GREEN CHEMISTRY

Laurea Magistrale in Scienze Chimiche

Prof. Leucio Rossi

6 CFU – AA 2016-2017

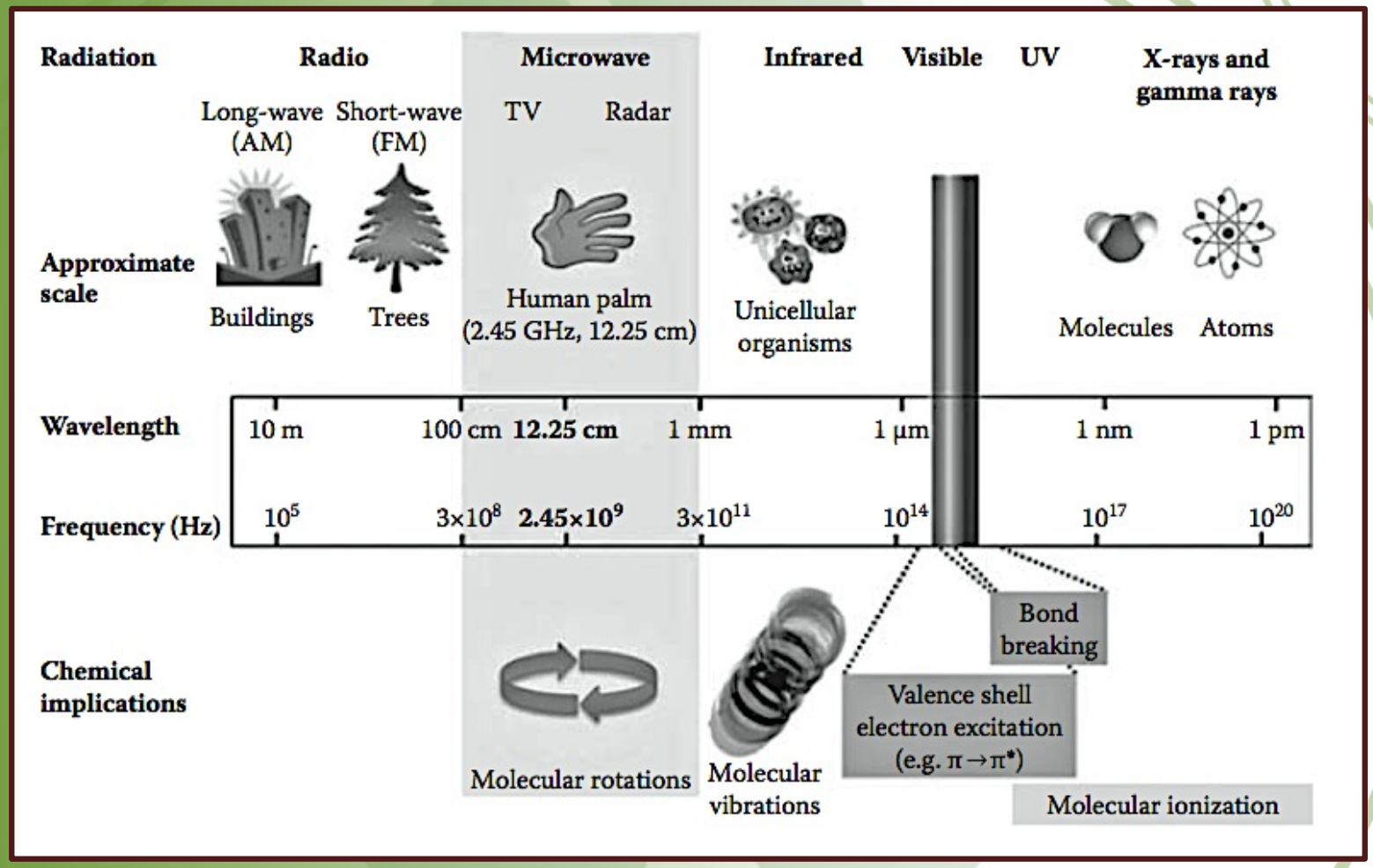
Green Chemistry 10

GREEN TECHNIQUES FOR ORGANIC SYNTHESIS II

MICROWAVE SYNTHESIS

INTRODUCTION

Introduction



Introduction

Since applications such as wireless devices (2.4 to 5.0 GHz; U.S.), satellite radio (2.3 GHz), and air traffic control operate in this range, regulatory agencies allow equipment for industrial, scientific, and medical (ISM) use to operate at only five specific frequencies: 25.125, 5.80, 2.45, 0.915, and 0.4339 GHz.

