Microwave-Assisted Organic Synthesis for Combinatorial Chemistry
Theory behind microwave heating

Microwaves:  
- $\lambda = 12.2$ cm (2450 MHz)  
- induce rotation of dipoles ($H_2O, DMF$)  
- rotation speed: about $5 \times 10^9$ s$^{-1}$  
- nonpolar molecules (toluene, $CCl_4$) are inactive  
- effect: fast heating (up to 10°C / s)  
- positive: local overheating is minimized
Microwaves in combinatorial chemistry?

**General problem in combinatorial chemistry:**
solid-supported reactions are slow, because of inhomogenity
For example: reaction times of Diels-Alder reactions:
- some hours in solution
- up to days with solid-support

**Positive effects of microwaves in combinatorial chemistry:**
- dramatic rate acceleration
- increased purity and yields of products (no overheating)
Microwave reactors

Two types of microwave reactors:

a) multi-mode reactor (kitchen microwave oven)
   inexpensive, but electric field is not homogenous (local hot spots)

b) mono-mode reactor:
   homogenous field, temperature control possible, used for small-scale reactions
Two major categories

1. Reactions with solvent:
   - Evaporation of solvent is dangerous, so teflon vials are necessary

2. Reactions without solvent:
   - Reactions in open vessels, fire hazards are minimized
Reactions with solvent

a) Peptide coupling:

with normal heating only 80% yield
Reactions with solvent

b) Reactions with fluorous compounds:
- highly fluorinated compounds: insoluble in organic solvents and water at 20°C
- become soluble when heated
- combine advantages from solid-phase and solution-phase chemistry

Example:

\[
\begin{align*}
(C_6F_{13}CH_2CH_2)_3SnR_1 + R_2-X & \xrightarrow{\text{PdCl}_2(PPh_3)_4, \text{LiCl, DMF, microwave (60W)}} \quad R_1-R_2 \quad 15.3 \\
& \quad \text{LiX} \quad \text{Organic Phase} \\
& \quad \text{1.5 - 2 min} \\
& \quad \text{(C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_3\text{SnCl} \quad \text{Fluorous Phase}
\end{align*}
\]

three phase extraction (fluoroheptanes, dichlormethane, water) gives good yield of Stille coupled product
Microwave-assisted solvent-free reactions

a) Reaction mixture adsorbed onto mineral oxides:

short reaction time, so it’s possible to make many derivates and screen them for antibacterial activity
Microwave-assisted solvent-free reactions

b) Use of phase-transfer-catalyst:

PEG is a soluble polymeric support for small-molecule synthesis. High molecular weight PEG is a solid at 20°C, but melts at 45-50°C. Easy purification after reaction.
Microwave-assisted solvent-free reactions

c) Neat solid reagents:

Dry mixture of reactants is heated with microwaves
Normally 24 h reaction time
Summary

Benefits of microwave heating:

• acceleration of reaction speed (important for drug design and screening)
• improved yield and purity of products

Literature: