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Microwave-Assisted Asymmetric Organocatalysis. A Probe for Nonthermal Microwave Effects and the Concept of Simultaneous Cooling

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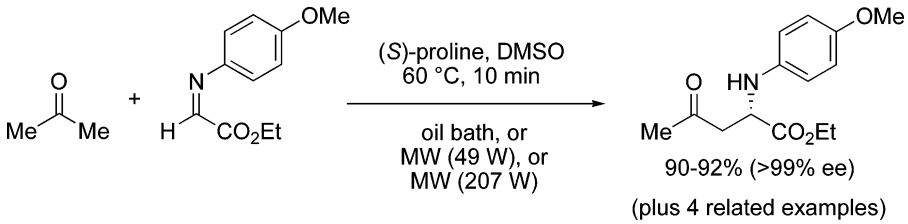

A series of five known asymmetric organocatalytic reactions was re-evaluated at elevated temperatures applying both microwave dielectric heating and conventional thermal heating in order to probe the existence of specific or nonthermal microwave effects. All transformations were conducted in a dedicated reactor setup that allowed accurate internal reaction temperature measurements using fiber-optic probes. In addition, the concept of simultaneous external cooling while irradiating with microwave power was also applied in all of the studied cases. This method allows a higher level of microwave power to be administered to the reaction mixture and, therefore, enhances any potential microwave effects while continuously removing heat. For all of the five studied (*S*)-proline-catalyzed asymmetric Mannich- and aldol-type reactions, the observed rate enhancements were a consequence of the increased temperatures attained by microwave dielectric heating and were not related to the presence of the microwave field. In all cases, in contrast to previous literature reports, the results obtained either with microwave irradiation or with microwave irradiation with simultaneous cooling could be reproduced by conventional heating at the same reaction temperature and time in an oil bath. No evidence for specific or nonthermal microwave effects was obtained.

Introduction

In recent years, it has been established that small chiral organic molecules, in addition to chiral metal complexes and biocatalysts, can be highly selective and efficient catalysts.[1] As a consequence, the field of "organocatalysis" is rapidly gaining importance in asymmetric synthesis, complementing bio and metal catalysis.[1−3] Organocatalysts are purely organic molecules, composed of mainly carbon, hydrogen, nitrogen, oxygen, sulfur, and phosphorus. The catalytic activity of organocatalysts resides in the organic molecule itself, and no metals are required. Unlike many metal−ligand complexes, organocatalysts generally are robust and stable molecules, are nontoxic and tolerate aerobic conditions, and do not require rigorous exclusion of water. They possess a wider substrate scope than enzymes and can be used in a variety of organic solvents. All of these advantages make organocatalysts very attractive for asymmetric synthesis, with impressive achievements being reported at an ever-increasing pace.[4]

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One distinct disadvantage of organocatalytic reactions, however, is the high catalyst loading (5−30%) that typically needs to be employed in order to achieve good conversions in a reasonable time frame.[1−3] Furthermore, in order to retain high enantioselectivity, organocatalytic transformations typically need to be carried out at room temperature, therefore, often requiring many hours or even days to reach completion.[1−3] In the context of the growing general interest in microwave-assisted organic synthesis[5,6] and, in particular, in the issue of microwave effects,[7] we became interested in performing an in-depth investigation of the influence of microwave irradiation on asymmetric organocatalytic reactions. Asymmetric organocatalytic transformations appear to be ideal probes for investigating nonthermal microwave effects since, apart from the standard parameter conversion that is typically monitored in comparing conventional heating and microwave heating experiments,[7] the enantioselectivity parameter can also be studied. The enantioselectivity for a particular asymmetric organocatalytic reaction would be expected to be rather sensitive to temperature and, therefore, a good probe to distinguish between thermal and nonthermal microwave effects.

The majority of organocatalytic reactions known today are amine-based reactions, proceeding as charge-accelerated reactions through the formation of polar iminium ion intermediates or related species.[3] According to some studies, transformations of this type involving polar intermediates or transition states are likely to be accelerated by microwave irradiation due to a specific interaction of the electric field with the polar reaction species, which is not connected to the reaction temperature.[7] In the context of three recently published reports on asymmetric organocatalytic reactions accelerated by microwave irradiation,[8−10] we herein describe our own findings on several proline-catalyzed asymmetric Mannich and aldol reactions performed by microwave and conventional heating under strictly comparable reaction conditions.

Results and Discussion

Microwave Versus Oil Bath Heating. Regardless of the relatively large body of published work on microwave chemistry,[5−7] the exact reasons why microwave heating enhances chemical processes are still unknown. There is experimental evidence that certain chemical transformations, when carried out at the same measured reaction temperature using either microwave or conventional heating, lead to different results in terms of product distribution (selectivity) and yield.[7] These difficult-to-rationalize effects have been referred to as "specific" or "nonthermal" microwave effects[11] and have been proposed to be the consequence of wave-material interactions, leading to a decrease in activation energy or an increase in the pre-exponential factor in the Arrhenius law due to orientation effects of polar species in an electromagnetic field.[7] A similar effect may be observed for polar reaction mechanisms, where the polarity is increased going from the ground state to the transition state, resulting in an enhancement of reactivity by lowering the activation energy.[7]

Related to the issue of nonthermal microwave effects is the recent concept that simultaneous external cooling of the reaction mixture (or maintaining subambient reaction temperatures) while heating by microwaves can, in some cases, lead to an enhancement of the overall process.[12,13] Here, the reaction vessel is cooled from the outside by compressed air or with the aid of a cooling fluid while being irradiated by microwaves. This allows a higher level of microwave power to be directly administered to the reaction mixture but will prevent overheating by continuously removing heat.[12,13]

