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Organocatalyzed Asymmetric Reactions via Microwave Activation

Sarah Mossé and Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, CH-1211, Geneva, Switzerland

alexandre.alexakis@chiorg.unige.ch

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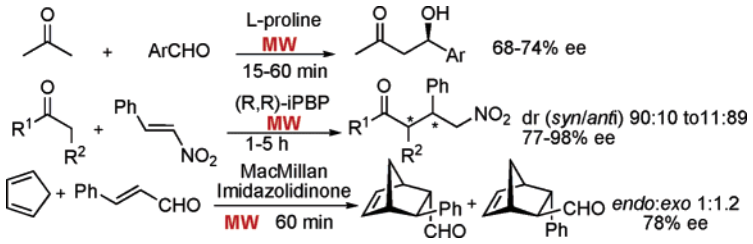
ABSTRACT



Organocatalyzed asymmetric microwave-assisted reactions are described. Significant rate enhancements and a decrease of catalyst loading via microwave activation have been observed, while maintaining good to high yields and selectivities compared to literature results.

In the past decade the field of organocatalysis has received considerable attention.[1,2] The efficiency and the scope of organocatalytic reactions have been broadly established. In this area, aminocatalysis is one of the most studied and operates via diverse mechanisms by converting the substrates into either activated nucleophiles or electrophiles. For instance, enamine catalysis and/or iminium catalysis allows aldol reactions,[3,4] Mannich reactions,[5] Michael additions,[6,7] cycloadditions,[8,9] and many other transformations with excellent selectivities. Major limitations of the asymmetric organocatalysis are the long reaction time and the high catalyst loading. Consequently, we considered microwave (MW) activation to remove these drawbacks. Indeed, since the initial

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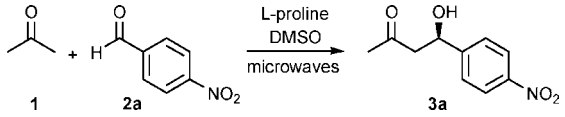
experiments in the mid-1980s, MW energy has shown tremendous benefits in organic synthesis and represents now a reliable tool for organic chemists.[10,11] Thus, Westermann pioneered the microwave-promoted organocatalytic Mannich reaction between a protected dihydroxyacetone and a preformed imine derived from glyoxylate and *p*-anisidine catalyzed by L-proline.[12] Under maximal irradiated power, an impressive decrease of reaction time was observed, whereas selectivities remained the same. Afterward, during our ongoing investigations, Bolm reported that the proline-catalyzed asymmetric Mannich reaction between cyclohexanone, formaldehyde, and various anilines is thermally accelerated under MW irradiation.[13] With a lower catalyst loading, the use of constant MW irradiation at low power allowed them to achieve both a shorter reaction time and an excellent enantioselectivity. To the best of our knowledge, there are no more examples of microwave-assisted organocatalyzed reactions.

Herein, we present the first L-proline-catalyzed asymmetric aldol reaction of acetone and various aldehydes under MW irradiation, innovatively developed by List and Barbas.[3] Furthermore, we describe the significant improvement of our *i*PBP-catalyzed asymmetric conjugate addition of hydroxyacetone and aldehydes to β-nitrostyrene via microwave activation.[7] Finally, we disclose the first microwave-assited organocatalyzed enantioslective Diels−Alder reaction between cyclopentadiene and cinnamaldehyde, ingeniously discovered by MacMillan.[8]

According to List and Barbas reports, aldol reaction of acetone with a variety of aldehydes allows isolation of the product with good to high enantioselectivities and yields but requires reaction times of 4−72 h and 20−30 mol % of L-proline.[3] Therefore, this reaction is a subject suitable for investigating the impact of microwaves on product selectivity, shortening reaction time, and catalyst efficiency.

Table 1. Aldol Reaction Optimized Studies



1 2a 3a

entry	mol % of catalyst	temp[a] (°C)	power[b] (W)	time (min)	yield[c] (%)	ee[d] (%)
1[e]	30	rt		240	68	76
2	30	200		15	nd[f]	
3	30	100		15	nd[f]	
4	30	60		15	nd[f]	
5	30	120	15	15	nd[f]	
6[g]	30	35	15	15	64	72
7[h]	30	35		15	42	62
8[g,i]	30	36	15	15	nd[f]	
9[g]	30	25	10	15	68	74
10[g]	20	35	15	15	69	70

[a] All temperatures were measured externally by an IR sensor. [b] Application of a constant power. [c] Isolated yields after purification by column chromatography on silica gel. [d] ee's were measured by chiral super fluid chromatography (SFC). [e] Result obtained without microwave irradiation by List and co-workers and Barbas and co-workers; see ref 3. [f] Many byproducts were observed including mainly bisaldol product and α,β-unsaturated ketone. [g] Simultaneous air-cooling was applied using compressed air with a constant pressure of 5 bar. [h] Experiment was performed in a conventional preheated oil bath. [i] DMF was used as solvent.

