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Rapid Organocatalytic Aldehyde-Aldehyde Condensation Reactions

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We report the results of the systematic optimization of the α-methylenation of aldehydes with aqueous formaldehyde. A simple combination of a secondary amine catalyst and a weak acid co-catalyst has been identified, allowing access to α-substituted acroleins in a matter of minutes. In the absence of formaldehyde, the catalytic system promoted the self-condensation reaction of α,β-unsaturated aldehydes. Both of these reactions exhibited linear relationships between co-catalyst acidities and reaction rates. A second-order dependence of catalyst concentration was observed, pointing to the involvement of two molecules of the ammonium catalyst in the rate-determining step.

Introduction

Condensation reactions between two aldehydes constitute a particularly facile method for the synthesis of unsaturated aldehydes.[1] Self-condensations of aldehydes have been carried out with several systems, including aqueous sodium hydroxide[2] and boric acid in refluxing xylenes.[3] Cross-condensation reactions between simple alkanecarboxaldehydes and formaldehyde, in turn, are typically performed using secondary amines and acid co-catalysts under relatively drastic conditions, including high temperature, high pressure, and rapid distillation of the product from the reaction mixture.[4] These α-methylenation reactions have only rarely been performed with more complex aldehydes.[5] In these cases, stoichiometric amounts of the amine and long reaction times have often been required. Milder protocols,[6] such as the use of Horner–Wadsworth–Emmons chemistry[7] or Mannich reactions with Eschenmoser's salt[8] (methylenediammonium chloride) have therefore been the methods of choice, especially in a total synthesis setting.[9]

Recently, we reported a particularly benign catalytic method for the synthesis of α-substituted acroleins with two different catalytic systems.[10] In this paper, we report the full details of these investigations, including further optimization of the reaction conditions. As a result of these experiments, we describe herein a simple catalyst combination that surpasses the previously disclosed catalyst system by at least a factor of 10, allowing α-methylenation reactions of aldehydes in *a matter of minutes*. The same catalyst is also active in self-condensation of aldehydes.

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

Results and Discussion

Our initial studies focused on the reaction of formaldehyde with propionaldehyde and citronellal. With these test systems we were able to identify that pyrrolidine/propionic acid (i) as well as L-Pro-β-Ala (ii) catalyze the methylenation of these test aldehydes. We were pleased to observe that the methylenation reaction has a wide scope with our first- and second-generation catalyst systems (Figure 1).

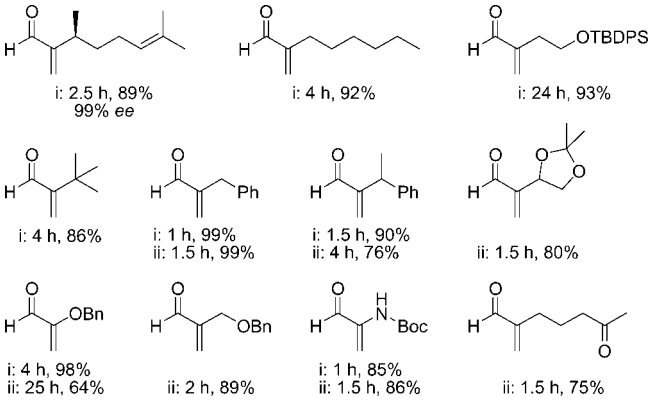
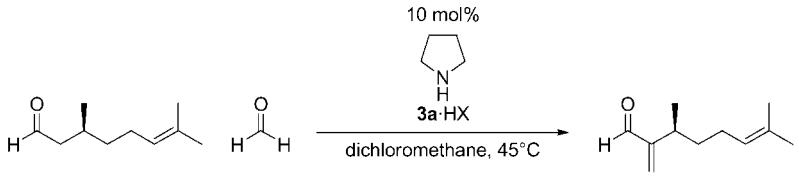


Figure 1. The scope of first- and second-generation catalysts systems.

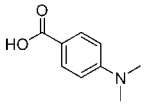
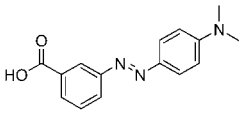
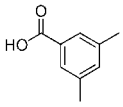
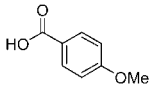
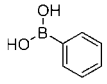
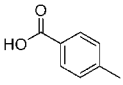
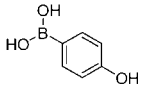
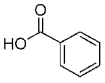
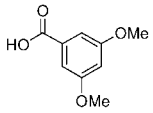
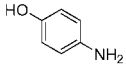
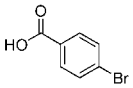
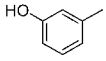
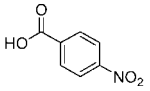
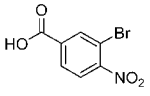
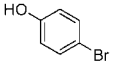
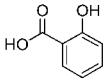
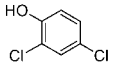
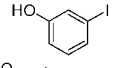
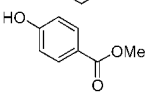
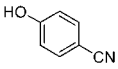
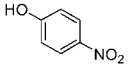
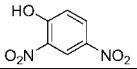
Although our first protocols were clearly successful, we felt that a more thorough survey of the reaction conditions would yield both further improvements in the protocol as well as additional insights into the reaction mechanism.

We initiated our study with the effect of acid co-catalyst in the reaction between citronellal and formaldehyde (Table 1). The reactions were carried out in dichloromethane[11] at 45 °C with 10 mol-% of both pyrrolidine and the acid co-catalyst. A series of Brønsted acids, including carboxylic acids, phenols, sulfonic acids and phosphonates were screened for their co-catalytic activity. The reaction

Table 1. Effect of acid co-catalyst on α-methylenation of citronellal.



1a 2 10a

Entry	HX		pK_a[a]	Time [min]	Conversion[b] [%]	Entry	HX		pK_a[a]	Time [min]	Conversion[b] [%]
1		**4a**	5.03	**30**	**100**	17	MCA	**6e**	2.87	90	12
2		**4b**	5.00	60	31[c]	18	DCA	**6f**	1.35	90	0
3		**4c**		30 60	51 100	19	TFA	**6g**	0.52	90	0
4		**4d**	4.47	30 60	53 100	20		**7a**	8.80	30	6
5		**4e**	4.36	30 60	50 100	21		**7b**		30	2
6		**4f**	4.20	60	91	22	TsOH	**8**	–2.80	30	0
7		**4g**		60	83	23		**9a**	10.30	30	9
8		**4h**	4.00	60	70	24		**9b**	10.08	30	5
9		**4i**	3.41	60	29	25		**9c**	9.95	30	11
10		**4j**		60	21	26		**9d**	9.34	30	21
11		**4k**	2.98	60	10	27		**9e**		30	29
12		**5**		90	0	28		**9f**	9.17	30	24
13		**6a**	5.03	30	67	29		**9g**	8.47	30	26
14		**6b**	4.87	30 60	37 90	31		**9h**	7.95	30	40
15		**6c**	4.76	60	76	31		**9i**	7.15	30	46
16		**6d**	3.77	60	3	32		**9j**	3.96	30	6

[a] The pK_a values are adopted from the pK_a compilation by R. Williams (http://research.chem.psu.edu/brpgroup/pka_compilation.pdf, accessed on May 31, 2007). [b] Determined by ^{1}H NMR spectroscopy. [c] The catalyst was poorly soluble.

with propionic acid was completed within 1 h under these conditions. Stronger acids, such as dichloroacetic acid and trifluoroacetic acid, failed to promote the reaction. However, benzoic acid and its derivatives exerted a beneficial effect on the reaction rate. We observed a clear dependence between the reaction rate and the pK_a of the aromatic acid co-catalyst (Entries 1–11). Interestingly, the weakest benzoic acid derivative, *p*(dimethylamino)benzoic acid (**4a**), turned out to be the most active, providing full conversion within 30 min.

The high activity of the weak acid **4a** prompted an investigation of other weak acids as co-catalysts. In addition to carboxylic acids, substituted phenols also exhibited catalytic activity (Entries 23–32). In general, electron-withdrawing substituents increased the activity of the phenol. The best phenol co-catalyst, 4-nitrophenol (**9i**), had an activity that was comparable to propionic acid (**6b**).

The structure/activity relationships could also be expressed in the form of linear free-energy relationship plots. With *para*-substituted benzoic acids, a clear linear relationship between equilibrium acidities and reaction rates was obtained with two different aldehyde donors **1a** and **1b** (Figure 2). These correlations can be interpreted either as Hammett plots (with ρ values of –0.5 and –0.6, respectively) or as Brønsted plots, with β values of the same magnitude but opposite sign.[12] In the case of phenols, the plot is also linear, although the correlation is weaker in this case (Figure 3a). In contrast to carboxylic acids, there is a clear *positive* correlation between the acidity of the phenol and the rate.

Plotting the relative rate (log k/k_0) against pK_a for both phenols and benzoic acids gives two lines that intercept at pK_a = 5.3 (Figure 3b). This suggests that ideal acid co-catalysts have pK_a values in the range 5–6. It should be noted

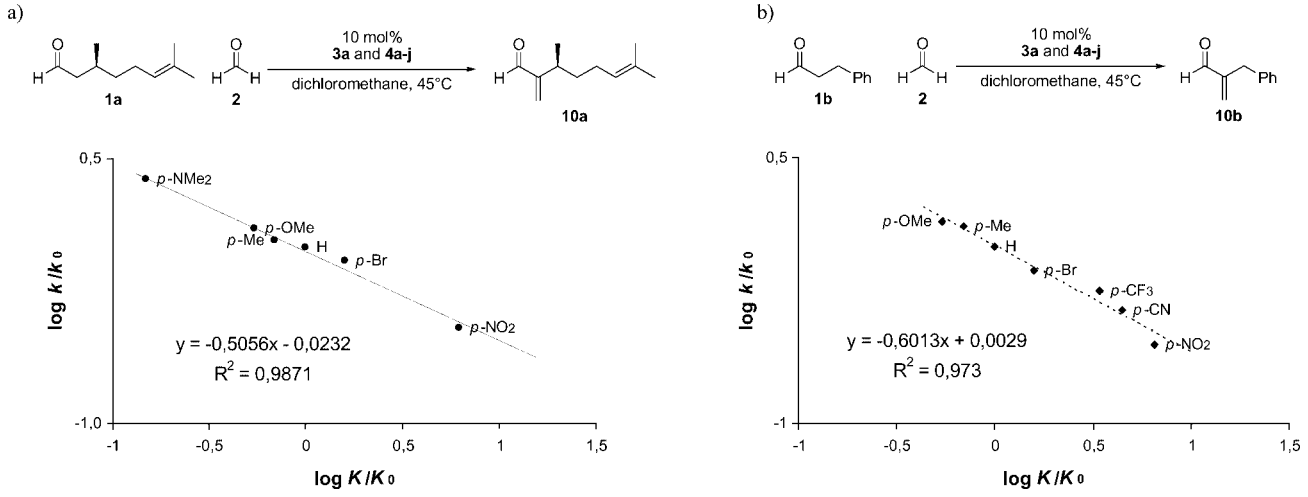


Figure 2. Correlation of benzoic acid dissociation constants with reaction rates of α-methylenation of a) citronellal (**1a**) and b) hydrocinnamaldehyde (**1b**).

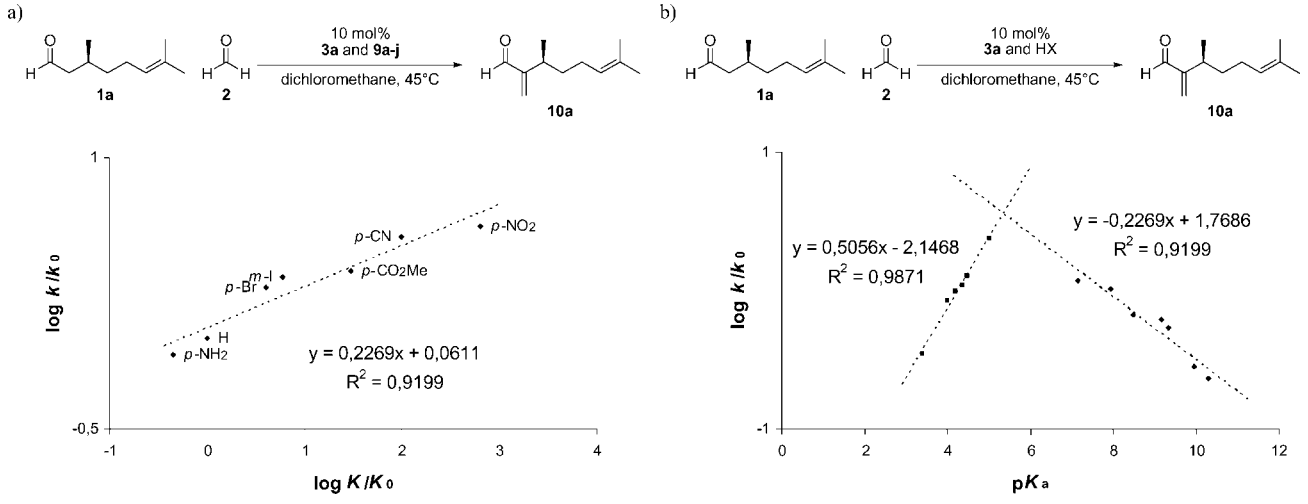
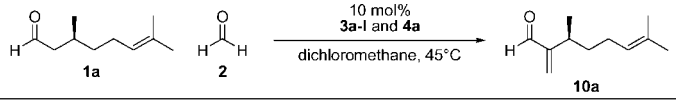
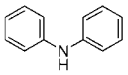
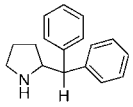
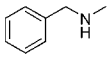
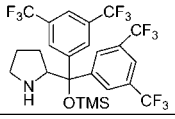
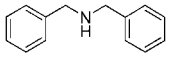


Figure 3. a) Correlation of phenol dissociation constants with reaction rates of α-methylenation of citronellal (**1a**) and b) comparison of benzoic acids and phenols as co-catalysts, plotted against pK_a of the acid.

Table 2. Effect of amine catalyst on the α-methylenation of citronellal.

