

## Microwave Effects in Metal-Catalyzed Reactions

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**Abstract:** Several reviews have been published on the application of microwaves to various aspects of chemistry, such as heterogeneous catalysis and eco-friendly green chemistry. In particular, the investigation of metal-catalyzed reactions, such as Suzuki-Miyaura and Heck reactions, has attracted the attention of organic chemists. The aim of this review is to show how microwave effects have been used in metal-catalyzed reactions.

**Keywords:** Microwave effect, metal catalyst.

### INTRODUCTION

Chemists and chemical engineers have been very interested in the construction of efficient systems for organic and inorganic reactions using microwave irradiation. Microwave-driven syntheses have been widely applied in the production of organic molecules and materials in laboratory-scale experiments, because microwave irradiation effectively promotes chemical reactions [1].

Microwave effects, observed as accelerated reaction rates, increased reaction yields, and controlled reaction selectivity in chemical reactions, can be at least partially attributed to the characteristic heating mode, through the interaction of oscillating electric and magnetic fields with the substances contained in the reaction systems.

A number of microwave-driven organic reactions have been investigated beginning in the late 1980s. Several reviews have been published on the application of microwaves to various aspects of chemistry, such as heterogeneous catalysis and eco-friendly green chemistry [1]. In particular, the investigation of metal-catalyzed reactions, such as Suzuki-Miyaura and Heck reactions, has attracted the attention of organic chemists. In the case of heterogeneous metal-catalyzed reaction system, solvent is heated by dielectric loss and the metal catalyst is directly heated by magnetic loss and/or dielectric loss under microwave irradiation. Furthermore, solid metal-catalyst with large magnetic loss and/or dielectric loss should act as a susceptor (microwave absorber) and could provide with the heated surface at much higher temperature than a bulk temperature as the reaction field under microwave irradiation. This characteristic heating mode "nonequilibrium local heating" can lead to microwave effects as accelerated reaction rates.

The aim of this review is to show how microwave effects have been used in metal-catalyzed reactions. In this review, most of the examples were published between 2008 and 2010.

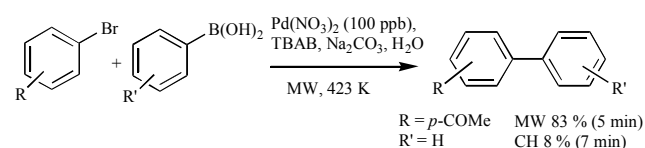
### LITERATURE SURVEY

#### Suzuki-Miyaura Coupling

The transition metal-catalyzed Suzuki-Miyaura cross-coupling reaction is one of the most efficient methods in organic chemistry for the construction of C-C bonds [2]. Palladium is a particularly efficient catalyst for the Suzuki-Miyaura reaction. However, many of these catalyzed reactions are sluggish under conventional heating. Furthermore, many of these procedures use expensive complex ligands and hazardous organic solvents. There have been several reports of the use of microwave heating [3].

In 2003, Leadbeater, *et al.* reported the Pd-catalyst-free Suzuki-Miyaura coupling of aryl halides with aryl boronic acids under microwave irradiation [4]. A focused, single-mode microwave synthesis system (CEM Discover) was used for the reactions. The temperature of the solution was monitored by an IR sensor in the microwave system. 4-Bromoacetophenone (1 mmol) and phenylboronic acid (1.3 mmol) were converted to *p*-phenylacetophenone (98%) without a Pd catalyst at 423 K for 5 min under microwave irradiation. In this reaction, water (2 mL) was used as a solvent, and Na<sub>2</sub>CO<sub>3</sub> (3.8 mmol) was used as a base. Compared to the microwave reaction system, conventional heating required a longer time (91%, 5 h).

In 2005, the same authors reassessed the Pd-catalyst-free Suzuki-Miyaura coupling methodology reported in 2003. They found the ppb level of palladium in the reaction mixture to be below the level of detection of their apparatus (0.1 ppm) [5]. 4-Bromoacetophenone (1.0 mmol) and phenylboronic acid (1.3 mmol) were converted to *p*-phenylacetophenone (98%) at 423 K for 5 min (MW power: 150 W), as shown in Scheme 1. In this reaction, Pd(NO<sub>3</sub>)<sub>2</sub> (0.000016 mol%, 100 ppb) and tetrabutylammonium bromide (TBAB) (1.0 mmol) were used as catalysts, water (2 mL) was used as a solvent, and Na<sub>2</sub>CO<sub>3</sub> (3.7 mmol) was used as a base. The optimal amount of catalyst for the reaction was much smaller under microwave irradiation than when using classical heating. The microwave irradiation not only provided the heating conditions, but also activated the catalyst.

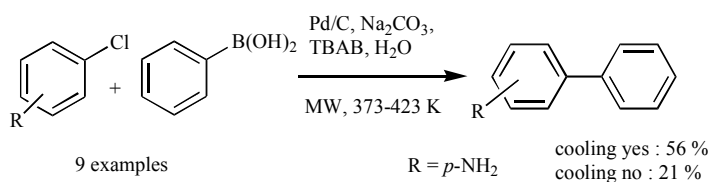
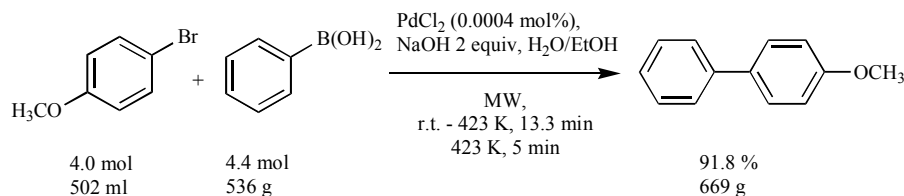
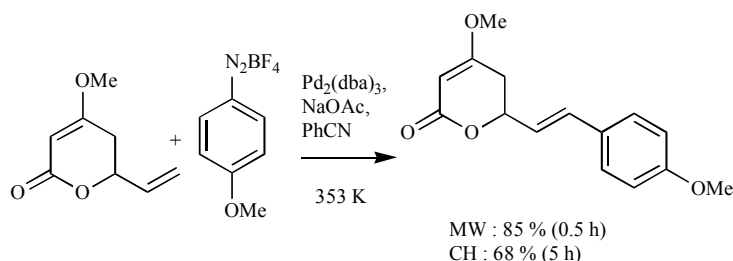


**Scheme 1.** Suzuki-Miyaura coupling using only a ppb level of Pd catalyst.

In the same year (2005), the same authors focused on a heterogeneous reaction system and presented a methodology for Pd/C catalyst Suzuki-Miyaura coupling of aryl chlorides with phenylboronic acid [6]. The temperature of the solution was measured with a fiber-optic device inserted into the reaction vessel. In this reaction system, the carbon was used as a microwave susceptor.

*p*-Chloroaniline (1.0 mmol) and phenylboronic acid (1.3 mmol) were converted to 4-aminobiphenyl (56%) at 393 K for 10 min (MW power: 300 W), as shown in Scheme 2. In this reaction, Pd/C (1 mol%, 0.5 ppm) and TBAB (1 mmol) were used as catalysts, water (2 mL) was used as a solvent, and Na<sub>2</sub>CO<sub>3</sub> (3.7 mmol) was used as a base. The authors reported that simultaneous cooling, in conjunction with microwave irradiation, prolonged the lifetime of the aryl chloride substrates during the course of the reaction.

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**Scheme 2.** Microwave-Assisted Suzuki-Miyaura Coupling Under Microwave with Cooling.**Scheme 3.** Suzuki-Miyaura Coupling on a Large Scale.**Scheme 4.** Pd-catalyzed Heck Reaction.

Very recently, the same authors focused on scaling up microwave synthesis through microwave batch processing [7]. The microwave unit designed by AccelBeam Synthesis made it possible to perform the synthesis on the scale of 2-12 L with three interchangeable reaction vessels (5-L, 9-L, and 13-L glass vessels (pressures up to 350 psi (24.1 bar)) with a fiber-optic temperature probe. The reactor employed three 2.45 GHz water-cooled magnetrons rated at 3 kW each, with accessible power of 2.5 kW each, for a total maximum allowed output of 7.5 kW.

4-Bromoanisole (502 mL, 4.00 mol) and phenylboronic acid (536 g, 4.4 mol) were converted to 4-aminobiphenyl (91.8%, 669 g) on a large scale (9.4 L), as shown in Scheme 3. The reaction was heated to 423 K using 7.5 kW (2.5 kW  $\times$  3) (ramp time 13.3 min). At 423 K the magnetron power was modulated to remain steady (300 W; 100 W  $\times$  3) for 5 min. In this reaction, 0.0004 mol% PdCl<sub>2</sub> (1.6 mg, 15  $\mu$ mol) was used as a catalyst, and NaOH (320 g, 8.0 mol) was used as a base. The reaction conditions of the scaled-up microwave batch experiments were similar to those of the small-scale experiments.

### Heck Reaction

Palladium-catalyzed Heck C-C coupling is an important protocol for the coupling of aryl halides or vinyl halides and olefins in the presence of a base [8]. The first report of Heck reactions under microwave irradiation was published in 1996 by Hallberg, *et al.* [9]. There have been several recent reports of the use of microwave heating [10].

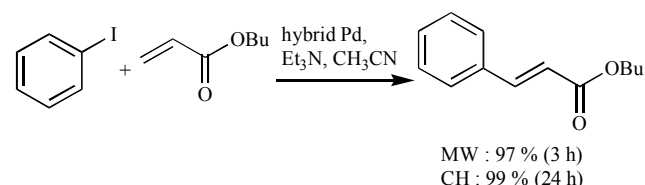
Correia *et al.* have described a highly efficient palladium-catalyzed Heck reaction of allylic esters with arenediazonium salts under microwave irradiation [11]. A focused, single-mode microwave synthesis system (CEM Discover) was used for the reactions. The temperature of the solution was monitored by an IR sensor in the microwave system.

(*E*)-4-Methoxy-6-vinyl-5,6-dihydro-2*H*-pyran-2-one (0.15 mmol) and *p*-methoxybenzenediazonium tetrafluoroborate (1.1

equiv, 0.17 mmol) were converted to (*E*)-4-methoxy-6-(4-methoxystyryl)-5,6-dihydro-2*H*-pyran-2-one (85%) at 353 K for 0.5 h, as shown in Scheme 4. In this reaction, Pd<sub>2</sub>(dba)<sub>3</sub> (4 mol%) was used as a catalyst, benzonitrile (2 mL) was used as a solvent, and sodium acetate (NaOAc) (3 equiv, 0.45 mmol) was used as a base. After conventional heating for an extended period of time (5 h), the conversion efficiency was 68%. The reaction time and reaction yields were much different when microwave heating was compared with conventional heating.

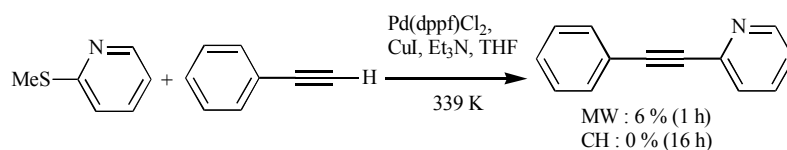
The same microwave effects were demonstrated by Vallribera, *et al.* [12]. A focused, single-mode microwave synthesis system with the PowerMax option enabled (CEM Discover) was used for the reactions. The temperature of the solution was monitored by an IR sensor in the microwave system.

Iodobenzene (53  $\mu$ mol) and butyl acrylate (81  $\mu$ mol, 1.5 equiv) were converted to 3-phenylpropenoic acid butyl ester (97%) at 403 K for 3 h, as shown in Scheme 5. In this reaction, hybrid Pd material (2.8 mg, corresponding to 1  $\mu$ mol Pd, 1.9 mol%) and Et<sub>3</sub>N (107  $\mu$ mol, 2.0 equiv) were used as catalysts, CH<sub>3</sub>CN (0.8 mL) was used as a solvent, and undecane (11.3  $\mu$ L, 53  $\mu$ mol) was added as an internal standard. Compared with the microwave reaction system, conventional heating required a longer time (99%, 24 h).

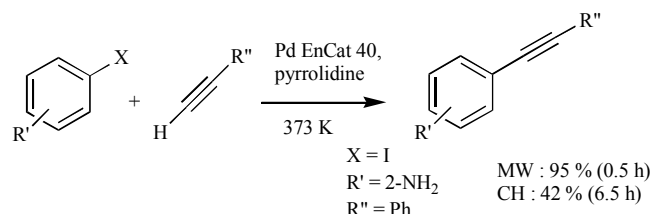
**Scheme 5.** Hybrid Pd-catalyzed Heck reaction.

### SONOGASHIRA REACTION

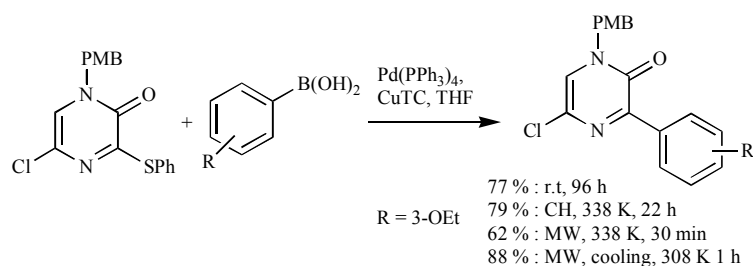
Palladium-catalyzed Sonogashira cross-coupling is an important protocol for the coupling of a terminal alkyne with an aromatic



Scheme 6. Pd-catalyzed Sonogashira reaction.



Scheme 7. Sonogashira reaction using Pd EnCat.