In order to accurately compare the results obtained by direct microwave heating with the outcome of a conventionally heated reaction, we have used a reactor system that allows us to perform both types of transformations in the identical reaction vessel and to monitor the internal reaction temperature in both experiments directly with a fiber-optic probe device. Monitoring reaction temperatures in microwave-assisted reactions by conventional infrared probes on the outside vessel wall is not an acceptable technique if an accurate temperature profile needs to be obtained.[14,15] Similar to the setup recently described by Maes and co-workers,[16] we have used a CEM Discover single-mode microwave reactor equipped with a fiber-optic probe for direct monitoring of the internal reaction temperature in a 10 mL sealed reaction vessel made either out of Pyrex or out of fully microwave-transparent quartz glass.[15] This setup (see Figure S1 in the Supporting Information) can be either immersed into the cavity of the microwave reactor or immersed into a preheated and temperature-equilibrated oil bath placed on a magnetic stirrer. In both cases, the software of the microwave instrument is recording the internal temperature, and similar heating profiles can be obtained. This system has the advantage that the same reaction vessel and the same method of temperature measurement is used. In this way, all parameters, apart from the mode of heating, are identical, and therefore, a fair

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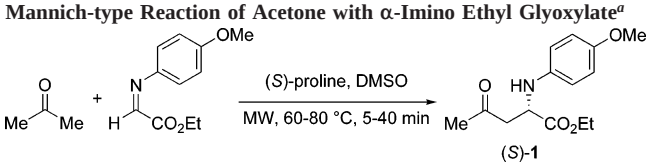
TABLE 1. Temperature Screen for Microwave-Assisted Mannich-type Reaction of Acetone with α-Imino Ethyl Glyoxylate[a]



entry	time (min)	temp (°C)	yield (%)[b]	ee (%)[c]
1	5	60	81	98
2	10	60	91	>99
3	20	60	84	*d*
4	30	60	81	*d*
5	40	60	83	*d*
6	15	80	57	*d*
7	30	80	51	*d*

[a] α-Imino ethyl glyoxylate (0.77 mmol) and (*S*)-proline (20 mol %) were reacted in an acetone/DMSO 1:4 (v/v) solvent mixture (5 mL). For further details, see the Experimental Section. [b] Isolated yields of pure product after silica gel column chromatography. [c] Determined by chiral-phase HPLC (Chiralcel OD−H) from the crude reaction mixture before chromatographic purification. [d] Not determined.

comparison between microwave heating and thermal heating can be made.

Proline-Catalyzed Asymmetric Mannich Reactions. As a starting point for our investigations, we have considered proline-catalyzed, enantioselective Mannich reactions using α-imino glyoxylates as acceptors and ketones as donors. This type of amino acid-catalyzed organocatalytic transformation was studied in detail by the Barbas group[17,18] and typically leads to functionalized α-amino acids with excellent regio-, diastereo-, and enantioselectivities. For reasons of experimental simplicity, we have decided to choose the reaction of readily available[19] *N*-(4-methoxyphenyl)-protected α-imino ethyl glyoxylate with acetone, leading to *β*-amino ketone (*S*)-**1**, possessing one stereogenic center as a model system (Table 1).[17] This organocatalytic process is typically run in DMSO solvent at room temperature,[17] but the use of other solvent systems (including ionic liquids) for this and related processes involving different ketone donors has also been explored.[18] According to the original Barbas work, employing 20 mol % of (*S*)-proline as a catalyst provides an 82% isolated product yield of (*S*)-**1** in 95% ee within 2 h at room temperature.[17] Having successfully reproduced the original conditions and results of Barbas at room temperature (86% yield, 96% ee), we next set out to explore if similar results could be achieved by applying controlled microwave irradiation at higher temperatures.

Our initial scouting of suitable time/temperature conditions using single-mode-controlled microwave irradiation revealed that full conversion to *β*-amino ketone (*S*)-**1** and a high isolated product yield (91%) could be achieved at 60 °C within only 10 min. The reaction proved to be somewhat sensitive to prolonged reaction times, as the yield diminished gradually with longer reaction times or higher temperatures, leading to unidentified decomposition products (Table 1). Performing a sensitive asymmetric reaction at elevated temperatures in order to achieve a higher rate of reaction typically results in reduced enantioselectivity.[20] In order for a reaction to occur with high enantioselectivity, there must be a sufficiently large difference in the activation energies for the processes leading to the two enantiomers. The higher the reaction temperature, the larger the difference in energy required to achieve high selectivity.[20] We were pleased to find that the enantiomeric excess in the asymmetric Mannich reaction did not decrease when raising the reaction temperature to 60 °C. Even at significantly higher reaction temperatures (120 °C), the product ee did not degrade to a significant extent, although at these temperatures, more byproducts were observed; therefore, isolated product yields proved to be low and of no practical use (data not shown).

Having found optimal microwave conditions for the asymmetric Mannich-type reaction shown in Table 1 that allow the rapid generation of enantiopure *β*-amino ketone (*S*)-**1** within only 10 min of total irradiation time, we were interested in investigating if nonthermal microwave effects[7,11] were involved in this process. According to the currently accepted mechanism of this Mannich-type reaction, the enamine derived from the proline catalyst and the ketone component reacts with the imine in the carbon−carbon bond-forming and enantioselectivity-determining step to furnish a charged iminium ion as the intermediate (enamine catalysis).[3] Transformations of this type involving polar intermediates or transition states have been advocated to be accelerated by microwave irradiation due to a specific interaction of the electric field with the polar reaction intermediates.[7]

We therefore have performed a detailed comparison between conventional heating in an oil bath and microwave heating using the dedicated setup described in the preceding discussion. In addition, to evaluate the concept of simultaneous cooling,[12,13] we have also performed the experiments in a microwave system that allows efficient simultaneous cooling of the reaction mixture by an external, microwave-transparent, cooling fluid in a properly designed reaction vessel (CEM Discover CoolMate, see Figure S2 in the Supporting Information). In all of the experiments, the preprogrammed reaction temperatures were monitored by a fiber-optic probe, and the heating profiles were, as far as possible, adjusted to be similar to each other by proper modulation of microwave power (see Supporting Information for more details).