Introduction

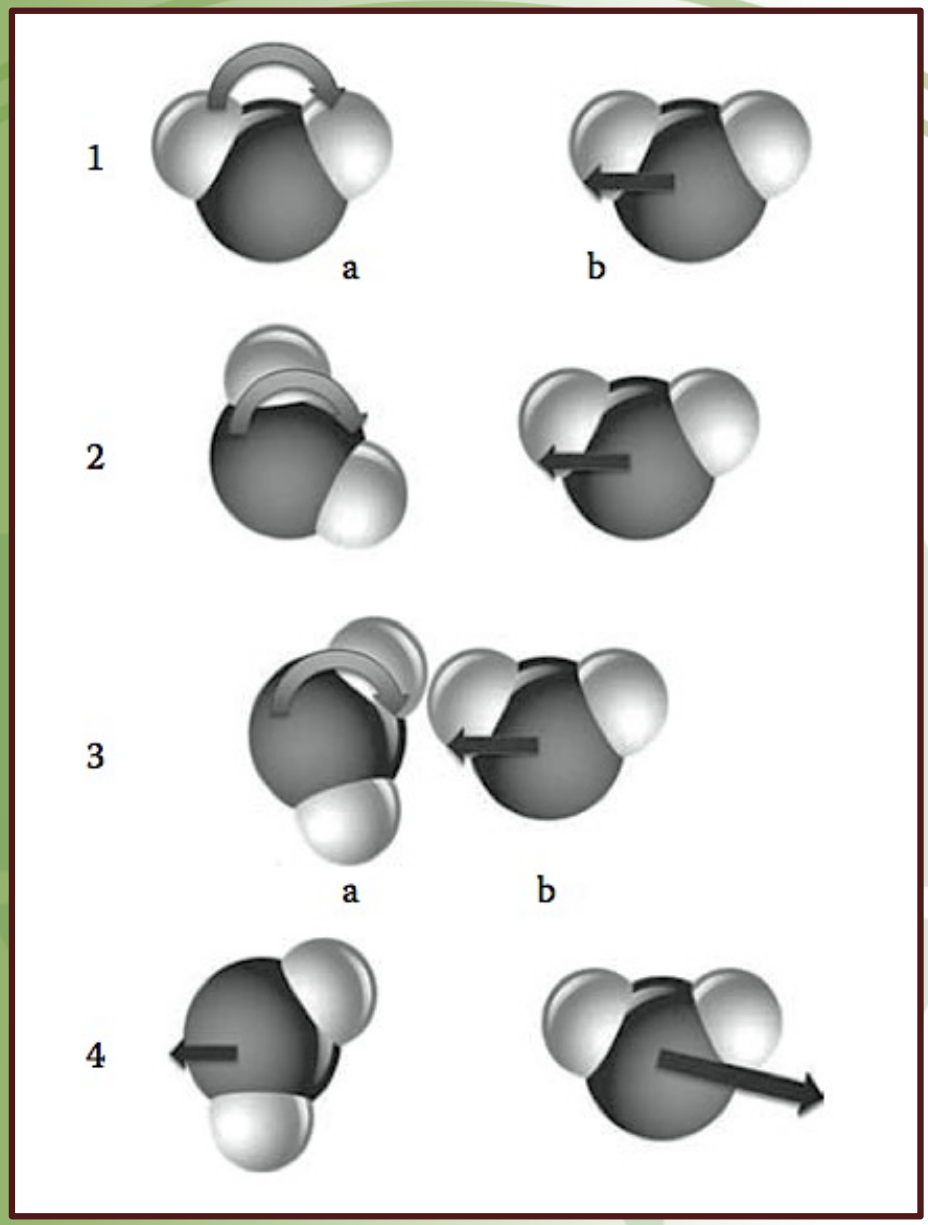
- Microwave heating is based on the ability of a particular substance such as a solvent or substrate to absorb microwave energy and effectively convert the electro- magnetic energy to heat (kinetic energy).
- Molecules with a dipole moment (permanent or induced) attempt to align themselves with the oscillating electric field of the microwave irradiation, leading to rotation.
- Molecules in the liquid or gas phase begin to be rotationally sympathetic to inci- dent electromagnetic irradiation when the frequency approaches 10^6 Hz.

Introduction

- **The optimal frequency at which a molecule turns incident electromagnetic radiation into kinetic energy is a function of many component parts, including the permanent dipole moment, the size of the molecule, and temperature.**

- **For most small molecules, the relaxation process is most efficient in the microwave region (0.3–300 GHz) of the electromagnetic spectrum.**

Introduction



Introduction

TABLE 1.1
Dielectric Constant (ε′), Dielectric Loss (ε″), and Loss Tangent (tan δ) for Selected Solvents at 2.45 GHz

Solvent	Dielectric constant (ε′)	Dielectric loss (ε″)	Loss tangent (tan δ)
Water	80.4	9.89	0.123
Ethanol	24.3	22.9	0.941
DMSO	45	37.1	0.825
DMF	37.7	6.07	0.161
Acetonitrile	37.5	2.32	0.062
Acetone	20.7	1.11	0.054
DCM	9.1	0.382	0.042
THF	7.4	0.348	0.047
Ethyl Acetate	6	0.354	0.059
Toluene	2.4	0.096	0.040
Hexane	1.9	0.038	0.020

Introduction

Table 12.1 *Categorization of common reaction solvents.*

Solvent	Tan δ	Dielectric constant, ε	Green category[a]
Ethanol	0.94	24	1
Dimethyl sulfoxide	0.82	47	1
Isopropanol	0.80	0.799	1
1-Propanol	0.78	0.757	1
Methanol	0.66	33	1
Water	0.12	80	1
Ethyl acetate	0.059	6	1
Acetone	0.054	21	1
2-Butanone	0.079	18.4	1
Ethlyene glycol	1.17	38	2
Acetic acid	0.17	6.1	2
Acetonitrile	0.062	38	2
Tetrahydrofuran	0.047	7.6	2
Toluene		2.4	2
Dimethylformamide	0.16	37	3
Chloroform	0.091	4.8	3
Dichloromethane	0.042	9.1	3
1,4-Dioxane		2.2	3
1,2-Dichloroethane	0.127	10.3	3

[a] Number corresponds to the rating described in reference [5]: 1, preferred; 2, usable; 3, undesirable.

Introduction

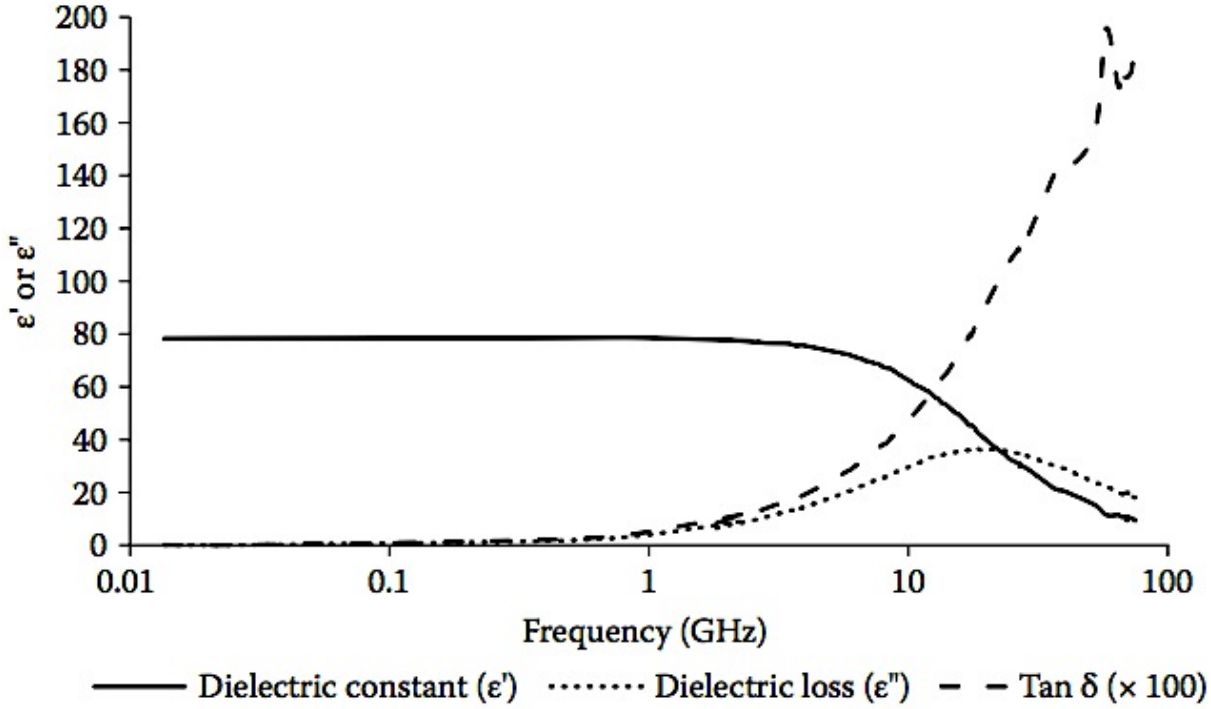


FIGURE 1.3 Dielectric constant (ε'), dielectric loss (ε"), and loss angle (tan δ) are all functions of irradiation frequency. Shown here are the plots for water, which heats most efficiently at approximately 18 GHz. Plot generated from data from Gabriel et al. (1998) and Craig (1995). Tan δ values are scaled (×100) for clarity.

