyst loading, with a higher aldol bias for low catalyst loadings (Final A/M ranging from ca. 2.5 at low catalyst loadings to ca. 0.5 at higher loadings, Figure 3), much less in all cases than data reported for prolinol **14** (Figure 1).

dx.doi.org/10.1021/cs100088m |ACS Catal. 2011, 1, 70–75

Table 1. Aldol/Mannich Ratios in Condensations of Isobutyraldehyde and Acetone Using Different Organocatalysts, At Room Temperature

Entry	Catalyst	Parameter	A/M (-)[a]
1	 Proline (**3**)	Catalyst loading (5–30 mol%)[b,c]	20 – 8
2	 Prolinol (**14**)	Catalyst loading (5–25 mol%)[c]	60 – 10
3	 *O*-Methylprolinol (**15**)	Catalyst loading (5–25 mol%)[c]	0.5 – 0.4
4	 Proline ^{t}butyl ester (**16**)	Catalyst loading (5–25 mol%)[c]	2.8 – 0.8
5	 Pyrrolidine (**17**)	Catalyst loading (0.1–15 mol%)[c]	2.5 – 0.3
6		Acetone: Isobutyraldehyde (20:1 to 1:20)[c,d]	2 – 0.8

[a] Range of aldol/Mannich ratios, determined by product areas in GC (see Supporting Information) at different conversions and reaction times (see below). [b] In the case of proline, the organocatalyst was not soluble in the reaction media. For the others, a homogeneous solution was obtained. [c] Catalyst loading (mol %) is related to isobutyraldehyde. [d] Catalyst loading fixed at 5 mol %.

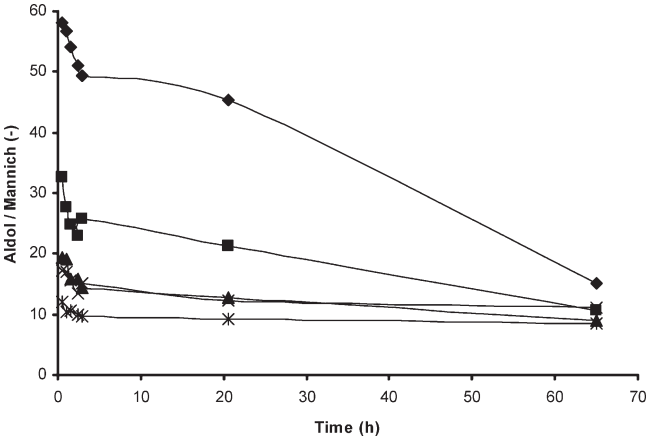


Figure 1. Aldol/Mannich ratios obtained with prolinol **14** as organocatalyst. Conditions: Acetone: Isobutyraldehyde (4:1 equiv/equiv), room temperature. Catalyst loading (mol %): (♦) 5%; (■) 10%; (▲) 15%; (X) 20%; (*) 25%. Full conversion was reached in all cases at about 30−40 h.

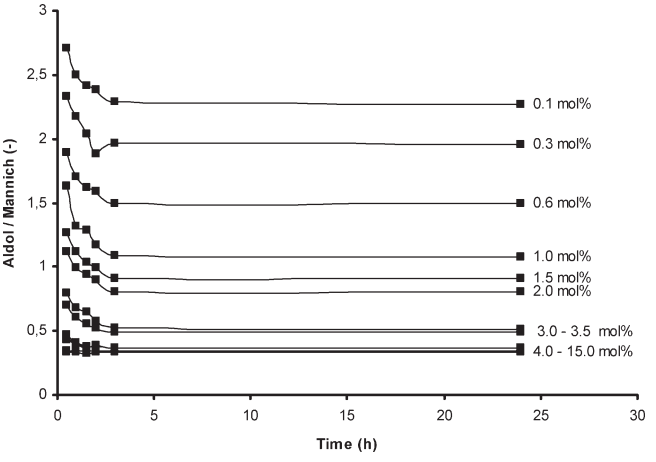


Figure 2. Aldol/Mannich ratio with pyrrolidine **17** as organocatalyst (loadings from 0.1−15 mol %). Conditions: Acetone/Isobutyraldehyde (4:1 equiv/equiv), room temperature. Full conversion was reached in all cases at about 4 h.