Our first experiment involved reproducing the run performed under microwave irradiation conditions at 60 °C (see Table 1) in an oil bath. For this purpose, the experimental setup was immersed into a preheated oil bath (bath temperature 60 °C), and the internal reaction temperature was monitored with the fiber-optic probe. In this way, a similar heating profile as that under microwave irradiation could be obtained, representing the true reaction temperatures in both experiments. To our surprise, the results of the oil bath run more or less exactly matched the data from the microwave experiment, both in isolated product yield of *β*-amino ketone (*S*)-**1** and in enantiomeric excess (Table 2, entries 1 and 2). In order to enhance any possible nonthermal microwave effects (effects of the electromagnetic field),[7] we next conducted a microwave irradiation experiment with intensive simultaneous cooling using the CEM CoolMate system. The simultaneous cooling (cooling fluid temperature

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TABLE 2. Comparison of Microwave Heating and Conventional Heating for the Two-Component Mannich-type Reaction (Scheme, Table 1)[a]

entry	heating method	solvent	power (W)[b]	temp (°C)[c]	time (min)	yield (%)[d]	ee (%)[e]
1	oil bath	DMSO		60	10	91	>99
2	MW[f]	DMSO	49	60	10	90	>99
3	MW (liquid cooling)	DMSO	207	60	10	92	>99
4	oil bath	DMSO		40	10	55	>99
5	MW	DMSO	1	40	10	57	>99
6	MW (liquid cooling)	DMSO	203	40	10	54	>99
7	oil bath	dioxane		60	180	48	>99
8	MW	dioxane	20	60	180	51	>99

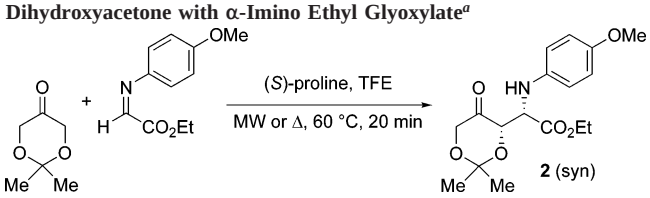
[a] α-Imino ethyl glyoxylate (0.77 mmol) and (*S*)-proline (20 mol %) were reacted in an acetone/DMSO 1:4 (v/v) solvent mixture (5 mL). For further details, see the Experimental Section. [b] Average magnetron output power during the experiment. [c] Internal reaction temperature measured by fiber-optic sensor. The heating profiles are reproduced in the Supporting Information (Figures S3−S5). [d] Isolated yields of pure product after silica gel column chromatography. [e] Determined by chiral-phase HPLC (Chiralcel OD−H) from the crude reaction mixture before chromatographic purification. [f] Microwave irradiation.

−35 to −10 °C) made it possible to dramatically increase the microwave power by a factor of four to reach the same target temperature of 60 °C. Despite this significant increase in microwave power and, therefore, in the electromagnetic field strength, there was no change in the outcome of the reaction (entry 3).

Since, in all three experiments, the organocatalytic reaction did reach full conversion, we felt that a control experiment, comparing the outcome of runs performed at lower temperatures not reaching full conversion, was additionally warranted. We therefore conducted an identical set of three experiments at 40 °C (Table 2, entries 4−6). Here, the reaction did not reach full conversion within 10 min, and the desired *β*-amino alcohol (*S*)-**1** was isolated in 55, 57, and 54% yield (>99% ee). In order to not only rely on isolated product yields, we have also compared reversed-phase HPLC data (284 nm) obtained from the crude reaction mixtures for those three experiments. The three HPLC traces were virtually identical, demonstrating the absence of any differences between conventional and microwave heating. It should be noted that, because of the comparatively low temperature and the fact that DMSO is a strong microwave absorber (tan δ = 0.825),[21] only a very small amount of microwave power was, in fact, delivered from the magnetron to reach the set target temperature of 40 °C (entry 5). Any difference between the microwave and oil bath experiment would, therefore, be extremely unlikely since virtually no microwave energy was delivered to the reaction mixture. However, using intensive simultaneous cooling (cooling fluid temperature −35 to −10 °C), a considerable amount of microwave power (ca. 200 W) was introduced to heat the reaction mixture to 40 °C (entry 6). Nonetheless, also under these conditions, the results were, within experimental error, identical to the experiments performed in the oil bath and using microwave heating without simultaneous cooling (entries 4−6).

(21) The ability of a specific solvent to convert microwave energy into heat is determined by the so-called loss tangent (tan δ), expressed as the quotient tan $\delta = \epsilon''/\epsilon'$. A reaction medium with a high tan δ is required for good absorption and, consequently, for efficient heating. Solvents used for microwave synthesis can be classified as high (tan δ > 0.5), medium (tan δ 0.1−0.5), and low microwave-absorbing (tan δ < 0.1).