We initially studied the reaction of acetone **1** with 4-nitrobenzaldehyde **2a** catalyzed by L-proline (30 mol %) in DMSO/acetone (4:1) under MW energy (Table 1).[14] All experiments were conducted in septum-sealed reaction vessels with a single-mode cavity (Biotage Initiator) to ensure an optimal reproducibility of the chemical transformations.

We investigated the reaction with a temperature-controlled program at 200 °C, corresponding to 11 °C above the boiling point of DMSO (entry 2). After performing the reaction for 15 min, a total conversion was observed, but a low quantity of desired aldol product **3a**, bis-aldol product, and many byproducts were obtained. According to this result, we deemed it necessary to decrease the temperature (entries 3 and 4). At the minimum temperature that could be applied with the temperature-controlled program (60 °C, entry 4), the reaction was cleaner; nevertheless side reactions have occurred. Consequently, we directed our attention toward irradiating at constant microwave power to improve the quality of reaction control (entry 5). Despite promoting low MW power (15 W), a high temperature was measured and many byproducts were once again detected. Fortunately, using simultaneous external cooling in order to generate low temperature,[13,15] total conversion was obtained with MW power of 15 W after 15 min, affording aldol **3a** in good yield and enantioselectivity (entry 6) comparable to the result of

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(8) For the pioneering findings, see: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Jen, W. S.; Wiener, J. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

(9) For selected references using imidazolidone-type catalysts, see: (a) Selkala, S. A.; Tois, J.; Pihko, P. M.; Koskinen, A. M. P. *Adv. Synth. Catal.* **2002**, *344*, 941. (b) Hamata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058. (c) Selkaelae, S. A.; Loskinen, A. M. P. *Eur. J. Org. Chem.* **2005**, 1620. (d) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616. (e) Gordillo, R.; Houk, K. N: MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 3543.

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(11) For selected books, see: (a) Kappe, C. O.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (b) Tiernay, J. P.; Lidström, P. In *Microwave Assisted Organic Synthesis*; Blackwell: Oxford, UK, 2005. (c) Loupy, A. In *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002.

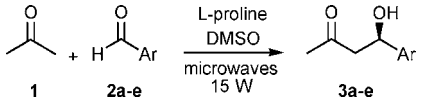
(12) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077.

(13) Rodriguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888.

(14) We have used the same conditions described by List and Barbas; see refs 3.

(15) For a review on the simultaneous cooling technique, see: Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

Table 2. L-Proline Asymmetric Aldol Reaction[a]



entry	Ar (aldehyde/aldol)	mol % of cat.	temp[b] (°C)	time (min)	conv[c] (%)	yield[d] (%)	ee[e] (%)
1	4-NO_2Ph (**2a/3a**)	20	35	15	100	69	70
2	4-CF_3Ph (**2b/3b**)	20	32	15	100	70	70
3	Ph (**2c/3c**)	30	31	60	89	70	68
4	2-Npt (**2d/3d**)	30	31	60	79	56	74
5	4-MePh (**2e/3e**)	30	32	60	82[f]	38	64

[a] Constant power (15 W) and simultaneous air-cooling using compressed air with a constant pressure of 5 bar were applied. [b] All temperatures were measured externally by an IR sensor. [c] Determined by ^{1}H NMR on the crude material. [d] Isolated yields after purification by column chromatography on silica gel. [e] ee's were measured by chiral super fluid chromatography (SFC). [f] A 1:1 ratio of aldol product **3e** and α,β-unsaturated ketone derived from aldol product **3e** was obtained.

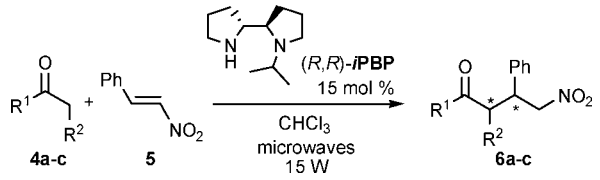
List and Barbas[3] (entry 1). Moreover, the yield and the enantioselectivity from the conventional heating (entry 7) have been slightly lower than those corresponding to MW conditions (entry 6). This result suggests that no significant specific MW effects occurs. The use of DMF as solvent led to a dirtier reaction profile (entry 8). The best result in term of selectivity was furnished with MW power of 10 W (entry 9), a result that is similar in terms of isolated yield and enantioselectivity to the original procedure (entry 1). Finally, the catalyst loading was reduced to 20 mol % of L-proline while maintaining the same reactivity and selectivity using MW power of 15 W (entry 10).