Scheme 8. Liebeskind-Srogl Cross-Coupling Reaction under Different Heating Conditions.

halide in the presence of a copper (I) co-catalyst [13]. The first report of Sonogashira cross-coupling reactions using microwave irradiation was published by Erdelyi, *et al.* in 2001 [14]. There have been several recent reports of the use of microwave heating [15].

Shook, *et al.* reported a novel microwave-assisted palladium-catalyzed Sonogashira-type coupling of terminal alkynes with a variety of heteroaryl thiomethylethers [16]. A focused, single-mode microwave synthesis system (CEM Explorer) was used for the reactions.

2-(Methylthio)pyridine (0.80 mmol) and phenylacetylene (1.60 mmol) were converted to 2-(phenylethynyl)pyridine (6%) at 339 K for 1 h under microwave irradiation, as shown in Scheme 6. In this reaction, CuI (0.16 mmol) and Pd(dppf)Cl<sub>2</sub> (0.08 mmol) were used as catalysts, Et<sub>3</sub>N (1.60 mmol) was used as a base, and tetrahydrofuran (THF) (1.60 mmol) was used as a solvent. After conventional heating for an extended period of time (16 h), no product resulted (0% yield).

The same microwave effects were demonstrated by Ribecai, *et al.* [17]. The authors described the copper- and solvent-free Sonogashira-type alkylation of aryl iodides and bromides using Pd EnCat<sup>TM</sup>. A CEM Explorer with an IR temperature control system was applied as a microwave unit.

2-Iodoaniline (4 mmol) and phenylethyne (6 mmol, 1.5 equiv) were converted to 2-(phenylethynyl)aniline (42%) at 373 K for 0.5 h, while conventional heating gave less than a 50% yield after 6.5 h, as shown in Scheme 7. In this reaction, Pd EnCat (0.01 mol%) was used as catalyst, and pyrrolidine (8 mmol, 2 equiv) was used as a base. Compared with conventional heating, microwave heating allowed a drastic reduction of the reaction time, enhancement of yields, and a 10-fold reduction of the catalyst loading.

### LIEBESKIND-SROGL CROSS-COUPLING

The Liebeskind-Srogl cross-coupling reaction is a typical palladium-catalyzed, copper(I)-mediated, base-free coupling of a boronic acid with a  $\pi$ -deficient heteroaromatic thioether under con-

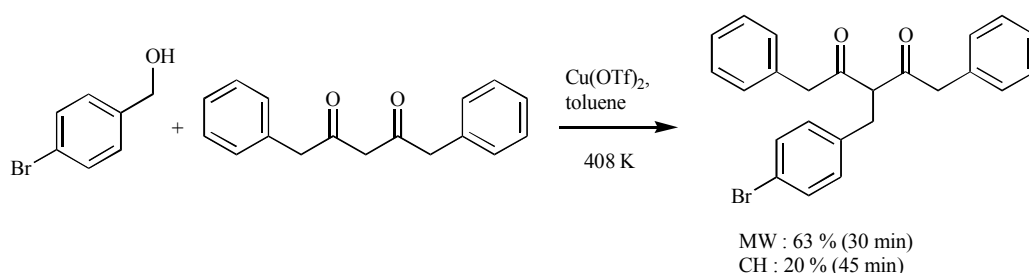
ventional heating [18], and under microwave irradiation [19]. In 2004, a trailblazing report about microwave-assisted Liebeskind-Srogl cross-coupling reactions was published by C. O. Kappe, *et al.* [20].

Eycken, *et al.* performed a palladium-catalyzed copper(I)-mediated cross-coupling of arylboronic acids and 2(1H)-pyrazinones under microwave irradiation with simultaneous cooling [21]. A focused, single-mode microwave synthesis system (CEM Discover CoolMate) was used for the reactions. The temperature was measured with a fiber optic device inserted into the reaction vessel.