TABLE 3. Comparison of Microwave Heating and Conventional Heating for the Mannich-type Reaction of Protected Dihydroxyacetone with α-Imino Ethyl Glyoxylate[a]



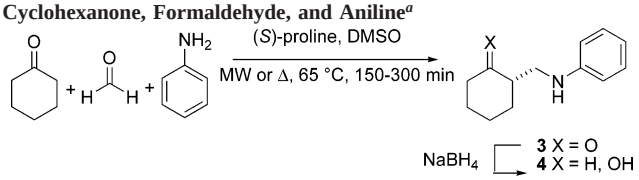
entry	heating method	power (W)[b]	temp (°C)[c]	yield (%)[d]	dr[e]	ee (%)[f]
1	oil bath		60	56	90:10	>99
2	MW	1	60	58	90:10	>99
3	MW (liquid cooling)	83	60	55	90:10	>99

[a] Equimolar amounts of α-imino ethyl glyoxylate and dihydroxyacetone acetonide (1.0 mmol each) were reacted with (*S*)-proline (30 mol %) in 2,2,2-trifluoroethanol (TFE, 1 mL) at 60 °C. For details, see the Experimental Section. [b] Average magnetron output power during the experiment. [c] Internal reaction temperature measured by fiber-optic sensor. The heating profiles are reproduced in the Supporting Information (Figure S6). [d] Isolated yields of pure product after silica gel column chromatography. [e] Diastereomeric ratio determined by ^{1}H NMR. Only the syn product is shown in the above Scheme. [f] Determined by chiral-phase HPLC (Chiralcel OD−H) from the crude reaction mixture before chromatographic purification.

The results of the experiments discussed may not seem surprising if one considers that most of the microwave energy will be directed at the strongly microwave-absorbing solvent, DMSO, and not at the reagents and/or intermediates formed during the reaction. It has been stated that, in a case like this, any potential microwave effect would be masked by the strongly microwave-absorbing solvent.[7] We have, therefore, additionally conducted experiments using anhydrous dioxane as the solvent under otherwise identical reaction conditions. This nonpolar solvent has previously been employed by Barbas and co-workers for this particular and closely related organocatalytic Mannich-type processes.[17] Dioxane can be considered as virtually microwave transparent (tan δ < 0.01),[21] and therefore, most of the microwave energy will indeed be absorbed by the polar reagents and the catalyst, rather than by the solvent. In our hands, the organocatalytic reaction between acetone and *N*-(*p*-methoxyphenyl)-protected α-imino ethyl glyoxylate using dioxane as the solvent and (*S*)-proline (20 mol %) as the catalyst required 3 h at 60 °C to reach a reasonable amount of conversion (48 h at room temperature) and was not as clean as the same process using DMSO as the solvent. Importantly however, the comparison of results between the oil bath experiment and the microwave run (entries 7 and 8) clearly demonstrated the absence of any nonthermal microwave effects also in this case. We can therefore safely conclude that the rate enhancements seen in this reaction in going from 25 °C (room temperature) to 60 °C (2 h versus 10 min) and the slightly improved yields (86 versus 92%) and ee's (96 versus 99%) using DMSO as the solvent are the result of a purely thermal/kinetic effect based on applying the Arrhenius equation.[11]

In the context of the results described, we became interested in a recent publication by Westermann and Neuhaus where a closely related proline-catalyzed Mannich-type reaction between a protected dihydroxyacetone and *N*-(4-methoxyphenyl)-protected α-imino ethyl glyoxylate was described (Table 3).[8] In their work, the authors used 2,2,2-trifluoroethanol (TFE) as a solvent and, apart from experiments at room temperature using 30 mol % of (*S*)-proline as the catalyst, also carried out the identical reaction under microwave irradiation conditions, albeit without stating a reaction temperature.[8] The authors describe

TABLE 4. Comparison of Microwave Heating and Conventional Heating for the Three-Component Mannich Reaction of Cyclohexanone, Formaldehyde, and Aniline[a]



entry	heating method	power (W)[b]	mol % of proline	time (h)	yield (%)[c]	ee (%)[d]
1	oil bath		10	2.5	63	98
2	MW	6	10	2.5	66	97
3	MW (air cooling)	15	10	2.5	61	98
4	MW (liquid cooling)	291	10	2.5	64	98
5	oil bath		1	5	79	97
6	MW	7	1	5	83	97
7	MW (liquid cooling)	57	1	5	81	98
8	MW (liquid cooling)	232	1	5	81	97

[a] A solution of aniline (1.1 mmol, 1 equiv), aqueous formaldehyde (1.1 equiv), cyclohexanone (2.6 equiv), and (*S*)-proline (1 or 10 mol %) was reacted in DMSO (4 mL) at 65 °C. For details, see the Experimental Section. [b] Average magnetron output power during the experiment. The heating profiles are reproduced in the Supporting Information (Figures S7 and S8). [c] Isolated yields of pure amino alcohol **4** after in situ reduction of the ketone product **3** with sodium borohydride and subsequent silica gel column chromatography. [d] Determined by chiral-phase HPLC (Chiralcel OD−H) from the crude reaction mixture (ketone **3**) before reduction.

an acceleration of this reaction by microwave irradiation that allowed the organocatalyzed reaction to be performed within 10 min, giving rise to 72% isolated yield of β-amino ketone **2** (94% ee, dr 90:10). In comparison, the same reaction at room temperature after 20 h furnished the same isolated product yield (72%) with slightly improved enantioselectivity (99% ee) and diastereoselectivity (dr 97:3).[8] On the basis of our experience with the closely related transformation described in Table 1, we decided to additionally perform a comparison study of this organocatalytic reaction (Table 3) using our dedicated microwave/oil bath setup. After some experimentation using controlled microwave irradiation conditions, we found that the best set of conditions for this Mannich-type process in the strongly microwave-absorbing TFE[21] again involved a 60 °C reaction temperature. After 20 min at 60 °C, the anticipated β-amino ketone **2** was isolated in 57% isolated yield (>99% ee) as a mixture of syn and anti diastereoisomers (dr 90:10). Shorter (10 min) or longer (30 min) reaction times provided somewhat lower isolated product yields.

The comparison studies between oil bath heating, microwave heating, and microwave heating with simultaneous cooling were performed in exactly the same manner as described for the Barbas reaction. Within experimental error, all investigated parameters (isolated yield and diastereo- and enantioselectivity) in this reaction were the same regardless of the mode of heating or the amount of microwave power used (Table 3). We, therefore, do not find any evidence for a nonthermal microwave effect and thus conclude that the observed rate accelerations[8] are a simple consequence of the elevated temperature used also in this case.

While our work was in progress, a publication by Rodriguez and Bolm described the influence of microwave irradiation on proline-catalyzed, direct, three-component asymmetric Mannich reactions between cyclohexanone, formaldehyde, and anilines (Table 4).[9] The authors were able to demonstrate that the originally reported reaction conditions for this classic α-aminomethylation first presented by Córdova and co-workers in 2004 (room temperature, 16−24 h, 10 mol % of (*S*)-proline)[22] could be significantly improved by microwave heating in conjunction with simultaneous cooling (compressed air cooling). Applying catalyst loadings as low as 0.5 mol %, Mannich products with up to 98% ee were obtained within only 3 h of microwave heating, with isolated product yields of the corresponding β-amino alcohols (after in situ reduction with sodium borohydride) of up to 83%.[9]

While the reduction in catalyst loading and the high-temperature tolerance of these asymmetric Mannich reactions could essentially be reproduced by conventional heating in an oil bath, the shortened reaction times appeared to be specifically connected to microwave heating under simultaneous cooling conditions.[9] Since accurate temperature measurements using fiber-optic probes were not applied in this study, we decided to reinvestigate this transformation employing our experimental setup.

Keeping as close as possible to the general experimental conditions given by the authors with respect to performing the reaction, isolating the product, and monitoring the enantiomeric excess,[9] we first performed a temperature screen with 10 mol % of (*S*)-proline using controlled microwave irradiation with concomitant monitoring of the reaction temperature with a fiber-optic probe. As with the other proline-catalyzed Mannich-type reactions described, a temperature of 60−70 °C provided a good balance between a rapid reaction rate, a good isolated yield, and a high product ee (97−98%). As reported by Rodriguez and Bolm,[9] reaction temperatures higher than 90 °C lead to a significant reduction in enantioselectivity. For the specific comparison studies between oil bath heating, microwave heating, and microwave heating in conjunction with simultaneous cooling, we have ultimately chosen a reaction temperature of 65 °C using two different catalyst loadings (10 and 1 mol % of (*S*)-proline). Experiments involving 10 mol % of (*S*)-proline were run for 2.5 h under four different heating conditions (Table 4, entries 1−4). As can be seen from the data presented in Table 4, there is virtually no difference in the outcome of the Mannich reaction, regardless of which heating mode is being employed. The experiment most closely mimicking the conditions described by Rodriguez and Bolm using microwave heating with simultaneous compressed air cooling (15 W average magnetron output power, compressed air temperature 4 °C) (entry 3) provides nearly the same results in terms of yield and enantioselectivity as the run performed in the oil bath (entry 1) or the experiment using intensive cooling with a low-temperature (−35 to −10 °C) cooling fluid (entry 4).

In the second set of control experiments using 1 mol % of (*S*)-proline (entries 5−8), the same trends were observed. Again, virtually identical yields and enantioselectivities were found, regardless of the heating mode. Note that, employing the CEM CoolMate (entries 7 and 8), the amount of delivered microwave power can be adjusted by choosing an appropriate cooling fluid temperature (or changing the flow rate). The lower the temperature of the cooling fluid, the more microwave energy that must be used in order to reach the desired set temperature. Using a cooling fluid temperature of 25−35 °C (entry 7), 57 W of magnetron output power is sufficient to reach the desired set temperature of 65 °C. By lowering the temperature of the

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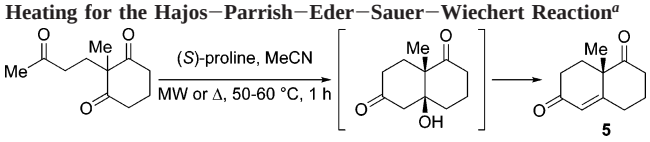
TABLE 5. Comparison of Microwave Heating and Conventional Heating for the Hajos−Parrish−Eder−Sauer−Wiechert Reaction[a]



entry	heating method	power (W)[b]	temp (°C)[c]	conversion (%)[d]	ee (%)[e]
1	oil bath		50	2.5	64
2	MW	1	50	2.0	62
3	MW (air cooling)	35	50	2.0	61
4	oil bath		60	7.8	61
5	MW	2	60	7.3	61
6	MW (air cooling)	37	60	6.6	60

[a] Triketone (0.56 mmol), (*S*)-proline (18 mol %), and MeCN (3 mL) were reacted for 1 h. For details, see the Experimental Section. [b] Average magnetron output power during the experiment. [c] Internal reaction temperature measured by fiber-optic sensor. The heating profiles are reproduced in the Supporting Information (Figures S9 and S10). [d] Conversion to product measured by calibrated HPLC−UV at 244 nm. For details, see the Supporting Information. [e] Determined by chiral-phase HPLC (Chiralcel OD−H) from the crude reaction mixture.

cooling fluid to −35 to −10 °C (entry 8), it is possible to deliver significantly more microwave power (232 W) to the system.