Following these encouraging results, with the optimal conditions in hand, we have examined several aromatic aldehydes **2a**−**e** to confirm the efficiency of MW activation for this aldol reaction (Table 2).

The reactivity differs significantly depending on the type of aldehyde. Aromatic aldehydes bearing an electron-withdrawing group such as α,α,α-trifluoro-*p*-tolualdehyde **2b** reacted similarly to the model substrate 4-nitrobenzaldehyde **2a**, and the aldol product **3b** was formed in the same range of yield and ee value (entry 2). However, benzaldehyde **2c**, a hindered aromatic aldehyde such as 2-naphthaldehyde **2d**, an and aromatic aldehyde bearing an electron-donating group such as *p*-tolualdehyde **2e** have shown a slower reactivity. Nevertheless, an increase of catalyst loading from 20 to 30 mol % has resulted in nearly complete conversion after only 60 min (entries 3−5). In contrast to other aromatic aldehydes **2a**−**d**, reaction of acetone **1** and *p*-tolualdehyde **2e** has provided a 1:1 ratio of aldol product **3e** and α,β-unsaturated ketone, probably due to electron-donating properties of the later (entry 5). Finally, irrespective of the substitution pattern, significant rate enhancements without affecting enantioselectivity were achieved regardless of the aromatic aldehyde (entries 1−5).

To further generalize the benefits of MW activation, we then studied our *i*PBP-catalyzed asymmetric conjugate addition of Michael donors **4a**−**c** to β-nitrostyrene **5** using MW technology (Table 3).

Table 3. Asymmetric Conjugate Addition[a]



entry	R^1, R^2 (substr. /prod.)	temp[b] (°C)	time (h)	conv[c] (%)	yield[d] (%)	dr[c] *syn*:*anti* (%)	ee[e] (%)
1[f]	Me,OH (**4a/6a**)	rt	168	100	79	17:83	98 (*R*,*R*)
2	Me,OH (**4a/6a**)	28	4	100	83	11:89	98 (*S*,*S*)
3[f]	H,*i*Pr (**4b/6b**)	rt	48	100	99	87:13	73 (*R*,*S*)
4	H,*i*Pr (**4b/6b**)	27	1	100	97	90:10	78 (*S*,*R*)
5[g]	H,*i*Pr (**4b/6b**)	28	5	80	79	88:12	79 (*S*,*R*)
6	H,$(Me)_2$ (**4c/6c**)	27	2	80	76		77 (*S*)

[a] Constant power (15 W) and simultaneous air-cooling using compressed air with a constant pressure of 5 bar were applied. [b] All temperatures were measured externally by an IR sensor. [c] Determined by ^{1}H NMR on the crude material. [d] Isolated yields after purification by column chromatography on silica gel. [e] ee's of the major diastereoisomer were measured by chiral super fluid chromatography (SFC). [f] Result obtained without microwave irradiation by our group using (*S*,*S*)-***i*PBP**; see ref 7. [g] 5 mol % of (*R*,*R*)-***i*PBP** was used.

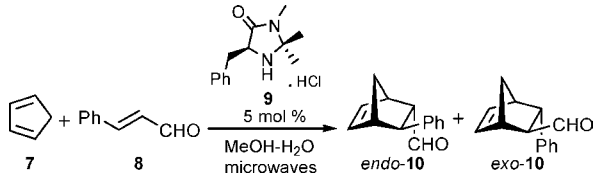
Although our methodology using *N*-^{i}Pr-2*S*,2′*S*-bipyrrolidine (*i*PBP) has afforded Michael adducts in high yields and with excellent selectivities, long reaction times were sometimes necessary to reach total conversion.[7d] Consequently, we were interested in improving the reaction rate thanks to MW irradiation. Under a power-controlled program using simultaneous external cooling, hydroxyacetone **4a** underwent the Michael addition in full conversion after 4 h (entry 2), whereas at room temperature without microwave activation the reaction was completed in 7 days (entry 1).[16] Furthermore, this impressive rate enhancement operated without loss of selectivity. Besides improving the reaction with ketone donor, microwave energy could be applied to hindered aldehydes donors. Isovaleraldehyde **4b**, under MW power of 15 W, yielded complete conversion after only 1 h (entry 4) with selectivities comparable to literature data (entry 3). MW irradiation has allowed the reaction rate to decrease from 2 days to 1 h in this case. Likewise, reaction with isobutyraldehyde **4c** has given 80% conversion after only 2 h (entry 6), whereas full conversion was reached in 3 days[7d] at room temperature. Hence, MW activation was revealed to be general with regard to Michael donors (entries 2, 4, and 6). Delightfully, a decrease of catalyst loading was allowed until 5 mol % with good reactivity and selectivity (entry 5). This difference between room-temperature reactions and microwave-assisted reactions in chloroform, a transparent nonpolar solvent for MW, could point to a specific microwave effect.[17] However, more extensive studies should be accomplished to confirm this hypothesis.

Next, we turned our attention to microwave-mediated enantioselective Diels−Alder reaction between cyclopentadiene **7** and cinnamaldehyde **8** catalyzed by MacMillan imidazolidinium salt **9** (Table 4).[18]

(16) We have used the same conditions described by our group; see ref 7.

(17) For a review on specific MW effects, see: Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

Table 4. Asymmetric Diels−Alder Reaction



entry	temp[a] (°C)	power[b] (W)	time (h)	conv[c] (%)	yield[d] (%)	dr[c] *exo*: *endo*	ee[e] *exo* *endo* (%)
1[f]	23		21	100	99	1.3:1	93(2*S*) 93(2*S*)
2	90[g]	70	0.5	80	79	1.2:1	50(2*S*)[h]50(2*S*)[h]
3	65[i]	50	1	84	82	1.2:1	78(2*S*)[h]78(2*S*)[h]
4[j]	65		1	75	72	1.5:1	85(2*S*)[h]85(2*S*)[h]

[a] All temperatures were measured externally by an IR sensor and simultaneous air-cooling using compressed air with a constant pressure of 5 bar was applied. [b] Application of a constant power. [c] Determined by ^{1}H NMR on the crude material. [d] Isolated yields after purification by column chromatography on silica gel. [e] ee's were measured by chiral super fluid chromatography (SFC). [f] Result obtained without microwave irradiation by MacMillan and co-workers; see ref 14. [g] A pressure of 3 bar was measured by a noninvasive sensor. [h] ee's were determined on the primary alcohols coming from the reduction of the aldehydes **10**. [i] A pressure of 1 bar was measured by a noninvasive sensor. [j] Experiment was performed in a conventional preheated oil bath using a sealed tube.

The higher the power, the higher was the temperature, and consequently, the lower was the enantioselectivity (entries 2 and 3). We have identified a MW power of 50 W as the best compromise in terms of reactivity and selectivity (entry 2). Even if the enantioselectivity in the microwave-assisted reactions decreased (entries 2 and 3) compared to the MacMillan result (entry 1), the reaction rate was clearly accelerated. No difference was observed under conventional oil bath heating, which led to comparable conversion with similar reaction time, emphasizing that no specific microwave effects took place (entry 4). Although a decrease of enantioselectivity was observed both under MW activation and conventional thermal conditions, this Diels−Alder reaction catalyzed by MacMillan imidazolidinium salt **9** was thermally accelerated.

In conclusion, we have shown the impact of MW activation in aldol reaction, conjugate addition, and Diels−Alder reaction where three different organocatalysts were used. In all cases, reaction time was dramatically shortened without loss of selectivity. Most importantly, the catalyst loading in the conjugate addition could be decreased from 15 to 5 mol % while maintaining good reactivity. A specific microwave effect may be involved in the Michael addition where a nonpolar solvent transparent to MW is used but probably not in aldol and Diels-Alder reactions where thermal effects should predominate as a result of the polar nature of the solvent: DMSO, MeOH/H_2O. The full scope and extensive mechanistic studies of microwave-assisted reactions are presently being investigated.

Acknowledgment. We thank Matthieu Tissot for synthesizing MacMillan imidazolidinium salt during his bachelor training period (University of Geneva), Gaëlle Bailat for technical assistance (University of Geneva), and the Swiss National Science Foundation (grant 200020-105368) for financial support.

Supporting Information Available: Experimental procedures, ^{1}H spectra, chiral separations for compounds **3a**−**e**, **6a**−**c**, and **10** and a few examples of temperature, pressure, and microwave power profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) We have used the same conditions described by MacMillan: see ref 8.