Thermal Effects in the Organocatalytic Asymmetric Mannich Reaction

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The proline-catalyzed direct asymmetric Mannich reaction between cyclohexanone, formaldehyde, and various anilines is thermally accelerated. With only 0.5 mol % of catalyst, Mannich products with up to 98% ee have been obtained after a short period of time in reactions performed under microwave irradiation. In situ reduction of the resulting ketones affords N-aryl amino alcohols in up to 86% yield.

The Mannich reaction is one of the most useful carbon−carbon bond-forming reactions for the synthesis of nitrogen-containing molecules. Several catalytic versions have been developed,[1] and some of them yield Mannich-type products with high enantioselectivities. Among all, the direct, one-pot, three-component Mannich reactions are the most elegant and synthetically attractive.[2,3] Recently, List and co-workers[4] and Barbas and co-workers[5] introduced a proline-catalyzed version (Scheme 1), and enantioselectivities up to 99% ee have been achieved.[6]

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(1) Reviews: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, Chapter 26.2. (c) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348.

(2) Review: Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(3) For a recent overview on multicomponent reactions, see: Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.

(4) (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.

(5) (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Córdova, A.; Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (d) Notz, W.; Watanabe, S.-I.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131. (e) See also: Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040.

(6) (a) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 5.2. (b) For a recent application in synthesis, see: Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.

SCHEME 1. One-Pot, Three-Component, Mannich Reaction Catalyzed by (*S*)-Proline
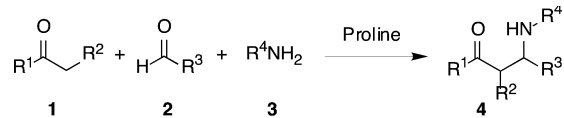

TABLE 1. Direct Asymmetric Mannich Reaction Catalyzed by (*S*)-Proline[a]

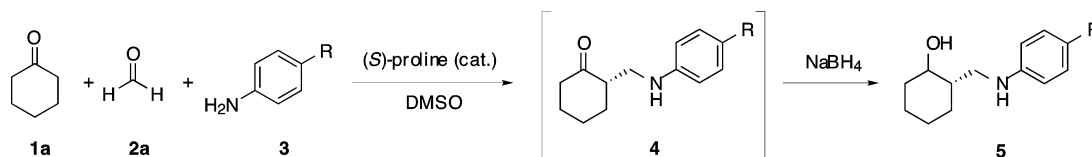| entry	3	Ar	mol % of catalyst	time (h)	yield[b] (%)	ee[c,d] (%)
1	a	Ph	10	26	58	97
2	b	4-CH₃OC₆H₄	10	21	55	95
3	c	4-(*i*-Pr)C₆H₄	10	24	40	98
4[e]	a	Ph	20	25	66	98
5[f]	a	Ph	20	30	81	98
6[g]	a	Ph	10	27	85	97

[a] Reaction conditions: ketone **1a** (2.6 equiv), aldehyde **2a** (1.1 equiv), amine **3** (1.0 equiv), and (*S*)-proline in DMSO (0.25 M with respect to **3**) at 21 °C. [b] Yields of amino alcohols **5**. [c] Determined by HPLC analysis of **4** using a chiral column (Chiralcel AD); see Supporting Information for details. [d] The absolute configuration of **4** was found to be *S*, as determined by a comparison with published HPLC retention times; comp. ref 7. [e] Performed at 25−30 °C. [f] Performed at 25−30 °C in DMF. [g] Performed at 45−50 °C.

Whereas the enantioselectivities are impressive, two other important factors of this catalysis are more critical: first, the catalyst loading is generally high (≥10 mol %), and second, the overall reaction time is long (5−48 h). Respective improvements would significantly increase the synthetic value of this important organocatalytic direct C−C bond-formation reaction and might eventually even have an impact on other transformations of this type.

Recently, Córdova reported excellent results for the proline-catalyzed enantioselective α-aminomethylation of ketones.[7] Typically, the reactions were performed using cyclohexanone (**1a**), formaldehyde (**2a**; 36% aqueous solution), and an aromatic amine **3** in a solvent such as DMSO or DMF. A catalyst loading of 10 mol % was reported to lead to excellent yields of α-arylaminomethylated ketones **4** with >99% ee after 16−24 h at room temperature. With the goal to improve the above-mentioned critical factors (catalyst loading and reaction time) and to develop an optimized protocol, we began to investigate the influence of various reaction parameters on both yield and enantioselectivity in the formation of Mannich product **4a**.[8] The results of these studies are summarized in Table 1.