Proline-Catalyzed Asymmetric Aldol Reactions. The Mannich-type reactions described displayed a remarkable insensitivity to temperature. In most instances, product ee's remained excellent (>96%) even at reaction temperatures above 80 °C. This fact evidently makes it possible to speed up otherwise sluggish transformations by employing a higher reaction temperature. While this constitutes a preparatively very valuable facet of proline-catalyzed Mannich-type reactions, the near perfect enantioselectivities over a wide temperature range make the investigation of nonthermal microwave effects difficult. We therefore considered other proline-catalyzed transformations that do not normally give such high product ee's under standard reaction conditions. One such transformation is the well-known Hajos−Parrish−Eder−Sauer−Wiechert reaction (Table 5).[23] The enantiomerically pure product of this reaction, the so-called Wieland−Miescher ketone (**5**), has proven to be a particularly useful synthon for the construction of a variety of natural products.[24]

Among the different solvents and conditions that have been reported to be effective for the Hajos−Parrish−Eder−Sauer−Wiechert reaction,[23,25] we have selected acetonitrile as the solvent of choice. Acetonitrile is a modest microwave-absorbing solvent (tan $\delta = 0.062$),[21] and therefore, most of the microwave energy would be expected to be absorbed by the substrates or polar intermediates,[26,27] thereby increasing the chance to observe a nonthermal microwave effect.[7] In our hands, using 18 mol % of (*S*)-proline as the catalyst, a 75% conversion was observed after 3 days at 25 °C. In good agreement with previously published data,[23,25] the enantiomeric excess of the crude Wieland−Miescher ketone obtained under these conditions was 71%. This value did not change after isolation and purification of the pure ketone (69% isolated yield) by vacuum distillation at 110 °C/0.7 mbar, demonstrating the configurational stability of the cyclic enone.[25]

In an initial set of experiments carried out by conventional oil bath heating, we studied the influence of reaction temperature on the product ee. In contrast to the Mannich-type organocatalytic processes described, a significant temperature dependence on the enantiomeric purity of the formed Wieland−Miescher ketone was observed. In going from room temperature to 70 °C, the product ee gradually decreased from 71% to a mere 14% after 3 days reaction time (see Table S1 in the Supporting Information). It is interesting to note, however, that continuous monitoring of product ee's during the first few hours revealed that the ee of the Wieland−Miescher ketone initially remained high even at a temperature of 50 °C and only degraded with time. The underlying details of this phenomenon, not being relevant to this work, were not further investigated.

With this information in hand, we set out to perform the usual control experiments between microwave heating and conventional heating in an oil bath. Since, for technical reasons, we were limited to 1 h of microwave irradiation in combination with simultaneous cooling (cooling gas temperature 4 °C), two series of 1 h runs involving heating at 50 and 60 °C were performed (Table 5). Although the overall conversions after only 1 h reaction time were rather low (full conversion at 60 °C requires more than 20 h), no significant differences both in conversion and in product ee were experienced when comparing the results obtained via the three different heating modes. We ascribe the minor differences seen between oil bath and microwave heating to inadvertent discrepancies in the stirring speed in the two systems. It has to be noted that, using acetonitrile as the solvent, not all of the proline catalyst is dissolved and that proper stirring is essential for the reaction to proceed.

The final example of our investigations involved the direct intermolecular, asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde (Table 6). Pioneered by List and co-workers in 2000, this organocatalyzed reaction furnishes the anticipated aldol (*R*)-**6** in 68% isolated yield and 76% ee within 4 h when run at room temperature (DMSO, 30 mol % of (*S*)-proline).[28] Recently, Mossé and Alexakis repeated the same reaction and have shown that, by using microwave heating in conjunction with simultaneous air cooling at 35 °C (measured by an external IR sensor), nearly identical results (69% yield, 70% ee) could be obtained in only 15 min, even with a reduced catalyst loading of only 20 mol %.[10] In our hands, these results could be reproduced (Table 6, entry 3), but a control experiment using oil bath heating under carefully controlled temperature conditions again revealed that the enhancement in rate is simply due to a thermal/kinetic effect.[11] Regardless of the heating mode or the level of microwave power applied to the reaction, the results in terms of both product yield and enantiomeric purity were identical.

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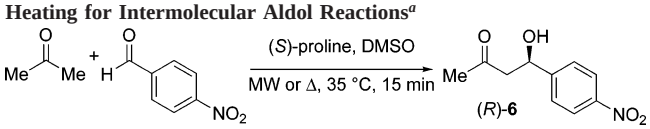
TABLE 6. Comparison of Microwave Heating and Conventional Heating for Intermolecular Aldol Reactions[a]



entry	heating method	power (W)[b]	temp (°C)[c]	yield (%)[d]	ee (%)[e]
1	oil bath		35	63	68
2	MW	2	35	62	69
3	MW (liquid cooling)	114	35	62	68

[a] 4-Nitrobenzaldehyde (0.27 mmol), (*S*)-proline (20 mol %), and acetone/DMSO 1:4 (v/v) (3 mL) were reacted for 15 min at 35 °C. For details, see the Experimental Section. [b] Average magnetron output power during the experiment. [c] Internal reaction temperature measured by fiber-optic sensor. The heating profiles are reproduced in the Supporting Information. [d] Isolated yields after silica gel column chromatography. [e] Determined by chiral-phase HPLC (Chiralpak AS-H) from the crude reaction mixture.

Concluding Remarks

In summary, we have conducted a detailed investigation of the existence of microwave effects in organocatalytic processes. For all of the five studied proline-catalyzed Mannich- and aldol-type reactions, we have shown that the observed effects (mainly rate enhancements) are a consequence of the increased temperatures attained by microwave dielectric heating and are not related to the microwave field. In fact, careful control experiments revealed that, in all cases, the results obtained with microwave irradiation could be reproduced by conventional heating at the same reaction temperature in an oil bath. Both isolated product yields and enantiomeric purities of the Mannich or aldol products obtained either by microwave or by conventional heating were virtually identical, clearly demonstrating the absence of any nonthermal microwave effects in these reactions.

Of critical importance for our work was the use of fiber-optic probes as accurate temperature measurement devices in both the microwave and the conventionally heated reactors. Fiber-optic probes allow the direct online monitoring of internal reaction temperatures and, therefore, eliminate many of the problems associated with the more commonly employed infrared sensors that measure reaction temperatures externally in most of the commercially available microwave reactors. In particular, when using simultaneous cooling by compressed air or with a cooling fluid, internal temperature probes must be used. The use of infrared sensors is not appropriate here and can easily lead to a misinterpretation of the results since the true reaction temperatures during microwave irradiation are not known.[14] For the particular chemistry examples studied herein, no effect of the simultaneous cooling was observed. The amount of microwave power delivered to the reaction mixture apparently proved to be irrelevant.

In this context, we would also like to caution against the uncritical use of terms such as "microwave-accelerated" or "microwave-enhanced" for describing processes that are performed using microwave dielectric heating. The use of these terms, in our opinion, implies an effect of the microwaves themselves and therefore an involvement of the electromagnetic field. This automatically suggests a specific or nonthermal microwave effect not reproducible by conventional heating, which may, in fact, not be the case. In the absence of carefully conducted control experiments that demonstrate significant differences between the outcome of a microwave-heated and a conventionally heated reaction, the use of the term "microwave-assisted" may be more appropriate.

Experimental Section

Microwave Irradiation Experiments. Microwave irradiation experiments were performed using a single-mode Discover System from CEM Corporation[29] using either custom-made high-purity quartz or standard Pyrex vessels (capacity 10 mL). The temperature profiles for microwave and oil bath experiments were recorded using a fiber-optic probe protected by a sapphire immersion well inserted directly into the reaction mixture (Figure S1 in the Supporting Information). Simultaneous gas jet cooling (3−5 bar) during microwave irradiation was performed by using either a compressor or a nitrogen cylinder. In both cases, the gas was precooled to ca. 4 °C by passage through a coil immersed in a cooling bath (ice−sodium chloride mixture, −10 °C) before reaching the reaction vessel. Microwave irradiation experiments using liquid cooling were performed in a CEM CoolMate[29] (see Figure S2 in the Supporting Information) employing a microwave-transparent cooling fluid (Galden HT 110). The temperature in the reaction vessel was controlled by a fiber-optic probe with temperatures up to +65 °C. By adjusting the microwave power of the magnetron and the temperature of the cooling fluid with dry ice or liquid nitrogen (−35 to +35 °C) in combination with changing the flow rate of the cooling medium, the desired reaction temperature in the reaction vessel could be attained. Silicon oil was used as a heating medium for the conventional heating experiments.

General Procedure for the Two-Component Mannich-type Reaction of Acetone with α-Imino Ethyl Glyoxylate (Tables 1 and 2). To a solution of freshly prepared *N*-(4-methoxyphenyl)-protected α-imino ethyl glyoxylate[19] (160 mg, 0.77 mmol) in anhydrous DMSO (4 mL) were added acetone (1 mL) and (*S*)-proline (18 mg, 0.16 mmol, 20 mol %). The mixture was subsequently heated with stirring in a 10 mL microwave process vial (Figure S1 in Supporting Information) for 10 min, applying the appropriate mode of heating (Table 2). The crude reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (3 × 20 mL), and the combined organic phases were dried over $MgSO_4$. A sample was taken for chiral-phase HPLC, and the remaining mixture was evaporated and purified by automated flash column chromatography (EtOAc/petroleum ether = 1:3) to afford β-amino ketone (*S*)-**1** as a yellow oil. The ee was determined by HPLC analysis of the crude product using a chiral column (Chiralcel OD−H, hexane/2-propanol 90:10, 0.6 mL/min, λ = 285 nm; minor isomer t = 21.00 min; major isomer t = 24.14 min): ^{1}H NMR ($CDCl_3$) δ 6.82−6.63 (m, 4H), 4.35 (t, J = 6.0 Hz, 1H), 4.19 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 2.97 (d, J = 5.6 Hz, 2H), 2.19 (s, 3H), 1.24 (t, J = 7.3 Hz, 3H). The NMR data were in accordance with those previously reported.[17]

The reactions performed in dioxane (Table 2, entries 7 and 8) were treated in the same manner while employing dioxane as the solvent instead of DMSO.

General Procedure for the Two-Component Mannich-type Reaction of Protected Dihydroxyacetone with α-Imino Ethyl Glyoxylate (Table 3). To a solution of (*S*)-proline (35 mg, 0.3 mmol, 30 mol %) in 2,2,2-trifluoroethanol (1 mL) was added

(29) For more information, see: CEM Corporation Website. www.cem-.com.