Microwave Effect

“Microwave heating can enhance the rate of reactions and in many cases improve product yields.”

“Heating can enhance the rate of reactions.”

Microwave heating *can* be different from “conventional,” solely convection-based, “stove-top” heating. Numerous attempts have been made to evaluate differences between microwave versus conventional heating, either real or perceived.

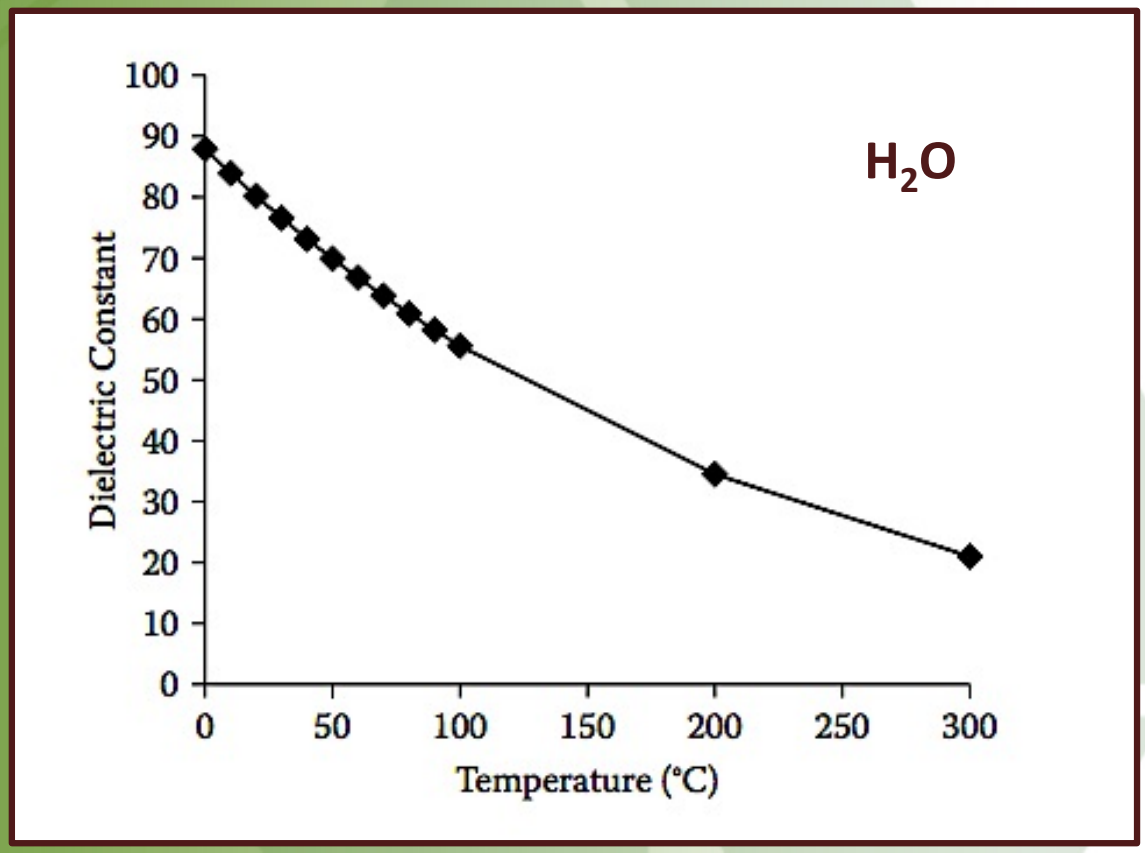
Microwave-Assisted Synthesis

TABLE 1.2
Percentage of Published Journal Articles for Five Major Organic Chemistry Publications Utilizing Microwave Irradiation (Article Hits for Keyword Search "Microwave" in all Fields/Total Articles Published)

	2002	2003	2004	2005	2006	2007	2008	2009
JOC	36/1465	52/1587	70/1473	98/1633	108/1510	134/1552	118/1524	146/1508
OL	28/1213	43/1305	56/1388	70/1502	66/1565	83/1438	86/1426	101/1470
TET	39/1334	47/1366	62/1480	105/1480	126/1522	167/1569	179/1525	173/1444
TL	61/2503	91/2396	132/2385	188/2207	226/2184	230/2175	213/1981	252/2057
OPRD	7/197	7/198	9/201	12	14/204	19/211	19/202	12/239
Total MW	171	240	329	473	540	633	615	684
% MW	2.55	3.50	4.77	6.75	7.73	9.11	9.24	10.18

Note: JOC—Journal of Organic Chemistry; OL—Organic Letters, TET—Tetrahedron, TL—Tetrahedron Letters; OPRD—Organic Process Research and Development.