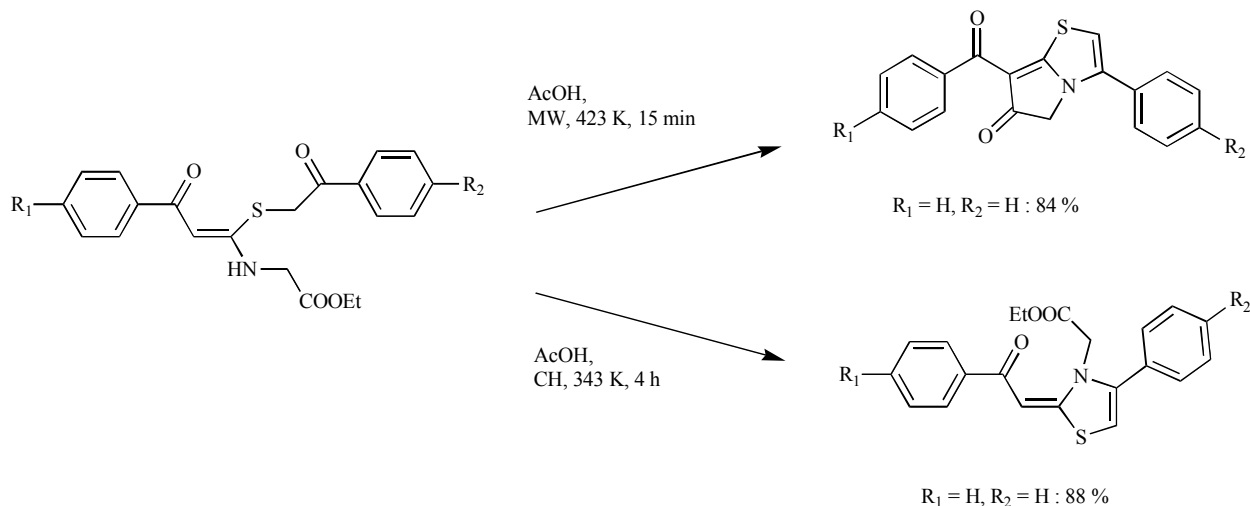
1-(4-Methoxybenzyl)-3-(phenylthio)-5-chloropyrazine-2(1H)-one (0.21 mmol) and 3-ethoxyphenylboronic acid (0.63 mmol, 3 equiv.) were converted to 1-(4-methoxybenzyl)-3-(3-ethoxyphenyl)-5-chloropyrazine-2(1H)-one (88%) in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) and copper (I) thiophene-2-carboxylate (CuTC) (2.0 equiv.) in 3 mL of THF solution, as shown in Scheme 8. In this reaction, the reaction mixture was heated at 308 K for 1 h by continuous microwave irradiation at a maximum power of 300 W with cooling. Compared with the microwave reaction system with cooling, the microwave reaction system at 338 K without cooling resulted in a lower yield (62%, 30 min). It is interesting that the full conversion at 338 K for 22 h under conventional heating (79%) was higher than that of the microwave system without cooling (62%). The authors concluded that the high and sustained microwave power input with cooling of the bulk solution clearly had an impact on the reactions.

### DEHYDRATIVE C-C COUPLING REACTIONS

C-C coupling reactions of alkyl halides and pseudohalides with active methylenes are imperative protocols in organic chemistry. In general, these procedures use an excess amount of base. Recently, Lewis or Bronsted acid-catalyzed C-C coupling reactions using alcohols under conventional heating have been reported [22]. However, in most of these methods, a long heating reaction time and special solvents such as MeNO<sub>2</sub> were essential.



Scheme 9. Dehydrative C-C coupling reaction.



Scheme 10. Products of cyclization REACTION Under Microwave Reaction and Conventional Reaction.

Baba and Yasuda, *et al.* performed a synthetically essential, rapid and efficient transition metal-catalyzed C-C coupling of benzylic/allylic alcohols with  $\beta$ -dicarbonyls and indoles under microwave irradiation [23]. A focused, single-mode microwave synthesis system (Biotage Initiator and CEM Discover) was used for the reactions. The temperature of the bulk solution was monitored by an IR sensor and a fiber optic thermometer (AMOTH<sup>TM</sup>-5886, Anritsu Meter Co., Ltd.) in the microwave system.

The  $\text{Cu(OTf)}_2$ -catalyzed reaction of *p*-bromobenzyl alcohol and 1,3-diphenylpropane-1,3-dione yielded 63% of the C-C coupling product in 30 min under microwave irradiation, while conventional heating gave less than a 20% yield, as shown in Scheme 9.

They screened solvents congenial to microwave irradiation for the coupling reaction of benzhydrol with acetyl acetone. Notably, the microwave-irradiated coupling reaction was effective even in more or less microwave-transparent nonpolar media, due to direct contact of the microwaves with the functional groups of reactants. The microwave irradiation not only provided the heating conditions, but also activated the substrates. Microwaves may have potential for organic synthesis as a non-thermal effect.

### CYCLIZATION REACTION

Mathew described the microwave-assisted one-pot synthesis of pyrrolo[2,1-*b*]thiazol-6-one from  $\alpha$ -aroyl ketene-*N,S*-acetals [24]. A multimode microwave reactor (Biotage Initiator) was used.

Ethyl[3-oxo-1-(2-oxo-2-phenyl-ethylsulfanyl)-3-phenylpropenylamino]acetate (1.0 mmol) was converted to 7-benzoyl-3-phenyl-pyrrolo[2,1-*b*]thiazol-6-one (84%) (denoted as A) at 423 K for 15 min under microwave irradiation, and to ethyl[2-{2-[(*Z*)-oxo(phenyl)ethylidene]-4-phenyl-1,3-thiazol-3-yl}acetate (88%) (denoted as B) at 343 K for 4 h under conventional heating, as

shown in Scheme 10. These different products were due to the fact that the geometry of the exocyclic double bond present in (initially formed) compound B was affected to a lesser extent, and the ethyl carboxylate functionality underwent rapid conformational change favoring the regioselective formation of compound A.

### DEHALOGENATION REACTION

Halogenated organic compounds must be removed from the environment. A wide variety of dehalogenation systems have been investigated over the years. There have been many reports of dehalogenation by electrochemical, biological and chemical methods. However, most of these reaction systems require long reaction times and/or the use of noble metal catalysts. In recent years, several dehalogenation methods using microwave irradiation have been reported: dehalogenation of a number of *N*-4-picoly-4-halogenobenzamides [25]; reductive dehalogenation of chlorinated phenols [26]; stereoselective dehalogenation of  $\alpha$ -halo  $\beta$ -lactams [27]; and the reduction of double bonds and hydrogenolysis of several functional groups [28].

Wada and Tsukahara, *et al.* have focused on the "nonequilibrium local heating" as an origin of the microwave effects. In order to demonstrate the enhancement in the chemical reaction caused by the "nonequilibrium local heating" they have constructed a heterogeneous reaction system containing the ferromagnetic metal particles, which can be extensively heated through the interaction with microwaves. A selected reaction system is a heterogeneous dehalogenation of the  $\text{C(sp}^3\text{)-Cl}$  bond of 4-phenylbutyl chloride with Fe particles functioning as a catalyst under microwave irradiation [29]. A microwave synthesis system (Biotage Initiator and CEM Discover) was used for the reactions. The temperature of the bulk solution was monitored by IR, and the validity of the measured tem-

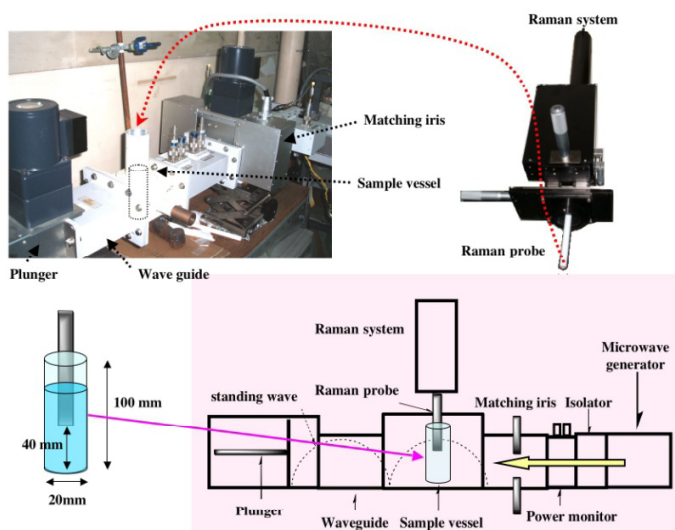
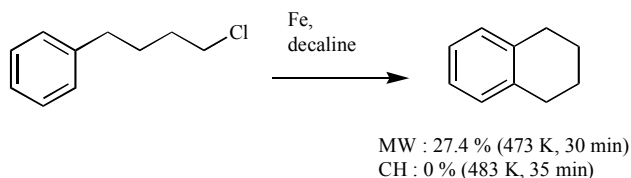


Fig. (1). Single-mode microwave apparatus and in situ Raman system.

perature was confirmed using a fiber optic thermometer (AMOTH<sup>TM</sup>-5886, Anritsu Meter Co., Ltd.).

Scheme 11 shows 4-phenylbutyl chloride converted to 1,2,3,4-tetrahydronaphthalene (27.4%) at 473 K for 30 min in the presence of iron particles (0.3 g) in decaline (1.9 g) solution. Conventional heating yielded no product at 483 K for 35 min (0% yield). In the case of the microwave system, the Fe particles must have been heated selectively, due to the large magnetic loss of the ferromagnetic metal particles, resulting in nonequilibrium local heating under microwave irradiation. The Fe particles must have had a much higher surface temperature than the bulk solution temperature as the reaction field under microwave irradiation. Activation energies were ( $E_a(\text{CH})$ ) of 178 kJ/mol ( $\ln(A) = 32$ ) and ( $E_a(\text{MW})$ ) of 154 kJ/mol ( $\ln(A) = 31$ ) for dehalogenation of 4-phenylbutyl chloride with the conventional system and the microwave system, respectively. Estimating from the difference in the activation energy ( $\Delta E_a = 24$  kJ/mol) in this dehalogenation reaction, the reaction field temperature for the microwave system can be estimated to be 55 K higher than the bulk solution temperature (473 K) under microwave irradiation.