2,2-dimethyl-1,3-dioxan-5-one (130 mg, 1.0 mmol). After stirring for 15 min, freshly prepared *N*-(4-methoxyphenyl)-protected α-imino ethyl glyoxylate[19] (207 mg, 1.0 mmol) was added, and the mixture was subsequently heated with stirring in a 10 mL microwave process vial (Figure S1) for 20 min, applying the appropriate mode of heating (Table 3). The crude reaction mixture was quenched with saturated NH_4Cl (1 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by automated flash column chromatography (EtOAc/petroleum ether = 1:3) to give β-amino ketone **2** as a mixture of syn and anti diastereoisomers as a yellow oil. The ee was determined by HPLC analysis of the isolated pure product using a chiral column (Daicel Chiralcel OD−H, hexane/2-propanol 90:10, 0.6 mL/min, λ = 254 nm; minor isomer t = 11.25 min; major isomer t = 15.79 min): ^{1}H NMR ($CDCl_3$) (syn diastereoisomer) δ 6.82−6.70 (m, 4H), 4.75 (bs, 1H), 4.60 (d, J = 2.3 Hz, 1H), 4.36−4.10 (m, 3H), 4.03 (d, J = 16.6 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.25 (t, J = 7.3 Hz, 3H). The NMR data were in accordance with those previously reported.[8]

General Procedure for the Three-Component Mannich Reaction of Cyclohexanone, Formaldehyde, and Aniline (Table 4). To a solution of cyclohexanone (284 mg, 0.30 mL, 2.9 mmol), formaldehyde (36 mg, 90 μL, 36% aqueous solution, 1.2 mmol), and aniline (102 mg, 100 μL, 1.1 mmol) in DMSO (4 mL) was added (*S*)-proline (13 mg, 0.11 mmol, 10 mol %). The mixture was subsequently heated with stirring in a 10 mL microwave process vial (Figure S1) for 2.5−5 h, applying the appropriate mode of heating (Table 4). Upon completion, a ca. 5 μL sample of the reaction mixture containing the β-amino ketone **3** was subjected to chiral HPLC analysis, and to the remaining mixture were added $NaBH_4$ (50 mg, 1.3 mmol, 1.2 equiv) and MeOH (2 mL). After stirring for 10 min at room temperature, water (15 mL) and EtOAc (15 mL) were added. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Subsequent purification by automated flash chromatography (EtOAc/petroleum ether = 1:9) afforded β-amino alcohol **4** as a low-melting solid: ^{1}H NMR ($CDCl_3$) δ 7.25−7.15 (m, 2H), 6.81−6.63(m, 3H), 3.52−3.42 (m, 1H), 3.32−3.31 (m, 2H), 3.16−3.07 (m, 2H), 2.03−0.99 (m, 9H). The ee of β-amino ketone **3** was determined by HPLC analysis of the crude product before reduction using a chiral column (Chiralcel OD−H, hexane/2-propanol 90:10, 0.6 mL/min, λ = 190 nm; major isomer t = 15.7 min; minor isomer t = 17.30 min). The NMR data were in accordance with those previously reported.[9,22]

General Procedure for the Hajos−Parrish−Eder−Sauer−Wiechert Reaction (Table 5). A mixture of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione[25] (110 mg, 0.56 mmol) and (*S*)-proline (11.5 mg, 18 mol %) in anhydrous acetonitrile (3 mL) was heated with stirring in a 10 mL microwave process vial (Figure S1) for 1 h, applying the appropriate mode of heating. An aliquot of the brown reaction mixture was taken and diluted with acetonitrile to 1 mL. The diluted solution was sealed in a vial and measured by HPLC to determine the conversion using a calibration curve method (see Supporting Information for details). For the determination of enantioselectivity, 100 μL from the original reaction mixture was taken and filtered through a small silica column. The acetonitrile was evaporated under reduced pressure, the residue was dissolved in hexane/2-propanol (90:10), and the ee was determined by chiral-phase HPLC (Chiralcel OD−H, hexane/2-propanol, 90:10, 0.5 mL/min, λ = 254 nm; t_S = 25.4 min, t_R =27.0 min).

For preparative isolation on a larger scale, the brown reaction mixture was filtered through a short silica gel column that was equilibrated with acetonitrile. Acetonitrile was evaporated under reduced pressure at 50 °C. Further purification was achieved by vacuum distillation to yield 69% of the theoretical yield of 8a-methyl-3,4,8,8a-tetrahydro-2*H*,7*H*-naphthalene-1,6-dione (Wieland−Miescher ketone **5**) as an oil. Crystals were obtained by dissolving the oil in hexane/2-propanol (90:10) and leaving the solution undisturbed overnight: mp 49 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3H), 1.66−1.77 (m, 1H), 2.11−2.19 (m, 3H), 2.44−2.53 (m, 4H), 2.67−2.77 (m, 2H), 5.86 (s, 1H). The NMR data were in accordance with those previously reported.[30]

General Procedure for the Intermolecular Aldol Reaction between Acetone and 4-Nitrobenzaldehyde (Table 6). A mixture of DMSO/acetone = 4:1 (3 mL) and (*S*)-proline (6.33 mg, 0.055 mmol, 20 mol %) was stirred for 15 min at room temperature. To this solution was added 4-nitrobenzaldehyde (41 mg, 0.27 mmol), and the mixture was subsequently heated with stirring in a 10 mL microwave process vial (Figure S1) for 15 min at 35 °C, applying the appropriate mode of heating (Table 6). The mixture was quenched with saturated aqueous NH_4Cl (1 mL), extracted with diethyl ether (3 × 20 mL), and dried over $MgSO_4$. A sample was taken for chiral HPLC, and the remaining mixture was evaporated and purified by automated flash column chromatography (EtOAc/petroleum ether = 1:3) to afford the aldol product (*R*)-**6** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 8.62 Hz, 2H), 7.55 (d, J = 8.96 Hz, 2H), 5.28 (bs, 1H), 3.60 (s, 1H), 2.92−2.83 (m, 2H), 2.24 (s, 3H). The NMR data were in accordance with those previously reported.[10,28] The ee was determined by HPLC analysis of the crude product using a chiral column (Chiralpak AS-H, hexane/2-propanol 90:10, 0.6 mL/min, λ = 284 nm; major isomer t = 16.59 min; minor isomer t = 20.24 min).

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Supporting Information Available: Description of general experimental and microwave procedures, heating profiles for all reactions, and calibration data for HPLC measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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