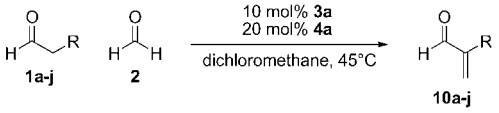


1a 2 10a

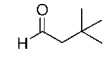
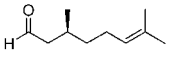
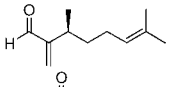
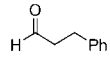
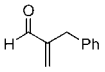
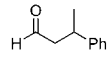
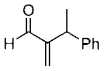
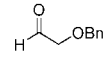
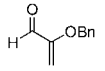
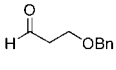
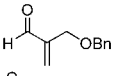
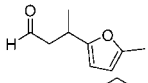
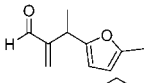
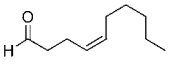
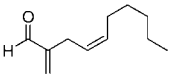
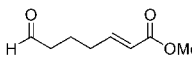
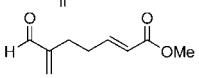
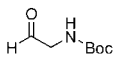
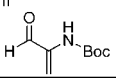
Entry	Amine		pK_{aH}	Time [min]	Conversion[a] [%]	Entry	Amine		pK_{aH}	Time [min]	Conversion[a] [%]
1		**3a**	11.27	15	47	7		**3g**	11.22	30	24
				30	100						
2		**3b**		15	67	8		**3h**	8.36	30	0
				30	100						
3		**3c**[b]	10.20	15	36	9		**3i**	11.02	15	46
				30	80					30	82
4		**3d**		15	46	10		**3j**	0.79	30	0
				30	81						
5		**3e**		30	35	11		**3k**	9.58	30	10
6		**3f**		30	0	12		**3l**		30	0

[a] Determined by ^{1}H NMR spectroscopy. [b] Mixture of *cis* and *trans* isomers.

Table 3. Catalytic α-methylenation of aldehydes.



1a-j 2 10a-j

Entry	Starting material		Product		Time [min]	Yield [%]	Time with previous method[b] [min]	Yield with previous method[b] [%]
1		**1c**		**10c**	180	85	240	86
2		**1a**		**10a**	30	quant.	240	89
3		**1b**		**10b**	5	99	60	99
4		**1d**		**10d**	25	quant.	90	90
5		**1e**		**10e**	60	quant.	240	98
6		**1f**		**10f**	10	85[a]	120	89
7		**1g**		**10g**	25	quant.	–	–
8		**1h**		**10h**	20	quant.	255	63[c]
9		**1i**		**10i**	40	quant.	3240 (48 h)	57
10		**1j**		**10j**	15	98	60	85

[a] Ca. 10% of benzyl alcohol is also formed as a side product. [b] See ref.[10] (Entries 1–6 and 10) and ref.[14] (Entries 8–9) for original data. [c] 80% isomeric purity.

that the pK_a is likely not the only factor affecting reaction rates, as evidenced by the higher activity of **4a** (Entry 1, Table 1) compared to pivalic acid (**6a**) (Entry 13), despite their similar pK_a values. The best co-catalyst, commercially available **4a**, was selected as the co-catalyst of choice for further optimizations.

The effects of the proportion of the catalysts were also examined. The loading of pyrrolidine was maintained at 10 mol-%, while the amount of the acid co-catalyst was altered. As expected, no catalytic activity was observed in the absence of the acid co-catalyst and substoichiomeric amounts of acid gave poorer reactivity than equal amounts of the catalyst partners. The highest rates were observed with a 1:2 amine/acid ratio. Adding more acid did not improve the rate.[13]

After optimization of the acid co-catalyst, we took a closer look at the amine component. A series of different amines were screened with the best acid co-catalyst **4a** (Table 2).

In our previous study, we had already identified the pyrrolidine skeleton as the optimal catalyst scaffold. In this study, pyrrolidine and its variants were confirmed as the best catalysts, with the highest activity obtained with the parent pyrrolidine (**3a**) or 2-methylpyrrolidine (**3b**). Increasing the size or the electronegativity of the 2-substituent had a detrimental effect on the activity (Entries 4–6), as did any further substitution in the ring (Entry 3). Piperidine, morpholine, and open-chain secondary amines were generally inferior to pyrrolidine as catalysts (Entries 7–12). Although **3b** had a slightly higher activity than **3a**, it is more than 300 times more expensive, and as such we selected the **3a/4a** catalyst combination for further screening.

The influence of solvents to our new catalyst system was re-evaluated at this point. As before, chlorinated solvents CH_2Cl_2 and $CHCl_3$ provided the best reaction rates. In addition, our original conditions, 10 M in *i*PrOH, was a competitive system, but the reactions were generally cleaner in CH_2Cl_2.[13]

After optimization of the reaction protocol, we evaluated the scope of the improved method with different donor aldehydes. As shown in Table 3, a wide variety of α-substituted acroleins are obtained in excellent yields after short reaction times. With a single exception, all reactions were completed within 1 h.

The reaction appears to be quite general with respect to the aldehyde structure, and donor aldehydes with varying steric demands and structures are tolerated. Remarkably, substrates prone to isomerization into conjugated systems (Entries 3, 4, 7, 8), acid-sensitive functionalities (Entry 10) as well as substrates prone to β-elimination (Entry 6) are all rapidly converted into α-methylenated products in good to excellent yields. As an example, under our first-generation conditions, the acrolein **10h** was obtained in 80% isomeric purity.[14] Our new improved conditions, in turn, provided **10i** without detectable isomerisation. Substrates that previously took several hours or even days (such as **1a** and **1j**) are now converted into the α-methylenated products in less than 1 h.

Self-Condensation of Aldehydes

The chemoselectivity of our α-methylenation reaction was high. Although similar conditions have been reported to promote the self-condensation of aldehydes,[15] we observed no evidence of formation of the self-condensation product of the donor aldehydes. We found this quite surprising and as such we decided to explore whether the self-condensation reaction would proceed in the absence of formaldehyde. Gratifyingly, when hydrocinnamaldehyde was subjected to our α-methylenation conditions in the absence of formaldehyde, the steady formation of the condensation product **11b** was observed.

We then began to investigate the optimal conditions for the self-condensation reaction. Influence of amine catalyst, acid co-catalyst as well as temperature and solvent effects were studied.[13] Of the amines studied, pyrrolidine (**3a**) was again the superior catalyst. The acid co-catalyst had exhibited strong influence on the activity of the catalytic system in the α-methylenation reactions. In contrast, the self-condensation reaction turned out to be much less sensitive to the pK_a of the acid, as attested by the small ρ value (–0.12) of the Hammett plot (Figure 4). Nevertheless, the weakest benzoic acids turned out to be the best co-catalysts for the self-condensation as well.

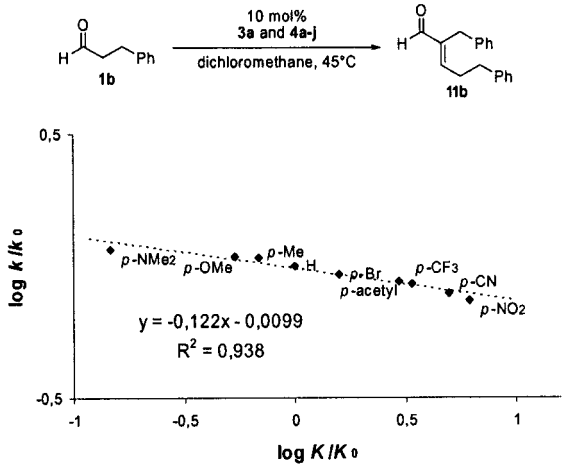
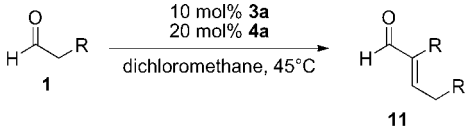


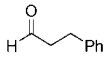
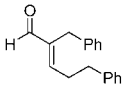
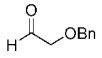
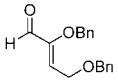
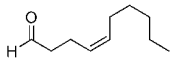
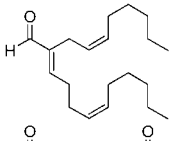
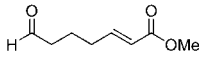
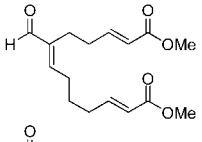
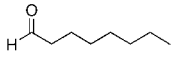
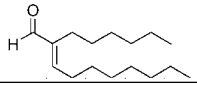
Figure 4. Correlation of benzoic acid dissociation constants with reaction rates of self-condensation of hydrocinnamaldehyde.