The authors proposed that the microwave effects observed as accelerated reaction rates and increased reaction yields in chemical reactions can be attributed, at least partially, to the characteristic heating mode “nonequilibrium local heating.”



Scheme 11. Dehalogenative cyclization reaction with Fe particles.

#### ORIGIN OF THE MICROWAVE EFFECT

Wada and Tsukahara, *et al.* proposed that one of the most important characteristic heating modes should be “nonequilibrium local heating” [29]. The authors successfully observed the phenomenon of “nonequilibrium local heating” occurring to the dimethyl sulfoxide molecules in proximity of Co particles under microwave irradiation, using real-time *in situ* Raman spectroscopy, as shown in Fig. (1). A microwave apparatus MMG-213VP (Micro Denshi Co., Ltd., 1500 W, 2.45 GHz) equipped with a single-mode

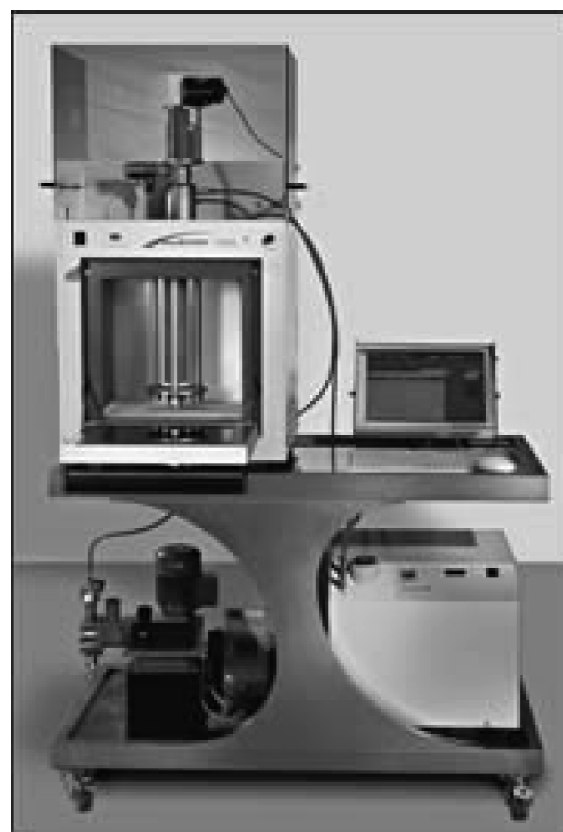
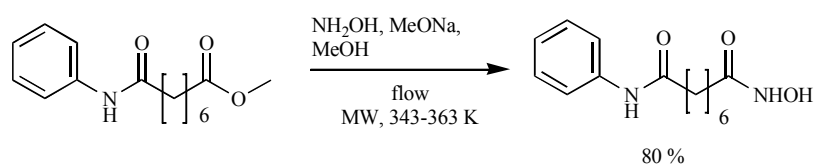


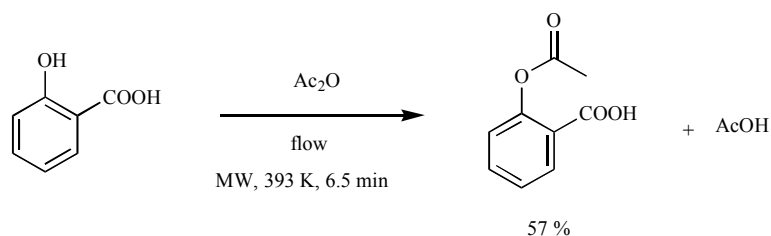
Fig. (2). Example of microwave flow reactor. Milestone FlowSYNTH (Milestone, Italy, 2.45 GHz, [www.milestonesci.com](http://www.milestonesci.com)). Reprinted with permission from [32]. Copyright 2010 American Chemical Society.

cavity was used. “Nonequilibrium local heating” is defined as the phenomenon of heating domains at much higher temperatures than the bulk solution temperature only induced under microwave irradiation. “Nonequilibrium local heating” can lead to such microwave effects as accelerated reaction rates.