Furthermore, the high stability of compounds, aldol **9** and Mannich-type **8** rules out the possibility of a base-mediated degradation of the aldol product to yield aldol-condensation adducts via non-organocatalytic routes.

The reaction was further studied by fixing the pyrrolidine loading (5 mol %), and assessing different acetone:isobutyraldehyde proportions. As observed in Figure 4, A/M ratios remained at low values (A/M < 2.5).

Likewise, analogous low A/M ratios (<3) were obtained for proline ^{t}butyl ester **16** (Table 1, entry 4), showing a different behavior compared to proline or prolinol. The aldol product remained stable during long reaction times again. Furthermore, also in this case slightly different A/M profiles were observed

dx.doi.org/10.1021/cs100088m |*ACS Catal.* 2011, 1, 70–75

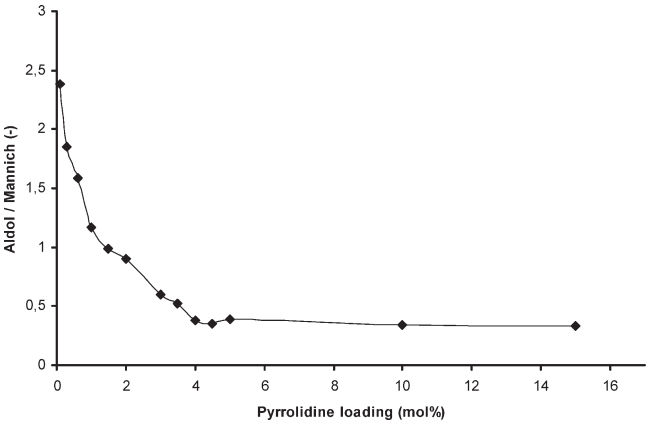


Figure 3. Different A/M ratios observed when pyrrolidine-catalyzed reactions are finished (>4 h reaction). Conditions: Acetone/Isobutyraldehyde (4:1 equiv/equiv). Pyrrolidine (catalyst loadings from 0.1 to 15 mol %). Room temperature. Magnetic stirring.

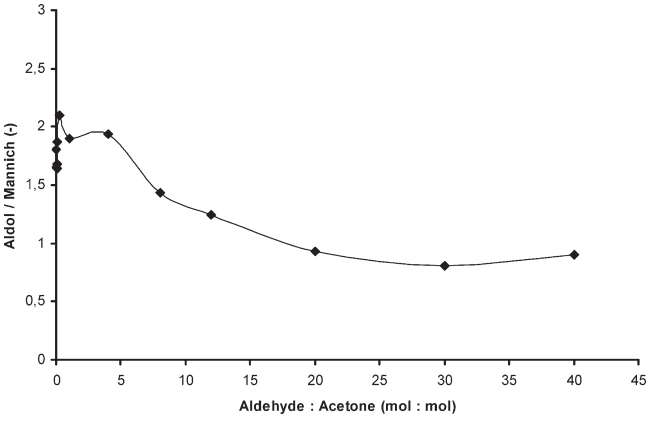


Figure 4. A/M ratios at full conversion (>4 h reaction) in pyrrolidine-catalyzed reactions (5 mol % catalyst loading) with different acetone: isobutyraldehyde proportions (equiv/equiv). Room temperature. Magnetic stirring.

depending on catalyst loadings, again with slightly higher aldol bias at low catalytic loadings (Figure 5).

Taken together, the results suggest that huge differences in A/M ratios are mainly driven by the possibility of forming Seebach's oxazolidinones (A/Ms of 60−10 in one group, to A/Ms of <2.8 in the other). Subsequently, the slight variations among the same organocatalysts may be ascribed to kinetic reasons, as well as to relative concentrations of reactive intermediates and substrates. All those parameters may surely influence the kinetic(s), leading to first-order, or second-order reactions, and to mono- or dual activations of species.[23,24]

Pyrrolidine **17** and related secondary amines are known to be efficient catalysts for the methylenation of aldehydes.[28,29] Pihko et al. reported a fast and selective (for Mannich-type products) iminium-based self-condensation of aldehydes (and with formaldehyde) by means of pyrrolidine-carboxylic acids as catalysts.[30,31] Conversely, when Córdova et al. studied the proline-catalyzed condensation of ketones and formaldehyde, a highly selective aldol process was observed, affording (enantiopure) β-hydroxyketones.[32] As explanation it may be proposed that, in the case of proline, almost all aldehyde will be in the form of oxazolidinone **5**, as a (non-reactive?) reservoir.[18−22] A small amount will be in

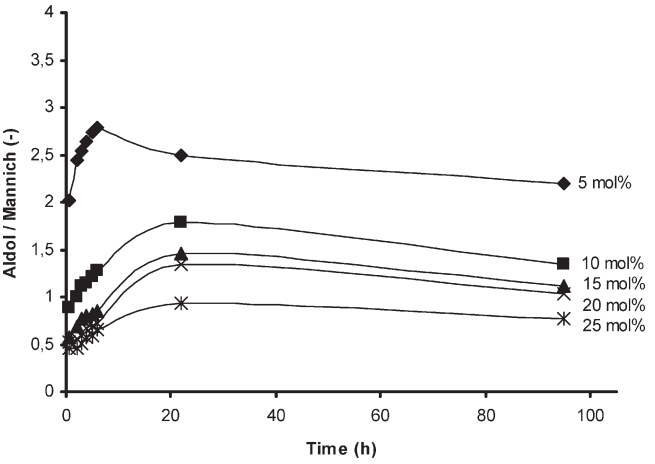


Figure 5. Aldol/Mannich ratio by using different loadings of proline ^{t}butyl ester **16** as catalyst. Conditions: Acetone/Isobutyraldehyde (4:1 equiv/equiv). Room temperature.

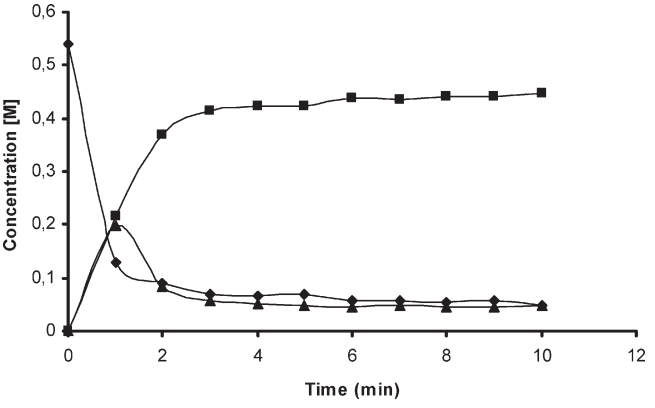
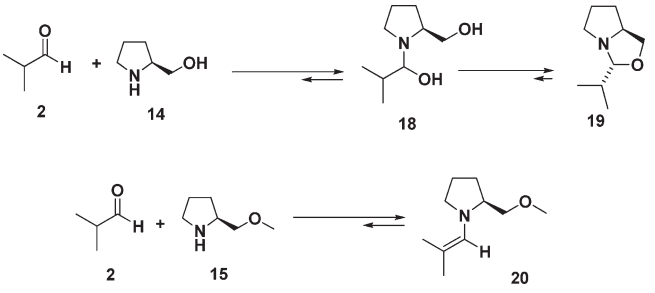


Figure 6. Evolution of prolinol **14** (♦) in neat isobutyraldehyde. Formation of Seebach's oxazolidinone **19** (■) and hemiaminal **18** (▲) (See Supporting Information).