In our experiments (with 10 mol % of (*S*)-proline in DMSO at 21 °C), the enantioselectivities in the conversions of anilines **3a−c** ranged from 95 to 98% ee, and to our disappointment, the yields reached a maximum of only 58% (after reduction to

(7) (a) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6528. (b) Ibrahem, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron* **2006**, *62*, 357. (c) See also: Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.—Eur. J.* **2005**, *11*, 7024.

TABLE 2. Microwave-Assisted Direct Asymmetric Mannich Reaction Catalyzed by (S)-Proline[a]

entry	3	R	mol % of catalyst	power[b] (W)	temp[c] (°C)	time (h)	yield[d] (%)	ee[e] (%)
1[f]	a	H	20	100	63	1	44	96
2[f]	a	H	20	15	42	2	79	98
3[f]	a	H	20	10	41	2.5	75	98
4	a	H	20	15	47	2	80	97
5	a	H	10	15	46	2.5	96	98
6	a	H	5	15	45	2.5	93	98
7	a	H	1	10	46	3.5	70	98
8	a	H	1	15	48	4	89	97
9	a	H	0.5	15	46	3	83	98
10	b	OCH$_3$	10	15	47	2.5	71	95
11	b	OCH$_3$	10	10	45	2.5	81	95
12	b	OCH$_3$	1	10	47	3	84	94
13	c	i-Pr	10	10	45	3	71	97
14	c	i-Pr	5	15	51	3.5	88	97
15	c	i-Pr	1	15	47	4	83	97
16	c	i-Pr	0.5	15	49	4	86	97

[a] Reaction conditions: same as those described in footnote a of Table 1, but under MW irradiation. [b] Application of constant MW power. [c] For cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment. See also refs 16 and 17. [d] Yields of amino alcohols **5**. [e] Determined by HPLC analysis of **4** using a chiral column (Chiralcel AD); see Supporting Information for details. [f] DMF was used as solvent.

amino alcohol **5**; Table 1, entries 1−3). Whereas longer reaction times did not affect the yield, better results were achieved by either raising the temperature or increasing the catalyst amount. For example, the reaction with amine **3a** and 20 mol % of proline in DMF at 25−30 °C led to a product with 98% ee in 81% yield after 30 h (Table 1, entry 5). To our surprise, the reaction mixture could even be heated to 40−50 °C (in a conventional oil bath), and under those conditions, with 10 mol % of the catalyst, the product was obtained in 85% yield, having an ee of 98% (Table 1, entry 6).

Still, the reaction required a high catalyst loading and an extended reaction time. However, the observed high-temperature tolerance indicated unexpected opportunities, leading us to consider exploring the effect of microwave (MW) irradiation on the proline-catalyzed direct Mannich reaction.[9,10] To the best of our knowledge, there is only a single report on a MW-induced accelerating effect in such asymmetric organocatalysis. In that study, Westermann showed that the Mannich reaction between 2,2-dimethyl-1,3-dioxan-5-one and preformed *p*-methoxy-phenylethyl-α-iminoethyl glyoxylate catalyzed by (S)-proline in TFE is accelerated under the action of MWs.[11−13] The best results were obtained using 30 mol % of the catalyst and 300 W of maximal irradiated power. Under those conditions, the product was obtained in 72% yield after only 10 min. Interestingly, in comparison to a reaction without a MW, performed at room temperature for 20 h, the stereoselectivity remained almost the same (94% de and 99% ee versus 80% de and 95% ee with a MW). Furthermore, the authors observed that a decrease in the irradiating power to 100 W led to a lower yield (64% yield) without affecting the stereoselectivity.[14] Based on this result, and taking into account our own observations on the temperature tolerance of the described Mannich reaction, we hypothesized that MW irradiation could not only have a positive effect on the reaction rate but that it might also prove useful in lowering the required catalyst loading. Consequently, a study focusing on this important issue was initiated.

First, we decided to search for the optimal conditions for a MW-assisted Mannich reaction. To ensure reproducibility and to standardize the reaction conditions, all experiments were performed in a Discover LabMate reactor from CEM Corporation. Furthermore, a constant MW irradiation power in conjunction with simultaneous air-cooling (PowerMax option) was applied.[15−17] For the screening studies, aniline (**3a**) was used as the amine component in the coupling with cyclohexane (**1a**) and formaldehyde (**2a**). As shown in Table 2, the initial

(8) Mannich adducts **4** were found to be rather sensitive to racemization during purification by column chromatography (even when aluminium oxide was used as the stationary phase). For structural characterization (and after ee determination), the crude products **4** were, therefore, immediately reduced with an excess of NaBH$_4$, and the resulting amino alcohols **5** (obtained as syn/anti mixtures, with the latter in excess) were then analyzed. For details, see Supporting Information.

