

## Extraordinary Effect of Microwave Irradiation on Asymmetric Catalysis

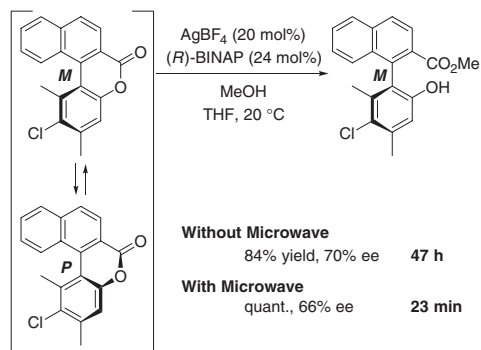
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We here report the effect of microwave irradiation on the *atropo*-enantioselective ring-opening reaction of biaryl lactones with dynamic-kinetic resolution catalyzed by AgBF<sub>4</sub>-phosphine complexes. The multimode microwave reactor with a cooling system was employed and the fiber-optic sensor was used for measurement of the accurate internal reaction temperature. It was found that the reaction was accelerated by microwave irradiation without any loss of enantioselectivity at almost the same internal temperature as the conventional conditions.

Since the first paper on the use of microwave irradiation in organic synthesis was published in 1986,<sup>1</sup> numerous articles have demonstrated the ability of microwave irradiation to shorten reaction time and drastically improve chemical yields over conventional procedures.<sup>2</sup> Although microwave acceleration in many different organic reactions has been observed, the mechanism of reaction enhancement remains controversial.<sup>3</sup> Moreover, the microwave effect on enantioselective syntheses has never been examined in detail.<sup>4</sup>

Recently we reported the *atropo*-enantioselective ring-opening reaction of biaryl lactones with dynamic-kinetic resolution<sup>5</sup> catalyzed by AgBF<sub>4</sub>-phosphine complexes.<sup>6</sup> The corresponding axially chiral compound was obtained in good-to-high yields with good-to-high enantioselectivities, though the reaction time was longer than 24 h. One effective solution to shorten the reaction time was the addition of a tertiary amine, such as triisobutylamine. This time, it was discovered that microwave irradiation at ambient temperature was also effective for enhancing this reaction. Under conventional conditions, the product was obtained in 84% yield with 70% ee in 47 h. In contrast, microwave irradiation with cooling afforded the product in quantitative yield with 66% ee in only 23 min (Scheme 1). These results encouraged us to investigate the details of the microwave irradiation effects on the present enantioselective reaction. Herein, we report the remarkable effect of microwave irradiation on the catalytic enantioselective



Scheme 1.

ring-opening reaction of biaryl compounds using AgBF<sub>4</sub>-phosphine complexes.

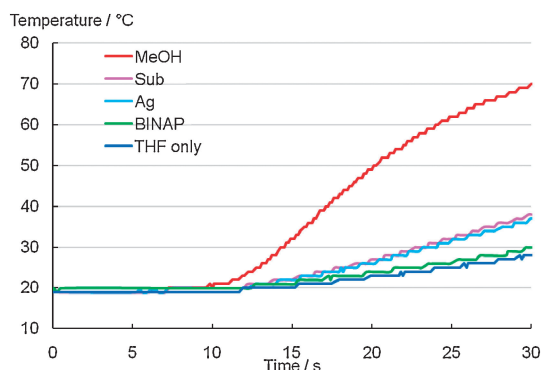
In this experiment, a EYELA Wave Magic MWO-1000S, a multi-mode microwave reactor with a cooling system, was employed. The reaction vessel was dipped in the silicon-oil bath cooled by an external chiller unit (ca. 0 °C). The fiber-optical sensor was used to get accurate internal temperature as well as the thermocouple sensor of Wave Magic.<sup>7,8</sup> The stirring rate was set at 1000 rpm which was enough to stir the reactant. All the reactions were monitored by TLC analysis and quenched when the biaryl lactone **1** was completely consumed. The results for several substrates with the microwave reactor and under conventional conditions are summarized in Table 1.

Under the microwave irradiation conditions at 21.5 ± 0.7 °C, 90 min were required to complete the reaction of the lactone **1a** with methanol to afford the product in 95% yield with 68.0% ee, whereas under the conventional conditions (21.9 ± 0.1 °C), it required 240 min to afford the product in 87% yield with 69.0% ee (Entry 1). The present reaction enhancement was not caused by a simple heating of the internal temperature because if the reaction acceleration were caused by a simple thermal effect, the corresponding enantioselectivity would be reduced by more than 1% ee according to the Arrhenius plot.<sup>8</sup> When the reaction temperature was decreased, the present reaction did not go to completion at all without microwave irradiation to afford the simple kinetic resolution product in half yield because the equilibrium between both *atropo*-enantiomers was very slow. On the contrary, under the microwave conditions, the reaction was completed in 540 min and the enantioselectivity was improved to 73.0% ee (Entry 2). The reaction time of the lactone **1b** was reduced under microwave irradiation conditions from 1340 to 450 min without any loss of enantioselectivity

Table 1. The microwave effect on the ring-opening reactions of biaryl lactones

Entry	Substrate	With microwave <sup>a</sup>				Without microwave <sup>b,c</sup>			
		Temp <sup>d,e</sup> /°C	Time /min	Yield <sup>f</sup> /%	ee <sup>g</sup> /%	Temp <sup>d,e</sup> /°C	Time /min	Yield <sup>f</sup> /%	ee <sup>g</sup> /%
1	R = Cl <b>1a</b>	21.5 ± 0.7	90	95	68.0	21.9 ± 0.1	240	87	69.0
2		11.7 ± 1.1	540	98	73.0	12.1 ± 0.2	8460	55	76.6
3 <sup>h</sup>	R = H <b>1b</b>	11.1 ± 1.0	450	99	70.6	9.7 ± 0.1	1340	92	71.3
4 <sup>h</sup>	R = Me <b>1c</b>	11.5 ± 0.7	660	98	70.1	10.2 ± 0.1	2700	90	71.1
5	R = AcO <b>1d</b>	11.5 ± 1.2	690	99	68.7	10.0 ± 0.2	3450	61	70.0

<sup>a</sup>The substrate **1** (0.27 mmol) was used. <sup>b</sup>The substrate **1** (0.1 mmol) was used. <sup>c</sup>An external aluminum block was used for temperature control (ChemiStation). <sup>d</sup>Temperature was monitored by fiber-optic sensor (AMOTH FL-2000). <sup>e</sup>Average temperature and 2σ (σ: Standard deviation). <sup>f</sup>Isolated yields. <sup>g</sup>Determined by HPLC analysis. <sup>h</sup>(*R*)-H<sub>8</sub>-BINAP was used instead of (*R*)-BINAP.



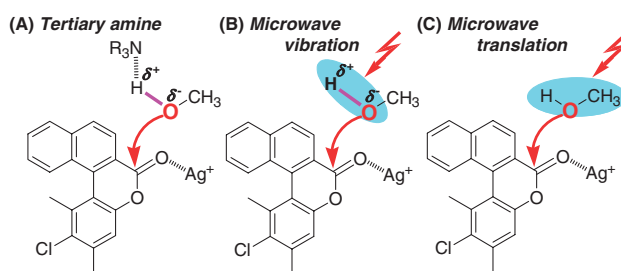
**Figure 1.** The effect of microwave irradiation (75 W) on each component of the reaction in THF using Biotage Initiator.

(Entry 3). Microwave irradiation also accelerated the reaction of the lactone **1c** to shorten the reaction time from 2700 to 660 min (Entry 4). The large acceleration effect (3450 min for 61% yield to 690 min for 99% yield) was observed in the reaction of the biaryl lactone **1d** bearing an acetoxy group (Entry 5).

According to the Arrhenius plots for these compounds,<sup>8</sup> the enantioselectivity decreased as the internal reaction temperature increased. It was observed that the value of enantioselectivity, which was obtained under the microwave irradiation conditions, was higher than the predicted value with error area in case the reaction could be accelerated by increasing the temperature of the solution. Therefore, it was confirmed on the basis of the enantioselectivity that the present acceleration was not caused by simple heating of the solution.

To determine the major component of microwave effect on the reaction acceleration, each component of this reaction was subjected to the same microwave conditions (Figure 1).<sup>9</sup> It was found that methanol was predominantly affected by microwave irradiation to increase the solution temperature. Thus, we would like to propose that the microwave irradiation affects the dipole of methanol causing the methanol molecule to rotate under an alternating electric field with high frequency. The energy of rotation might be next transferred to the vibration mode and then to the translation mode. Eventually, the solvent media would be activated to raise temperature. Based on the present observations, we would like to propose that the reaction energy might be provided through the activated methanol before the solvent media would be activated.<sup>2c</sup> For example, the O–H bond vibration in methanol could increase its nucleophilicity to enhance the whole reaction (Figure 2B). This hypothesis would be consistent with the triisobutylamine effect mentioned above (Figure 2A). Alternatively, the methanol molecule activated in translation mode could effectively attack the substrate to enhance the whole reaction (Figure 2C). In both cases, the reaction might effectively proceed by the activated nucleophile before the energy was transferred to the reaction media to raise the reaction temperature. As a result, the reaction temperature is maintained, and the enantioselectivity is not affected.

In conclusion, the *atropo*-enantioselective ring-opening reaction of biaryl lactones catalyzed by silver–phosphine complexes was drastically enhanced under microwave irradiation conditions while maintaining the enantioselectivity. This remarkable effect would not be a simple thermal effect but an activation of the nucleophile methanol by microwave irradiation.



**Figure 2.** Postulated activation models for methanolysis.<sup>10</sup>

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- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.
- MeOH (10.1 mmol), substrate **1a** (0.10 mmol), AgBF<sub>4</sub> (0.020 mmol), and BINAP (0.024 mmol) were examined in THF (1.5 mL) respectively. The increase of temperature was used as probe for the investigation of component which was most affected by microwave irradiation among these reactants.
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