In conclusion, we identified the **3a/4a** catalyst combination as an optimal choice for the self-condensation reactions as well.

The scope of the self-condensation reaction was explored with a variety of aldehydes (Table 4). The reaction times were significantly longer than in the cross-condensation reaction with formaldehyde. Interestingly, in most cases the reactions reached 80% conversion within 30 min. However, full conversions were difficult to attain. Nonetheless, we were able to force the reactions to 96–98% conversion before quench without increasing the catalyst loading or unacceptably long reaction times. The remaining starting materials could then be removed by concentration in vacuo.

Table 4. Catalytic self-condensation of aldehydes.

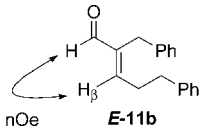


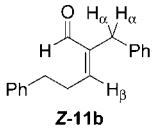
Entry	SM		Product		Time [h]	Yield [%]	*E*:*Z* ratio
1		**1k**		**11k**	0.3	96[a]	97:3
2		**1b**		**11b**	2	98	97:3
3		**1e**		**11e**	3	40	90:10
4		**1h**		**11h**	2.5	91	97:3
5		**1i**		**11i**	6	96	97:3
6		**1l**		**11l**	4.5	95	97:3

[a] Conversion determined by ^{1}H NMR spectroscopy.

The self-condensation reaction was also tolerant of different functionalities. Neither isomerization of the potentially labile products nor polymerization was observed. However, the reaction appears to be quite sensitive to steric effects, and no self-condensation of β-branched aldehydes was observed, even with extended reaction times and 10 mol-% of the catalyst.[16]

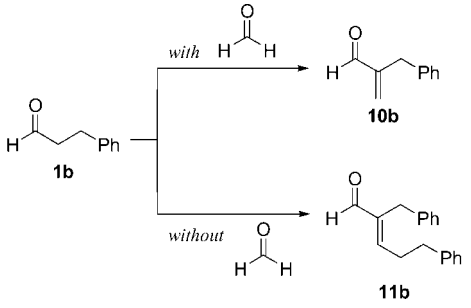
It should be noted that in all cases the stereochemistry was in favour of the (*E*) stereoisomer, as shown by the presence of an nOe enhancement between the aldehyde proton and the proton of the double bond (β-proton) and the absence of an nOe between the protons of the α-substituent and the β-protons.





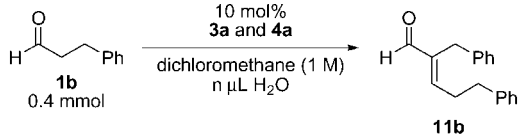
Insights into the Reaction Mechanism

Although both self-condensation and α-methylenation of aldehydes could be promoted by a single catalyst system, in the presence of formaldehyde the α-methylenation was a prevailing reaction pathway. What is the reason for this remarkable selectivity?



The formaldehyde was used as an aqueous solution. As such, control experiments were performed to determine whether the presence of water could be the decisive factor in preventing the self-condensation of hydrocinnamaldehyde to form **11b** (Table 5). Although the addition of

Table 5. Effect of water in the self-condensation of hydrocinnamaldehyde.



Entry	$V(H_2O)$ [μL]	$c(H_2O)$ [mM]	Conversion [%][a]
1	0	0	71
2	10	2.8	64
3	20	5.6	55
4	50	14	40
5	100	28	19

[a] Conversion determined by ^{1}H NMR spectroscopy.

small amounts of water clearly decreased the reaction rate, the influence was not strong enough to totally halt the formation of the condensation product. Moreover, the amount of water equivalent to that of formaldehyde solution resulted in only minor retardation of the rate (Entry 2).[17]

We then performed a series of competition experiments between hydrocinnamaldehyde and formaldehyde by varying the amount of hydrocinnamaldehyde. These reactions were performed at room temperature in $CDCl_3$ and monitored at 5 min intervals by ^1H NMR spectroscopy. As we already had observed in our preparative experiments, no self-condensation of hydrocinnamaldehyde occurred when equal amounts of the donor and acceptor aldehyde were mixed together (Figure 5a). However, when a two- or three-fold excess of cinnamaldehyde was present in the reaction, slow formation of the self-condensation product could be detected after approximately half of the formaldehyde had reacted to form **10b** (Figure 5b and c).

The effect of the presence of formaldehyde on the reaction rate can be clearly seen from Figure 6. It is evident that the presence of formaldehyde clearly retards the rate of self-condensation.

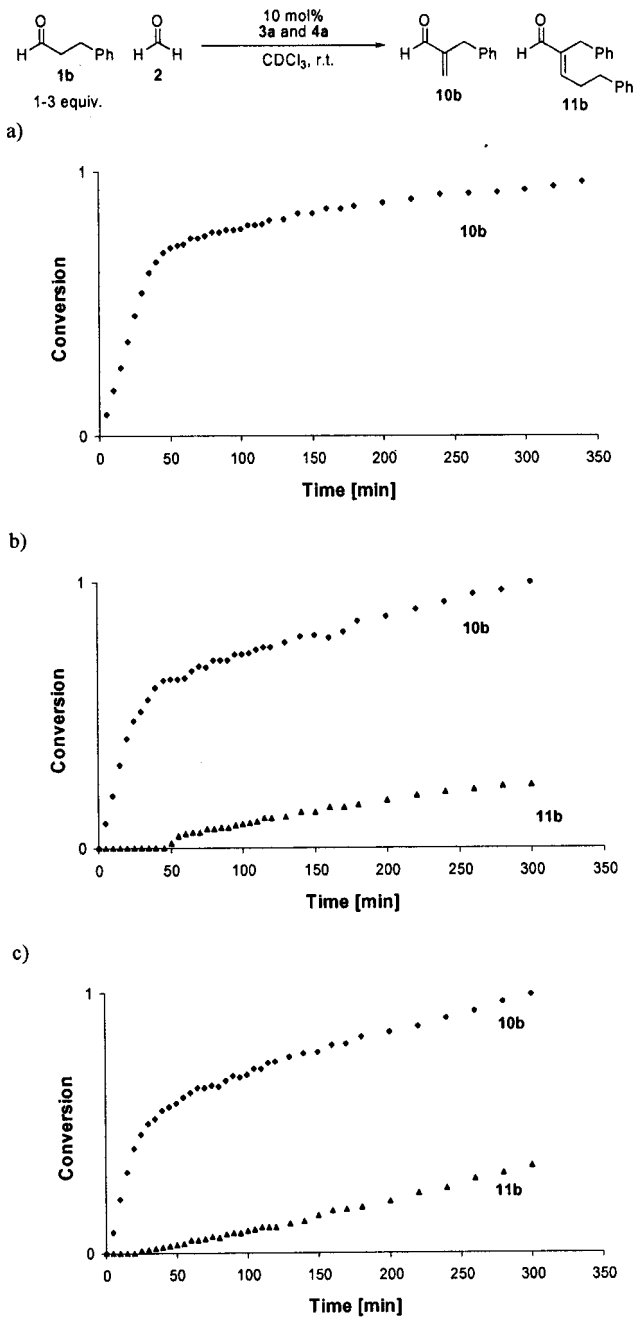


Figure 5. Competition experiment with a) 1:1, b) 2:1, and c) 3:1 ratio of hydrocinnamaldehyde (**1b**)/formaldehyde (**2**).