(9) For recent reviews on the use of MWs in organic synthesis, see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (d) *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidström, P., Eds.; Blackwell: Oxford, U.K., 2005. (e) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002. (f) Lee, J.; Hlasta, D. J. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 597.

(10) For a study describing the effect of MW in (nonasymmetric) Mannich-type reactions catalyzed by CuCl in conjunction with an ionic liquid, see: Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Mol. Diversity* **2003**, *7*, 135.

(11) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077.

(12) For an interesting study on MW-promoted reactions with supported enzymes in dry media, see: Carrillo-Muñoz, J.-R.; Bouvet, D.; Guibé-Jampel, E.; Loupy, A.; Petit, A. *J. Org. Chem.* **1996**, *61*, 7746.

(13) For a review on MW-accelerated homogeneous (metal) catalysis, see: Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717.

(14) Unfortunately, information on the reaction temperature of the experiments performed under MW irradiation is lacking in this article. Furthermore, a comparison with conventional methods of heating has not been reported.

(15) For a recent excellent study of MW-assisted reactions under simultaneous cooling, see: Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

TABLE 3. Direct Asymmetric Mannich Reaction between Ketone 1a, Formaldehyde (2a), and Aniline (3a) Catalyzed by (S)-Proline[a]

entry	mol % of catalyst	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	1	45−50	23	82	97
2	10	64−66	3	70	97
3	10	64−66	4.5	79	96
4	5	64−66	3	67	98
5	5	64−66	4.5	82	98
6	1	64−66	4	55	98
7	1	64−66	8	68	98
8	10	69−71	4.5	64	96
9	5	69−71	4.5	69	98
10	1	69−71	4.5	71	97
11	10	75−77	6	72	95
12	5	75−77	6	75	98
13	1	75−77	6	84	98
14	10	84−86	4.5	72	85
15	10	90−93	4	68	78

[a] Reaction conditions: same as those described in footnote a of Table 1, but in a preheated oil bath with the given reaction temperature. [b] See footnote b of Table 1. [c] See footnote c of Table 1.

conditions with DMF as solvent and using 100 W of MW power led to the corresponding product in only poor yield (44% yield, Table 2, entry 1). However, positive effects on both yield and enantioselectivity were observed, when the MW power was reduced to 15 or 10 W (Table 2, entries 2 and 3). Finally, the use of DMSO as solvent led to consistently high yields and excellent enantioselectivities. For example, with 10 mol % of (S)-proline and a MW power of 15 W, the product was isolated (after only 2.5 h) in 96% yield, having an ee of 98% (Table 2, entry 5). The most important observation concerned the catalyst loading. Here, it was found that even with *0.5 mol % of (S)-proline*, 83% of the product with 98% ee could be obtained (Table 2, entry 9)! Under the same MW conditions, substituted anilines **3b** and **3c** reacted similarly and gave the corresponding products in up to 84 and 88% yields, respectively (Table 2, entries 10−16). To our delight, no decrease in enantioselectivity was observed even with only 1 or 0.5 mol % of catalyst (Table 2, entries 12 and 16).

To further evaluate the beneficial effect of MW irradiation and to the determine its real impact on the catalysis, we performed comparative studies using conventional oil bath heating.[18] In these experiments, aniline (**3a**) was used as the amine component in the coupling with cyclohexane (**1a**) and formaldehyde (**2a**). As a result of the potential inaccuracy of the measurement by IR sensor,[16] a wide temperature range was scanned (Table 3). As expected, higher temperatures (also in

(16) In our setup, all temperatures were measured externally by an IR sensor. The temperature indicated in Table 2 corresponds to the maximum temperature reached during the experiment. Attempts to use a Discover CoolMate reactor from CEM Corporation equipped with an internal fiber-optic sensor device failed due to the temperature limitation ($T_{max} = 40$ °C) of the instrument. Thus, at the present stage, a reliable error margin of the given temperatures (Table 2) cannot be given. This should, however, not affect the reproducibility of the experiments. For a comparative study of temperature determinations under MW irradiations, see: Ondruschka, M. N. B.; Weiβ, D.; Beckert, R.; Bonrath, W.; Gum, A. *Chem. Eng. Technol.* **2005**, *28*, 871.