Scheme 2. Equilibria for Isobutyraldehyde with Prolinol 14, and with *O*-methylprolinol 15, Observed by GC and NMR (see Supporting Information)



the iminium form **4**, and another part is expected to be in the enamine form **6**, as stable intermediate.[33] Other enamines of aldehyde (e.g., from unbranched aliphatic ones) lead rapidly to further self-condensations and polymerizations.[18,19,23,24] An analogous approach has been applied to develop prolinol-based organocatalysts, able to perform efficient Michael addition reactions (iminium-based) by a smart combination of steric hindrance together with the need of having aldehydes mainly in the

dx.doi.org/10.1021/cs100088m |*ACS Catal.* 2011, 1, 70–75

iminium form, and not as oxazolidinone reservoir.[34−37] In this respect, only when aldehydes are added in the form of (protected) acetals, good conversions in pyrrolidine-catalyzed aldol reactions have been reported.[38,39] Overall, it can be assumed that a successful organocatalytic process, in terms of no byproduct formation, is a delicate equilibrium of species and reactivities.

To further explore this possibility, prolinol **14** (10 mol %) was added to a neat solution of isobutyraldehyde. The organocatalyst disappeared almost completely very fast (<2 min, GC), and two new peaks appeared (in a relationship ca. 80:20). NMR studies revealed that those peaks were the Seebach's oxazolidinone **19** and hemiaminal **18** (Figure 6, Scheme 2, see also Supporting Information).

In this case, neither iminium nor enamine form were observed (total absence of double bonds in NMR spectra). Conversely, when the same experiment was performed with *O*-methylprolinol **15**, equilibrium between the free catalyst **15** and the enamine form **20** was observed (Scheme 2).

3. CONCLUSIONS

The formation of aldol and Mannich-type adducts via organocatalytic C−C bond forming reactions is driven by the possibility of forming Seebach's oxazolidinones. Organocatalyts able to form those oxazolidinones yield Aldol/Mannich ratios of 60−10 (depending on conditions, conversions, and reaction times), whereas the other organocatalysts provide A/M ratios 2.8−0.5 in all cases. Subsequently, variations on A/M ratios within both groups may be related to kinetic aspects of each reaction performance, depending on actual acetone:isobutyraldehyde (equiv/equiv) relationship, level of conversion, catalyst loading, and so forth. Those findings are also in line with other works, in which even different reaction orders have been reported, depending on the catalyst loading. Overall, our results show (part of) an extremely complex scenario of reactivities, equilibria, and different mechanisms acting at the same time.

4. EXPERIMENTAL SECTION

Chemicals. All reagents and catalysts (proline, pyrrolidine, prolinol, proline ^{t}butyl ester, *O*-methylprolinol, acetone, isobutyraldehyde, decane) were obtained from Sigma-Aldrich, and were used without further purification.

Products. Aldol-type **9** and Mannich-type **8** compounds were characterized by NMR and GC, and data are fully consistent with those reported in previous literature.[26,27] Compound **9** (aldol adduct): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.8 (t, 6H), 1.6 (m, 1H), 2.1 (d, 3H), 2.5 (d, 2H), 3.8 (m, 1H, -CH−OH). Compound **8** (Mannich-type adduct): ^{1}H NMR (300 MHz, DMSO d6): δ (ppm) 1.2 (d, 6H), 2.3 (s, 3H), 2.6 (m, 1 H), 6.1 (d, 1H, CO-CH=), 6.9 (dd, 1H, $(CH_3)_2$-CH-CH=CH).