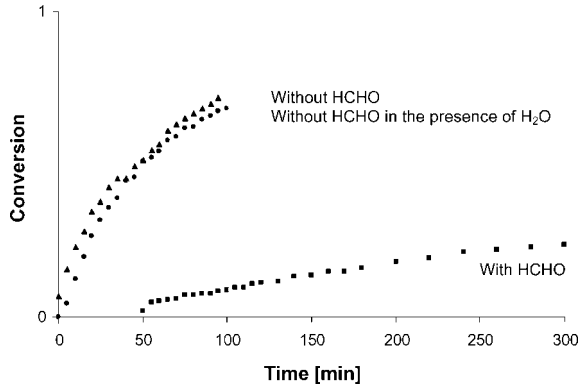
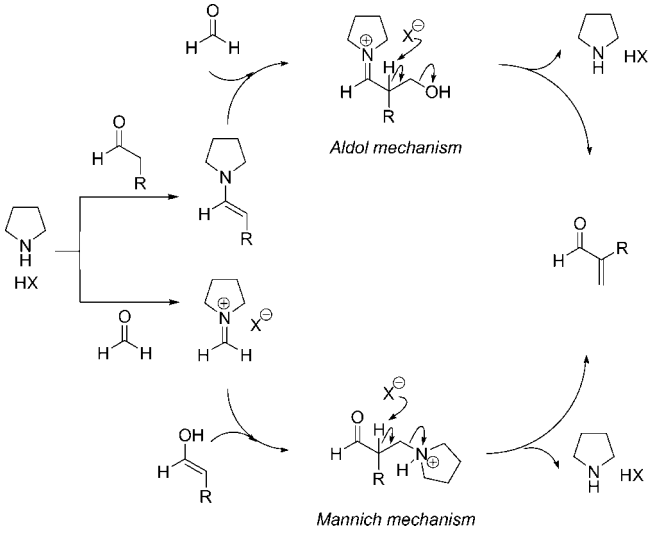


Figure 6. Self-condensation of hydrocinnamaldehyde (**1b**) to **11b** in $CDCl_3$ a) under standard conditions, b) in the presence of H_2O, c) in the presence of formaldehyde (ratio **1b**/formaldehyde = 2:1).

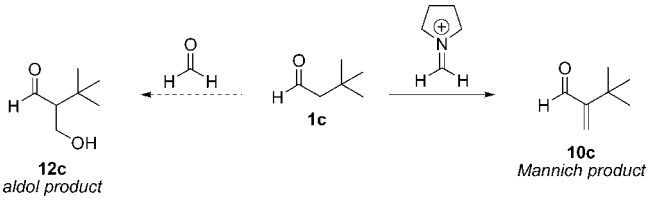
A plausible explanation for this finding is provided by kinetic partitioning of the catalyst between formaldehyde and other aldehydes. Presumably, the formation of the formaldehyde/catalyst complex (or covalent intermediate) is favored over the formation of related compounds with other aldehydes.

The textbook mechanism for the Mannich condensation of aldehydes suggests that the enol form of the donor aldehyde reacts with the iminium compound formed by the acceptor aldehyde (usually formaldehyde) (Scheme 1).[18]



Scheme 1. Possible mechanisms for the α-methylenation reaction.

In an alternative mechanistic scenario, the condensation reaction proceeds by an enamine-catalyzed aldol reaction that is followed by an acid- or base-catalyzed elimination of the β-hydroxy group.[19] In this regard, the α-methylenation of *tert*-butylacetaldehyde (**1c**) afforded an interesting result. Unlike the reactions with less hindered aldehydes, where the only observed product was the α-methylenation product, with **1c** we observed the formation of the corresponding aldol product **12c** in 15% conversion. The ratio of aldol **12c**/condensation product **10c** remained the same throughout the reaction (see Supporting Information). This result suggests that the aldol and the condensation pathways are *competing* reactions. The formation of the aldol product with a bulky *tert*-butyl substituent could be explained by steric hindrance in the Mannich addition step that disfavors the iminium electrophile and provides the smaller formaldehyde electrophile a chance (Scheme 2).



Scheme 2. Competing reaction pathways with **1c**.

While the conventional Mannich paradigm suggests an attack of the enol species to an imine or iminium ion, it is interesting to note that enantioselective organocatalytic Mannich reactions have been reported to proceed by an enamine-catalyzed addition.[20] As such, a third mechanistic possibility involves the activation of both, the donor and the acceptor aldehyde, with the amine catalyst – the donor as an enamine and the acceptor as an iminium ion. It is, however, easy to distinguish between the enol/iminium and the enamine/iminium catalytic paradigms, since the latter would entail the involvement of two catalyst molecules in the addition step. If this step is rate-determining, the reaction should be of second order with respect to the catalyst. Indeed, in the α-methylenation of hydrocinnamaldehyde (**1b**) in $CDCl_3$ (used as a model reaction), we observed a clear second-order dependence of the rate on the catalyst concentration (Figure 7a, b).

The α-methylenation reaction exhibited clear saturation kinetics with respect to the aldehyde donor component **1b** (Figure 7c; $K_M = 0.82$ M, $k_{cat}/K_M = 1.4 \times 10^{-4}$ $M^{-1} s^{-1}$). Interestingly, the reaction was inhibited by increases in the formaldehyde concentration (Figure 7d). The rate was observed to be inversely proportional to the formaldehyde concentration. This is consistent with the hypothesis that formaldehyde is competing with the donor aldehyde for the amine catalyst, effectively suppressing the rate.[21] This hypothesis is supported by the competition experiments, which suggest that formaldehyde is also able to suppress the competing self-condensation reaction.

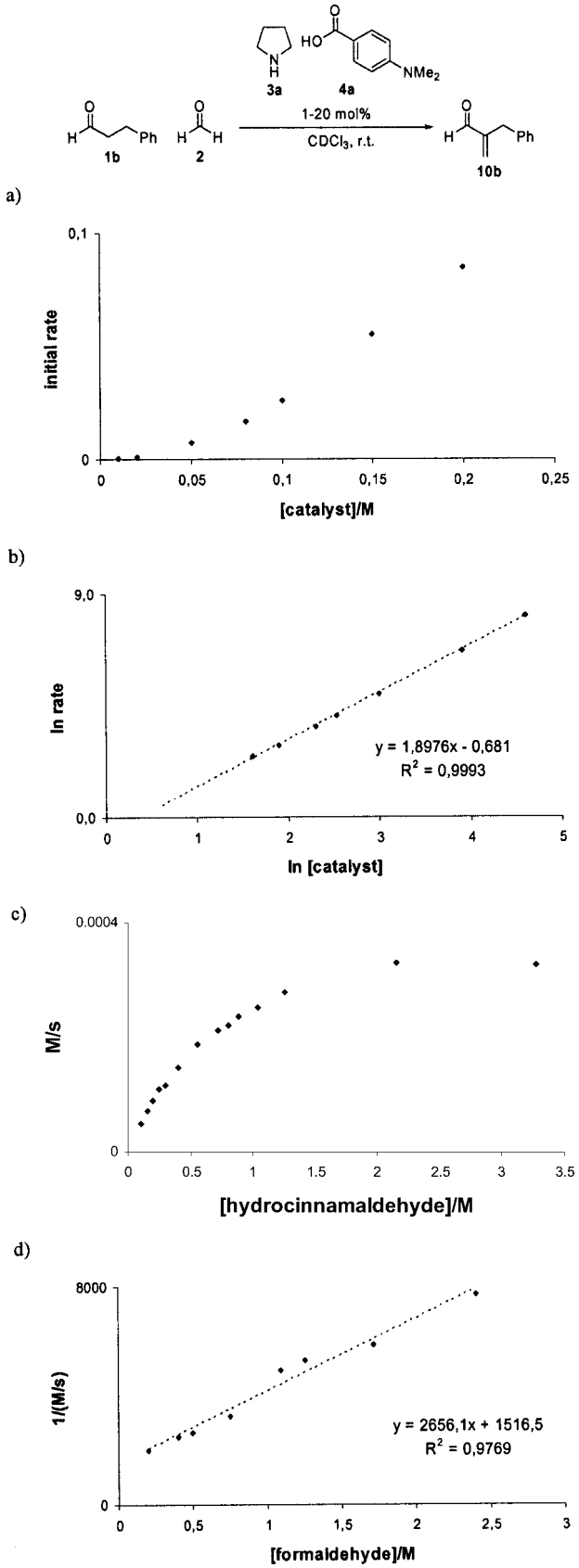
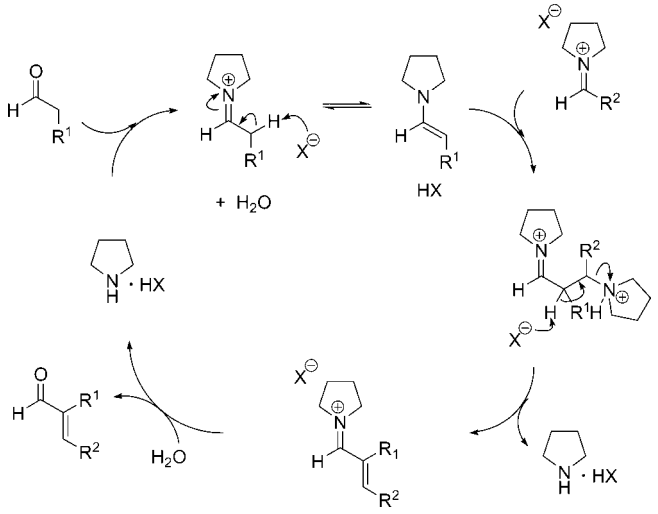


Figure 7. a), b) Second-order dependence of the reaction rate on catalyst concentration, c) saturation kinetics observed with aldehyde **1b**, and d) inverse rate relationship observed with formaldehyde. All rates were determined by ^1H NMR spectroscopy using the method of initial rates (see Supporting Information for details).

Taken together, these data indicate that the reaction most likely proceeds according to a Knoevenagel–Mannich-type mechanism where the iminium species of formaldehyde (or the acceptor aldehyde) reacts with the enamine species of the donor aldehyde (Scheme 3).[22] The acid co-catalyst is expected to assist in both the iminium ion formation as well as the formation of the enamine. The steep dependence of the reaction rate on the pK_a value of the acid co-catalyst in cross-condensations with formaldehyde indicates that the acid (or perhaps its conjugate base) is intimately involved in the rate-determining step: The measured β value of 0.5–0.6 for the α-methylenation reaction suggests general base catalysis for the rate-determining step.[23] If the addition step were rate-determining, the formation of the enamine would take place in concert with the addition step.



Scheme 3. Double activation of the reaction components by an enamine/iminium mechanism.

Other possible explanations for the pK_a dependence include the following: 1) the acid co-catalyst also influences the kinetic partitioning of the catalyst between formaldehyde and the donor aldehyde, resulting in very low concentrations of the aldehyde enamine with more acidic co-catalysts or 2) the final elimination step is rate-determining. Although we find the latter scenario unlikely, the present data does not allow us to fully deconvolute the different roles of the amine and the acid in this reaction. Further studies to understand the dual activation by the catalyst pair in enamine/iminium reactions are ongoing.

Conclusions

As a result of a systematic optimization study, a substantially improved method for the α-methylenation of aldehydes has been developed, allowing convenient access to a number of α-substituted acroleins.[24] The same catalyst system, pyrrolidine *p*-(dimethylamino)benzoate, was also active in the self-condensation of aldehydes.

With the help of kinetic experiments, we have shown that the reaction is of second order in the catalyst concentration and displays saturation kinetics regarding the donor aldehyde and an inverse rate relationship with formaldehyde. In conclusion, we propose a catalytic cycle that involves two molecules of the catalyst salt in the rate-determining step. The reaction most likely involves two amine molecules to activate both reaction partners, one as the enamine and the other as an iminium salt.

Future work will focus on the implications of this mechanistic proposal and the use of these processes in two-step organocatalytic protocols.

Experimental Section

General: All reactions were carried out under ambient atmosphere in capped vials. Solvents and reagents were purchased from commercial sources and used as received. Temperatures were controlled by aluminium block heater units. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a 400 MHz (^{1}H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to residual $CHCl_3$ signals for ^{1}H NMR spectroscopy (δ = 7.26 ppm). The coupling constants are reported in Hz. For the ^{13}C NMR spectra, $CDCl_3$ (δ = 77.0 ppm) was used as internal standard.

General Procedure for the Optimization of Experiments of Methylenations: To a solution of amine **3** (0.02 mmol, 10 mol-%) and acid **4**–**9** (0.02 mmol, 10 mol-%, *or the amounts indicated*) in dichloromethane (0.2 mL), were added formaldehyde (36.5% solution in H_2O, 16.5 μL, 0.2 mmol, 100 mol-%) and aldehyde (0.2 mmol, 100 mol-%) at room temp. The reaction mixture was rapidly heated to 45 °C and stirred at this temperature for the indicated period of time. The reactions were monitored by ^{1}H NMR spectroscopy by integration of the aldehyde CHO peaks. See the Supporting Information for full details.

General Procedure for the Optimization of Experiments of Condensation Reactions: To a solution of amine **3** (0.02 mmol, 10 mol-%) and acid **4** or **6** (0.02 mmol, 10 mol-%) in dichloromethane (0.2 mL), was added aldehyde **1b** or **1c** (0.4 mmol, 200 mol-%) at room temp. The reaction mixture was stirred at room temperature in the case of aldehyde **1c**. In the case of **1b**, the reaction mixture was rapidly heated to 45 °C and stirred for the indicated period of time. The reactions were monitored by ^{1}H NMR spectroscopy by integration of the aldehyde CHO peaks. See the Supporting Information for full details.

General Procedure for the Kinetic Experiments: To a solution of amine **3a** (0.02 mmol, 10 mol-%, *or the amount indicated*) and acid **4a** (0.02 mmol, 10 mol-%, *or the amount indicated*) in $CDCl_3$ (0.2 mL), were added formaldehyde (36.5% solution in H_2O, 16.5 μL, 0.2 mmol, 100 mol-%) and aldehyde (0.2 mmol, 100 mol-%) at room temp. The reactions were monitored by ^{1}H NMR spectroscopy in 300 s, 120 s, or 60 s intervals. See the Supporting Information for full details.

General Procedure for the Preparative Methylenations: To a solution of amine **3a** (8.5 μL, 0.1 mmol, 10 mol-%) and acid **4a** (33.0 mg, 0.2 mmol, 20 mol-%) in dichloromethane (1.0 mL) were added formaldehyde (36.5% solution in H_2O, 80 μL, 1.0 mmol, 100 mol-%) and aldehyde **1** (1.0 mmol, 100 mol-%) at room temp. The reaction mixture was rapidly heated to 45 °C and stirred for the indicated period of time. The reaction mixture was then added to 7%

$NaHCO_3$ (5 mL) and the resulting mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed with brine, dried (Na_2SO_4), and concentrated in vacuo. For the isolation of **10f**, the reaction mixture was added to H_2O (5 mL) and the resulting mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed with 7% $NaHCO_3$ (5 mL), brine, dried (Na_2SO_4), and concentrated in vacuo.

(*S*)-3,7-Dimethyl-2-methyleneoct-6-enal (10a): Yield 170.1 mg (quant.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.53 (s, 1 H); 6.23 (s, 1 H); 5.98 (s, 1 H); 5.07 (tt, J = 1.2, 7.2 Hz, 1 H); 2.70 (sext, J = 6.8 Hz, 1 H); 1.92 (m, 2 H); 1.67 (s, 3 H); 1.56 (s, 3 H); 1.51 (m, 1 H); 1.37 (m, 1 H); 1.06 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 194.7; 155.5; 133.2, 131.5, 124.1; 35.6; 30.9; 25.7; 25.6; 19.5; 17.6 ppm. The spectroscopic data match those reported in the literature.[25]

2-Benzylacrylaldehyde (10b): Yield 165.8 mg (99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.61 (s, 1 H); 7.32–7.17 (m, 5 H); 6.11 (s, 1 H); 6.07 (s, 1 H); 3.57 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.9, 149.7, 138.1, 135.2, 129.1, 128.5, 126.4, 34.1 ppm. The spectroscopic data match those reported in the literature.[26]

3,3-Dimethyl-2-methylenebutanal (10c): Yield 95.6 mg (85%). IR: $\tilde{\nu}_{max}$ = 3380, 2961, 2872, 1702, 1460, 1364, 1306, 1195, 953, 848, 670 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.54 (s, 1 H); 6.30 (s, 1 H); 5.90 (s, 1 H); 1.19 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 195.0, 158.1, 133.6, 33.8, 28.5 ppm. HRMS (ESI+): calcd. for [$C_7H_{12}O$ + H] 113.0966; found 133.0931.

2-Methylene-3-phenylbutanal (10d): Yield 161.2 mg (quant.). IR: $\tilde{\nu}_{max}$ = 2986, 2305, 1693, 1421, 1265, 950, 896, 741, 705, 409 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.54 (s, 1 H); 7.33–7.16 (m, 5 H); 6.24 (s, 1 H); 6.08 (s, 1 H); 4.06 (q, J = 7.2 Hz, 1 H); 1.43 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.8, 154.4, 143.6, 133.6, 128.4, 127.5, 126.4, 37.2, 20.0 ppm. HRMS (ESI+): calcd. for [$C_{11}H_{12}O$ + H] 183.0786; found 183.0765.

2-(Benzyloxy)acrylaldehyde (10e): Yield 171.5 mg (quant.). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.30 (s, 1 H); 7.38–7.30 (m, 5 H); 5.25 (d, J = 3.0 Hz, 1 H); 5.14 (d, J = 3.0 Hz, 1 H); 4.93 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.0, 158.1, 135.5, 128.6, 128.1, 127.3, 103.8, 70.1 ppm. The spectroscopic data match those reported in the literature.[6b]

2-[(Benzyloxy)methyl]acrylaldehyde (10f): Yield 150.1 mg (85%). IR: $\tilde{\nu}_{max}$ = 3436, 3088, 3064, 3031, 2863, 1954, 1693, 1496, 1454, 1368, 1101, 960, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.60 (s, 1 H); 7.38–7.28 (m, 5 H); 6.58 (s, 1 H); 6.16 (d, J = 1.6 Hz, 1 H); 4.59 (s, 2 H), 4.26 (t, J = 1.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.3, 146.7, 137.8, 134.0, 128.4, 127.7, 127.6, 73.0, 65.8 ppm. HRMS (ESI+): calcd. for [$C_{11}H_{12}O_2$ + Na] 199.0735; found 199.0732.

2-Methylene-3-(5-methylfuran-2-yl)butanal (10g): Yield 164.9 mg (quant.). IR: $\tilde{\nu}_{max}$ = 2976, 2923, 1693, 1627, 1565, 1455, 1359, 1219, 1022, 954, 784 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.58 (s, 1 H), 6.18 (d, J = 0.8 Hz, 1 H), 6.05 (s, 1 H), 5.59 (d, J = 3.0 Hz, 1 H), 5.85 (dd, J = 1.0, 3.0 Hz, 1 H), 4.04 (q, J = 7.2 Hz, 1 H), 2.23 (br. s, 3 H), 1.37 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 193.4, 154.7, 152.5, 150.9, 134.2, 106.1, 105.8, 31.1, 18.2, 13.4 ppm. HRMS (ES+): calcd. for [$C_{10}H_{12}O_2$ + H] 164.0837; found 164.0735.

(*Z*)-2-Methylenedec-4-enal (10h): Yield 170.1 mg (quant.). IR: $\tilde{\nu}_{max}$ = 3583, 3367, 3011, 2927, 2857, 1691, 1638, 1466, 1437, 1377, 1234, 959, 861, 717 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.59 (s, 1 H), 6.25 (m, 1 H), 6.01 (m, 1 H), 5.60–5.52 (m, 1 H), 5.45–5.35 (m, 1 H), 2.98 (dd, J = 1.1, 7.4 Hz, 2 H), 2.02 (dq, J = 1.1, 6.8 Hz, 2 H), 1.39–1.24 (m, 6 H), 0.88 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 194.4, 149.0, 134.0, 133.0, 124.4, 31.5, 29.2, 27.1, 25.5, 22.5, 14.0 ppm. HRMS (ESI+): calcd. for [$C_{11}H_{18}O$ + Na] 189.1255; found 189.1265.

Methyl (*E*)-6-Formylhepta-2,6-dienoate (10i): Yield 171.6 mg (quant). IR: $\tilde{\nu}_{max}$ = 3154, 2993, 2925, 2848, 1793, 1719, 1690, 1438, 1282, 1207, 910, 734, 650 cm^{-1}. ^{1}H NMR (CDCl3, 400 MHz): δ = 9.53 (s, 1 H), 6.91 (dt, J = 6.6, 15.7 Hz, 1 H), 6.27 (s, 1 H), 6.05 (s, 1 H), 5.82 (dt, J = 1.5, 15.7 Hz, 1 H), 3.71 (s, 3 H), 2.43–2.35 (m, 4 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 194.2, 166.8, 148.5, 147.6, 134.8, 121.7, 51.4, 30.0, 26.5 ppm. HRMS (ES+): calcd. for [$C_9H_{12}O_3$ + Na] 191.0684; found 191.0675.