(17) For comparison, the reaction between ketone **1a**, formaldehyde (**2a**), and aniline (**3a**), catalyzed by 10 mol % of (S)-proline, was performed using MW irradiation without simultaneous cooling (15 W, 2.5 h; see also Table 2, entry 5). Under these conditions, the maximum temperature reached was 89 °C, and the product was obtained in just 53% yield, having an ee of 91%. (The temperature profile is included in Supporting Information).

(18) Reactions in oil bath were performed in the 10 mL glass vessels used in the MW-assisted experiments.

combination with increased catalyst loadings) resulted in faster reactions. Gratifyingly, also under those conditions, a reduction of the catalyst loading was possible. For example, at 45−50 °C, the use of 1 mol % of (S)-proline afforded 82% of the product after 23 h (Table 3, entry 1), while at 75−77 °C, the desired product was obtained in high yield (84%) after only 6 h (Table 3, entry 13). In both reactions, the enantioselectivities were excellent (97−98% ee), confirming the previously observed high-temperature tolerance. Above a critical point, however, the enantioselectivities deceased significantly, and in reactions performed at 84−86 °C and 90−93 °C with 10 mol % of catalyst, the products had only moderate enantiomeric excesses (Table 3, entries 14 and 15).

The only main difference to the MW experiment was the required reaction time, which under thermal conditions had to be extended to achieve comparable conversion and yield. However, the observed rate enhancement could be a consequence of the fast heating of the reaction mixtures when irradiated in a MW field. For example, in those experiments, which were ran at 64−66 °C with 5 and 10 mol % of catalyst, the reaction was found to be almost complete after 4.5 h (see Table 3, entries 2−5). Thus, it has been proved that this direct asymmetric Mannich reaction catalyzed by (S)-proline is thermally accelerated. It allows the reduction of the reaction times and, most importantly, the catalyst amount. Concretely, the use of constant MW irradiation at low power (10−15 W) in conjunction with simultaneous cooling appears to access a reaction window, which is well-balanced for achieving both a high reaction rate and an excellent enantioselectivity.[19] In this particular *organocatalytic* case, previously unseen low catalyst loadings could be employed. Although no specific MW effect has been found,[20] the results are synthetically promising and guided us to examine other organocatalytic asymmetric transformations on their sensitivity toward temperature.

Experimental Section

General Experimental Procedures. See the Supporting Information.

General Procedure for the Proline-Catalyzed Asymmetric Mannich Reaction under Microwave Irradiation. Preparation of (1R,2S)-2-Phenylaminomethyl-1-cyclohexanol (*anti*-5a)[21] as a Detailed Representative Example. In a 10 mL vessel was placed cyclohexanone (**1a**, 3.0 mL, 2.9 mmol, 2.6 equiv), formaldehyde (**2a**, 90 μL, 36% aq solution, 1.2 mmol, 1.1 equiv), aniline (**3a**, 0.10 mL, 1.1 mmol, 1.0 equiv), (S)-proline (13 mg, 0.11 mmol, 10 mol %), DMSO (4 mL), and a magnetic stir bar. The vessel was sealed with a septum, placed into the MW cavity, and locked with the pressure device. Constant MW irradiation of 15 W as well as simultaneous air-cooling (0.7 bar, 10 psi) were used during the entire reaction time (2.5 h). After cooling to room temperature, an aliquot of the crude reaction mixture (0.1 mL) was quenched with phosphate buffer pH 7.2, and was then extracted with ethyl acetate (3 × 0.5 mL). The combined organic phases were dried over MgSO$_4$, and volatile organic materials were removed under reduced pressure. The ee was 97%, as determined by HPLC analysis of the crude Mannich product **4a**[7] (Daicel Chiralpak AD; heptane/2-propanol, 98:2, 0.5 mL/min; λ = 254 nm; major isomer, t_S =

(19) Analogous observations have also been made in other organocatalytic Mannich-type reactions. Kappe, C. O.; Barbieri, V. Personal communication.

(20) For an excellent discussion on MW effects in organic synthesis, see: Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

(21) (a) Masamune, T.; Takasugi, M.; Suginome, H.; Yokoyama, M. *J. Org. Chem.* **1964**, *29*, 681. (b) Modak, A. S.; Sahasrabudhe, S. D. *Indian J. Chem., Sect. B* **1984**, *23*, 980.

