



## マイクロ波化学のルネサンス 9

# International perspectives on microwave heating in organic synthesis

There is renewed interest in microwave chemistry research

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After some initial false-starts, the international synthetic organic community is slowly warming to the possibility of certain strategic advantages of microwave heating in chemical synthesis.

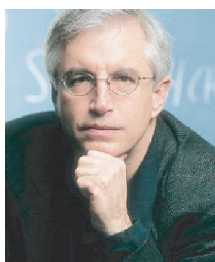
### Introduction

The Japanese chemistry community seems to have an advanced appreciation of microwave (MW) heating effects in organic synthesis. This may be due to over-exuberance in the United States and Europe during the early days of MW chemistry in attributing observed reaction outcomes to MW-specific phenomena. Once proper temperature

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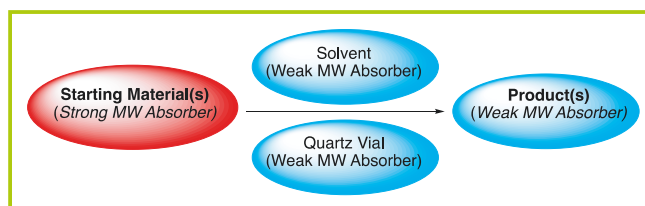


data was obtained, most observations were fully consistent with conventional heating (CH) outcomes. Eventually, a few systematic studies and influential reference books on MW chemistry advanced the unqualified conclusion that MW heating in organic synthesis is no different — nor can it be any different — than CH<sup>1,2</sup>. Meanwhile, MW chemistry gained traction as an important tool for convenient heating of reaction mixtures to high temperatures and pressures, offering clear tactical advantages for chemical synthesis.

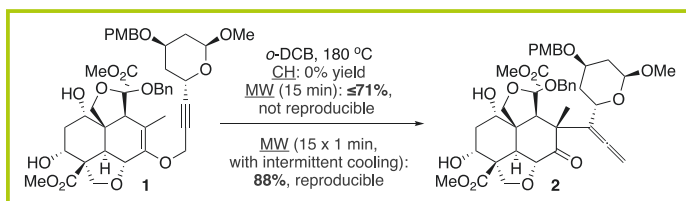
Some reaction observations, however, remain difficult to reconcile with physical organic theory, contributing to a persistent anecdotal lore of nonobvious and/or poorly understood MW-specific effects. Indeed, synthetic chemists typically note the use of MW heating as an experimental detail in their synthetic procedures. Strategic applications of microwave chemistry are now coming back into focus<sup>3</sup>.

### Strategic application of MW heating in organic synthesis

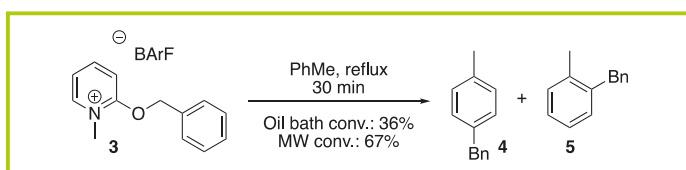
One design philosophy is based on maximizing selective heating of solutes by focusing on three main variables: solvent polarity, solute polarity, and reaction vessel material (Scheme 1). In order to maximize heating of the solutes, the MW absorption of the other components is minimized as much as possible. Reactions conducted using poorly MW absorbing solvents serve two purposes: namely, to minimize direct heating of the solvent and to facilitate aggregation of the



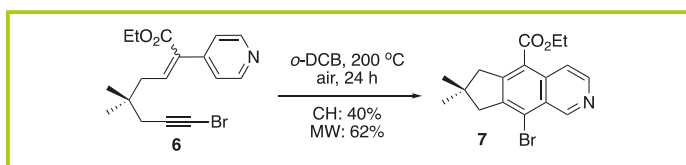
Scheme 1 Design of MW reaction system to allow maximum MW radiation absorption of starting materials.



**Scheme 2** Strategic application of MW heating in a thermal Claisen rearrangement.



**Scheme 3** MW-specific acceleration of a thermal Friedel-Crafts benzylation reaction.



**Scheme 4** MW-specific improvement in a thermal oxidative cycloisomerization.

polar solutes. MW absorption by the reaction vessel can be minimized using quartz vessels, which absorb significantly less MW radiation than standard Pyrex vessels. Finally, if the solutes themselves possess differential polarity, namely that a specific starting material and/or key reagent is uniquely susceptible to MW heating, then maximum differences between MW and CH should be observable throughout the course of the reaction.

Specific examples of MW heating providing a strategic advantage — i.e., to achieve a reaction outcome that cannot be achieved with CH — are provided in Schemes 2–4. The top example (Scheme 2) comes from a multi-step synthesis endeavor from the Ley group, in which a key Claisen rearrangement could only be achieved using MW heating. Moreover, cycling between heating and cooling cycles provided superior results as compared with continuous MW heating<sup>4</sup>. It is hard to rectify the benefits of periodic cooling of a thermal reaction with current physical organic reaction theory, highlighting the need for further research into MW-specific effects. The next example

(Scheme 3) highlights our research into the rational design, execution, and quantitative analysis of reactions that benefit from selective MW heating, in accord with the design criteria outlined above (cf. Scheme 1). We ultimately observed >7x-fold rate enhancements in MW reactions of salt **3**, and we eventually achieved similar outcomes in other systems<sup>5,6</sup>. Finally, the strategic advantage of MW heating in a key oxidative cycloisomerization from our synthesis of illudinine is recounted in Scheme 4<sup>7</sup>. We found that MW heating outperformed CH, including in providing a higher yield of product at all temperatures and times measured. These (and perhaps other) examples of MW-specific advantages may be attributable to selective MW heating of starting materials over products, with MW heating perhaps specifically arising by unique interactions with polar solute aggregates in nonpolar solution<sup>3</sup>.

### Future directions and conclusions

The strategic value of MW heating for reaction enhancement is recognized in Japan and regaining traction internationally. A great step forward will be to design reaction systems that exhibit broader generality, either in terms of substrate scope for a single type of transformation or in which MW enhancements can be observed for several different types of reactions. Current efforts should be aimed at realizing these goals.

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