***tert*-Butyl 1-Formylvinylcarbamate (10j):** Yield 83.6 mg (98%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.12 (s, 1 H); 6.97 (s, 1 H); 6.70 (s, 1 H); 5.35 (s, 1 H); 1.46 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.6, 152.3, 140.2, 114.8, 81.0, 28.1 ppm. The spectroscopic data match those reported in the literature.[27]

General Procedure for the Preparative Self-Sondensations of Aldehydes: To a solution of amine **3a** (8.5 μL, 0.1 mmol, 10 mol-%) and acid **4a** (33.0 mg, 0.2 mmol, 20 mol-%) in dichloromethane (1.0 mL), was added aldehyde **1** (2.0 mmol, 200 mol-%) at room temp. The reaction mixture was rapidly heated to 45 °C and stirred for the indicated period of time. The reaction mixture was then added to 7% $NaHCO_3$ (5 mL) and the resulting mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were then washed with brine, dried (Na_2SO_4), and concentrated in vacuo.

(*E*)-2-Methylpent-2-enal (11k): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.30 (s, 1 H), 6.47 (tq, J = 1.3, 7.4 Hz, 1 H), 2.36 (ddq, J = 0.9, 7.4, 7.4 Hz, 2 H), 1.72 (dt, J = 0.9, 1.3 Hz, 3 H), 1.11 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 195.4, 156.2, 138.8, 22.3, 12.8, 9.0 ppm. These spectroscopic data match those reported in the literature.[28]

(*E*)-2-Benzyl-5-phenylpent-2-enal (11b): Yield 122.2 mg (98%). IR: $\tilde{\nu}_{max}$ = 3027, 2924, 1683, 1639, 1601, 1495, 1453, 1075, 912, 735, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.49 (s, 1 H), 7.36–7.13 (m, 10 H), 6.66 (t, J = 7.1 Hz, 1 H), 3.63 (s, 2 H), 2.84–2.74 (m 4 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 194.5, 154.7, 142.7, 140.4, 140.0, 128.5, 128.4, 128.3, 128.2, 126.3, 126.0, 34.4, 31.0, 29.6 ppm. HRMS (ES+): calcd. for [$C_{18}H_{18}O$ + Na] 251.1436; found 251.1446.

(*Z*)-2,4-Bis(benzyloxy)but-2-enal (11e): Yield 116.7 mg (40%). IR: $\tilde{\nu}_{max}$ = 3033, 2857, 1694, 1644, 1496, 1454, 1322, 1179, 1100, 1026, 911, 732, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.31 (s, 1 H), 7.45–7.22 (m, 10 H), 6.13 (t, J = 6.0 Hz, 1 H), 5.13 (s, 2 H), 4.48 (s, 2 H), 4.29 (d, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 188.7, 153.3, 137.5, 136.7, 135.9, 128.4, 128.3 (2 C), 128.2, 127.8, 127.7, 72.9, 72.8, 64.6 ppm. HRMS (ES+): calcd. for [$C_{18}H_{18}O_3$ + Na] 305.1154; found 305.1156.

(2*E*,6*Z*)-2-[(*Z*)-Oct-2-enyl]dodeca-2,6-dienal (11h): Yield 132.3 mg (91%). IR: $\tilde{\nu}_{max}$ = 3009, 2956, 2926, 2856, 1688, 1640, 1456, 1377, 1156, 913, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.27 (s, 1 H), 6.46 (t, J = 7.3 Hz, 1 H), 5.48–5.28 (m, 3 H), 5.21–5.14 (m, 1 H), 3.00 (d, J = 2 H, 7.1 Hz), 2.45 (q, J = 7.4 Hz, 2 H), 2.23 (q, J = 7.2 Hz, 2 H), 2.11 (q, J = 7.1 Hz, 2 H), 2.02 (q, J = 6.8 Hz, 2 H), 1.40–1.18 (m, 12 H), 0.93–0.82 (m, 3 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 194.5, 154.5, 142.8, 131.7, 131.0, 127.5, 125.7, 31.6, 31.5, 29.3, 29.2, 29.1, 27.2 (2 C), 26.1, 22.6, 22.5, 22.3, 14.0 (2 C) ppm. HRMS (ES+): calcd. for [$C_{20}H_{34}O$ + Na] 291.2688; found 291.2694.

Dimethyl (2E,6*E*,11*E*)-6-Formyltrideca-2,6,11-trienedioate (11i): Yield 282.6 mg (96%, 0.5 mmol scale). IR: $\tilde{\nu}_{max}$ = 2951, 1722, 1685, 1658, 1437, 1274, 1202, 1041, 981, 913, 852, 732, 647 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.38 (s, 1 H), 6.94 (td, J = 7.0, 15.6 Hz, 1 H), 6.88 (dt, J = 7.0, 15.6 Hz, 1 H), 6.49 (t, J = 7.5 Hz, 1 H), 6.85 (dt, J = 1.6, 15.6 Hz, 1 H), 5.80 (dt, J = 1.5, 15.6 Hz, 1 H), 3.74 (s, 3 H), 3.74 (s, 3 H), 2.40 (t, J = 7.5 Hz, 2 H), 2.37 (q, J = 7.5 Hz, 2 H), 2.27 (m, 4 H), 1.68 (qn, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 194.5, 166.7 (2 C), 154.5, 147.8, 147.7, 142.3, 121.7, 121.6, 51.4, 51.3, 31.6, 30.8, 28.3, 26.8, 22.8 ppm. HRMS (ES+): calcd. for [$C_{16}H_{22}O_5$ + Na] 317.1365; found 317.1368.

(*E*)-2-Hexyldec-2-enal (11l): Yield 226.3 mg (95%). IR: $\tilde{\nu}_{max}$ = 2927, 2857, 2709, 1689, 1640, 1465, 1377, 1096, 913, 725 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.36 (s, 1 H), 6.43 (t, J = 7.4 Hz, 1 H), 2.34 (q, J = 7.4 Hz, 2 H), 2.22 (dd, J = 6.1, 7.8 Hz, 2 H), 1.49 (m, 2 H), 1.34–1.21 (m, 16 H), 0.86 (t, J = 6.7 Hz, 3 H), 0.84 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CHCl_3$, 100 MHz): δ = 195.2, 155.2, 143.8, 31.7, 31.6, 29.3 (2 C), 29.0, 28.9, 28.7, 28.6, 24.0, 22.6, 22.5, 14.0 (2 C) ppm. HRMS (ES+): calcd. for [$C_{16}H_{30}O$ + H] 239.2375; found 239.2378.

Supporting Information (see footnote on the first page of this article): Full details on optimization of the reaction conditions, details on kinetic experiments, and NMR spectra for compounds **10a**–**10j**, **11b**, **11e**, **11h**–**i**, **11l**.

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[24] In preliminary experiments, these catalyst systems are also active in the α-methylenation reactions with ketones. However, these products are much more sensitive to dimerization and oligomerization reactions than the corresponding aldehydes.
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