26.88 min; minor isomer, t_R = 32.33 min). The remaining crude reaction mixture was immediately reduced to the corresponding alcohol by an excess of NaBH$_4$ (100 mg, 2.6 mmol, 9.5 equiv). After stirring for 16 h, MeOH (5 mL) was added to the mixture, followed by a phosphate buffer solution (pH 7.2, 10 mL) and ethyl acetate (20 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over MgSO$_4$. After removal of the solvent, the product was purified by column chromatography (silica gel, pentane/ethyl acetate, 9:1) to afford amino alcohol **5a** as a white solid (212 mg, 96% after two steps; syn/anti = 1:5, determined by ^{1}H NMR). After recrystallization from pentane/Et$_2$O (8:2), the product (*anti*-**5a**) was obtained as white needles in almost diastereomerically pure form (syn/anti = 1:40), mp 80−82 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.99−1.09 (m, 1H), 1.18−1.34 (m, 3H), 1.49−1.63 (m, 1H), 1.67−1.82 (m, 3H), 1.95−2.00 (m, 1H), 3.11 (dd, J = 12.3, 4.3 Hz, 1H), 3.26 (dd, J = 12.3, 8.2 Hz, 1H), 3.43−3.49 (m, 1H), 6.68−6.69 (m, 2H), 6.76 (tt, J = 7.3, 1.1 Hz, 1H), 7.17−7.22 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 24.5 (CH$_2$), 25.3 (CH$_2$), 29.4 (CH$_2$), 35.4 (CH$_2$), 44.4 (CH), 50.4 (CH$_2$), 76.1 (CH), 113.9 (CH, 2C), 118.3 (CH), 129.2 (CH, 2C), 148.2 (C).

Preparation of (1*S*,2*S*)-2-(4-Methoxyphenylaminomethyl)-1-cyclohexanol (*syn*-5b) and (1*R*,2*S*)-2-(4-Methoxyphenylaminomethyl)-1-cyclohexanol (*anti*-5b).[7] Following the general procedure using *p*-anisidine (**3b**, 1.1 mmol scale) and a constant MW irradiation of 10 W during 3 h afforded amino alcohol **5b** as white solid (213 mg, 84% after two steps; syn/anti = 1:2, determined by ^{1}H NMR) after purification of the crude product by column chromatography (silica gel, pentane/ethyl acetate, 85:15). *anti*-**5b** (major): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.93−1.07 (m, 1H), 1.19−1.36 (m, 3H), 1.41−1.82 (m, 4H), 1.93−1.99 (m, 1H), 3.02−3.25 (m, 2H), 3.41−3.49 (m, 1H), 3.75 (s, 3H), 6.66−6.70 (m, 2H), 6.76−6.81 (m, 2H). *syn*-**5b** (minor): ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.19−1.36 (m, 1H), 1.41−1.82 (m, 8H), 3.02−3.25 (m, 2H), 3.74 (s, 3H), 4.02−4.05 (m, 1H), 6.60−6.63 (m, 2H), 6.76−6.81 (m, 2H). *anti*-**5b** (major): ^{13}C NMR (75 MHz, CDCl$_3$) δ 24.3 (CH$_2$), 25.3 (CH$_2$), 29.3 (CH$_2$), 35.1 (CH$_2$), 44.2 (CH), 52.0 (CH$_2$), 55.7 (CH$_3$), 76.4 (CH), 114.7 (CH, 2C), 115.7 (CH, 2C), 142.1 (C), 152.9 (C). *syn*-**5b** (minor): ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.6 (CH$_2$), 24.9 (CH$_2$), 25.1 (CH), 32.9 (CH$_2$), 40.5 (CH), 47.9 (CH$_2$), 55.7 (CH$_3$), 68.7 (CH), 114.7 (CH, 2C), 114.8 (CH, 2C), 142.5 (C), 152.2 (C). The ee was 94%, as determined by HPLC analysis of the crude Mannich product **4b**[7] (Daicel Chiralpak AD; heptane/2-propanol, 96:4, 0.5 mL/min, λ = 254 nm; major isomer, t_S = 44.34 min; minor isomer, t_R = 61.28 min).

Supporting Information Available: General experimental details, typical procedures, analytical data of products, ^{1}H and ^{13}C NMR spectra of compounds **5**, and four examples of temperature, pressure, and power profiles for the MW-assisted reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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