Reaction Conditions. Organocatalytic reactions were set by mixing variable amounts of acetone and isobutyraldehyde under magnetic stirring, and organocatalysts were subsequently aggregated. Samples (0.2 mL) were taken and analyzed by GC, using decane as external standard for the calculation of the conversion. Calibration curves of products (Mannich, aldol) and organocatalysts were built (range 0−150 mM) using ethyl acetate as solvent, with a fixed concentration of decane (150 mM). A "Response Factor" [Area Molecule]/[Area 150 mM decane] was calculated, and plotted in a graphic (Response Factor vs [Molecule]). For the GC analysis, a stationary phase Ph-Wax column (5 m × 100 μm × 0.1 μm) was used. An initial column temperature of 40 °C was set. This temperature was increased 75 °C/min until 225 °C. The injector temperature was 250 °C, and a constant column flow of 1.2 mL/min using Helium as carrier gas. Detector temperature was 250 °C. Samples of 5 μL were analyzed.

■ ASSOCIATED CONTENT

Supporting Information. GC chromatograms, and NMR and GC data regarding the formation of enamine and oxazolidinone. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +49 2418020468. Fax: +49 241 8022177. E-mail: dominguez@itmc.rwth-aachen.de.

Present Addresses

‡Institute of Technical and Macromolecular Chemistry, RWTH Aachen University, Worringerweg 1, D-52074 Aachen, Germany.

■ REFERENCES

(1) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660.
(2) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171.
(3) Barbas, C. F., III *Angew. Chem., Int. Ed.* **2008**, *47*, 42–47.
(4) List, B. *Tetrahedron.* **2002**, *58*, 5573–5590.
(5) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
(6) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497.
(7) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
(8) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.
(9) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957–959.
(10) Marquez, C.; Metzger, J. O. *Chem. Commun.* **2006**, 1539–1541.
(11) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839–5842.
(12) Cheong, P.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912–13913.
(13) Allemann, C.; Gordillo, R.; Clemente, F.; Cheong, P.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569.
(14) Clemente, F.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766–5678.
(15) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16–17.
(16) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.
(17) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 5155–5159.
(18) Orsini, F.; Pelizzoni, F.; Forte, M.; Sisti, M.; Bombieri, G.; Benetollo, F. *J. Heterocycl. Chem.* **1989**, *26*, 837–841.
(19) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
(20) Córdova, A.; Sundén, H.; Xu, Y.; Ibrahem, I.; Zou, W.; Engqvist, M. *Chem.—Eur. J.* **2006**, *12*, 5446–5451.
(21) Isart, C.; Bures, J.; Vilarrasa, J. *Tetrahedron Lett.* **2008**, *49*, 5414–5418.
(22) Seebach, D.; Beck, A. K.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszvich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425–471.

(23) Nozière, B.; Córdova, A. *J. Phys. Chem. A* **2008**, *112*, 2827–2837.
(24) Córdova, A.; Notz, W.; Barbas, C. F., III *J. Org. Chem.* **2002**, *67*, 301–303.
(25) Chi., Y.; Scroggins, S. T.; Boz, E.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2008**, *130*, 17287–17289.
(26) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575.
(27) Chandrasekhar, S.; Reddy, N. R.; Sultana, S.; Narshihmulu, Ch.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338–345.
(28) Basu, K.; Richards, J.; Paquette, L. A. *Synthesis* **2004**, *17*, 2841–2844.
(29) Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synlett* **1999**, *4*, 450–452.
(30) Erkkila, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205–4216.
(31) Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538–2541.
(32) Casas, J.; Sunden, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117–6119.
(33) Isobutyraldehyde has been reported as a very selective acceptor when cross aldol reactions of aldehydes are intended, which suggests that isobutyraldehyde−enamine is non-reactive: Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
(34) Diner, P.; Kjaersgaard, A.; Lie, M. A.; Jorgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 122–127.
(35) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880.
(36) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.
(37) Betancort, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737–3740.
(38) Zhang, F.; Peng, Y.; Liao, S.; Gong, Y. *Tetrahedron.* **2007**, *63*, 4636–4641.
(39) Funabiki, K.; Yamamoto, H.; Nagaya, H.; Matsui, M. *Tetrahedron Lett.* **2006**, *47*, 5507–5510.