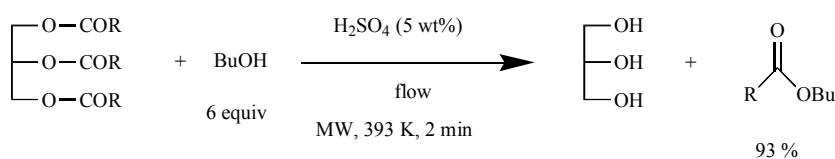
Conner, *et al.* proposed that the most significant microwave effect of chemical reactions is that microwaves can change the reaction profile (or relative temperatures) instantaneously, and often



**Scheme 12.** Synthesis of suberoylalanide hydroxamic acid under a microwave flow system.



**Scheme 13.** Synthesis of aspirin under a microwave flow system.



**Scheme 14.** Synthesis of buto-biodiesel under a microwave flow system.

periodically [30]. These changes are due to the significant differences in microwave absorption by different molecular species, particularly at their interfaces. Microwave exposure could, thus, increase reaction rates significantly by periodically providing a more favorable reaction coordinate (selective heating: changing the reaction profile).

#### SCALE-UP OF MICROWAVE PROCESSING

The scale-up of microwave processing may be the most significant challenge for microwave-driven chemistry. One of the most important factors of microwave scale-up technology should be the penetration depth of microwave irradiation into absorbing materials, depending on the frequency of the irradiating microwaves and the dielectric constant of the materials. As a result of the limitations of scale-up batch microwave systems, recent investigations of microwave scale-up processing have focused on a continuous flow microwave system with precise temperature control and efficient heating. Many of the advantages of small-scale microwave systems would be maintained when using a flow system, such as shown in Fig. (2).

Martinelli, *et al.* have reported efficient flow synthesis of hydroxamic acids and suberoylanilide hydroxamic preparation under microwave irradiation [31]. The microwave flow system was performed in a Personal Chemistry Emrys™ Optimizer apparatus. The measurement of the reaction temperature during microwave heating was achieved by a remote IR sensor. The process used was a combination of the R-2 Pump Module and the R-4 Reactor Module (Vapourtec system).

As shown in Scheme 12, in the second step, methyl suberilate (255 mg, 0.97 mmol, 1 equiv) and 50% aq hydroxylamine (0.58 mL, 9.7 mmol, 10 equiv) were converted to suberoylalanide hydroxamic acid (80% overall yield) in MeOH/MeONa solution at 363 K under the microwave flow system.

Hulshof, *et al.* reported the microwave flow processing of heterogeneous organic reactions with a Milestone FlowSynth tubular reactor (2.45 GHz) [32].

In a continuous-flow reactor, salicylic acid (207 g, 1.5 mol) and acetic anhydride (307 g, 3.0 mol) were converted to aspirin (57%) in an acetic acid solution (1228 g, 1.12 L), as shown in Scheme 13. In this reaction, the reaction mixture was heated to 393 K (253 W), the flow rate was 27 mL/min, and the residence time was 6.5 min.

Leadbeater, *et al.* reported the microwave flow processing of biodiesel derived from butanol [33]. The microwave flow system was performed in a CEM MARS unit (1600 W, 2.45 GHz). Reactions were performed in a 4 L flow-through reactor vessel. For continuous-flow experiments, a Teflon inlet tube (9.53 mm i.d.) and a Teflon outlet tube (9.53 mm i.d.) were used. The temperature of the contents of the vessel was monitored using a fiber optic probe inserted directly into the reaction mixture by means of a Teflon thermometer.

Vegetable oil (10 L) and butanol (20 L, 6 equiv) were converted to buto-biodiesel (93%) at 393 K for 2 min. In this reaction H<sub>2</sub>SO<sub>4</sub> (5 wt%) was used as a catalyst, as shown in Scheme 14.

#### SUMMARY

In almost all cases, dramatic enhancements of the reaction rate have been reported using microwave irradiation. Especially, solid metal-catalyst with large magnetic loss and/or dielectric loss should act as a susceptor (microwave absorber) and could provide with the heated surface at much higher temperature than a bulk temperature as the reaction field under microwave irradiation. This microwave effect could lead to increment of the chemical reaction rates by 10-100 fold. Compared with conventional heating processes, microwave processes could be more useful for metal-catalyzed reactions.

However, no researcher has yet identified the origin of the microwave effect or developed a full understanding of microwave-driven chemistry. In order to apply microwave-driven chemistry to various chemical reactions, it is essential to understand the mechanisms for the promotion of chemical reactions observed under microwave irradiation, and to systemize the knowledge obtained to develop microwave-driven chemistry.

Elucidation of the "microwave effect" would open up a new field of microwave-driven chemistry.

#### ACKNOWLEDGMENT

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