Microwave-Assisted Synthesis



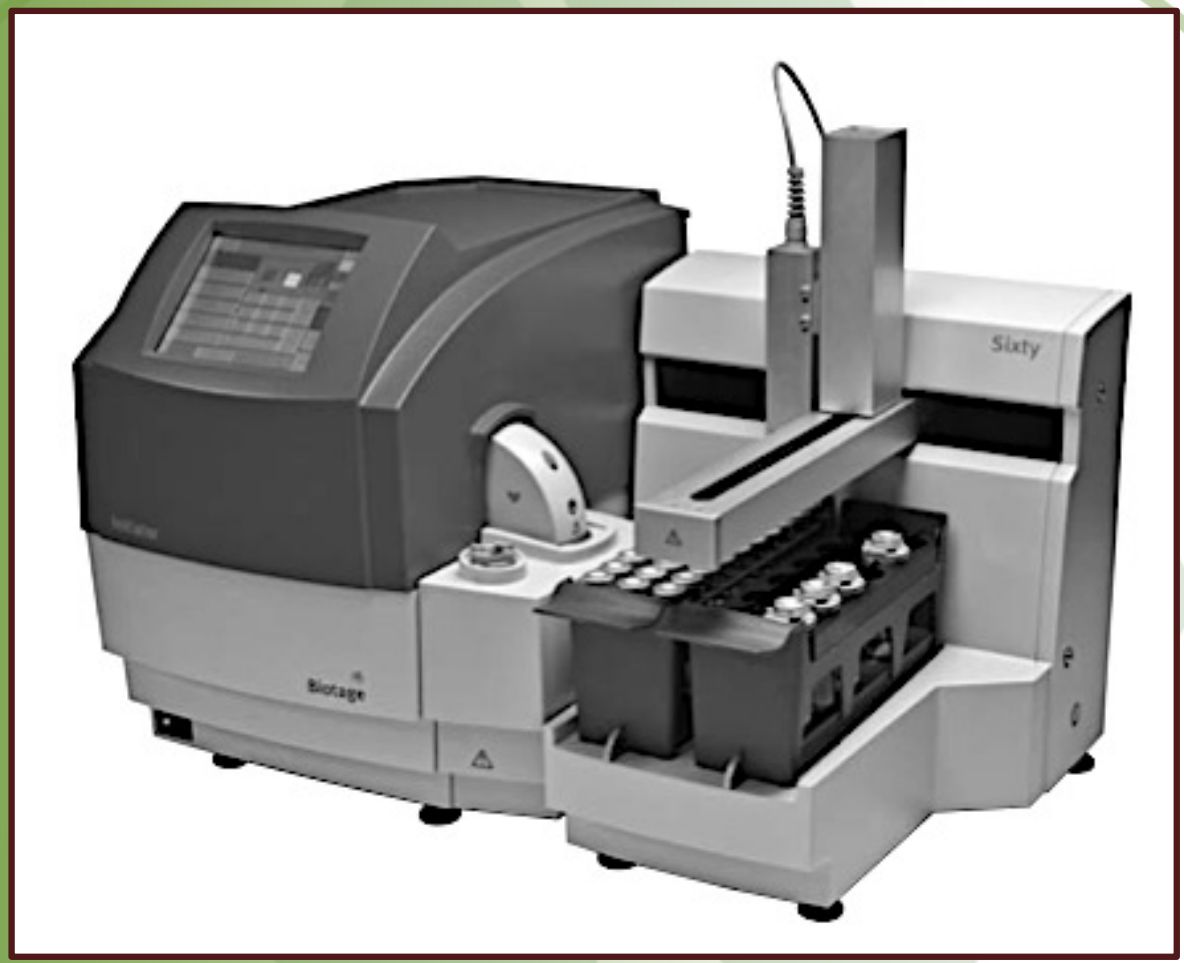
Small-Scale Equipment

(a)

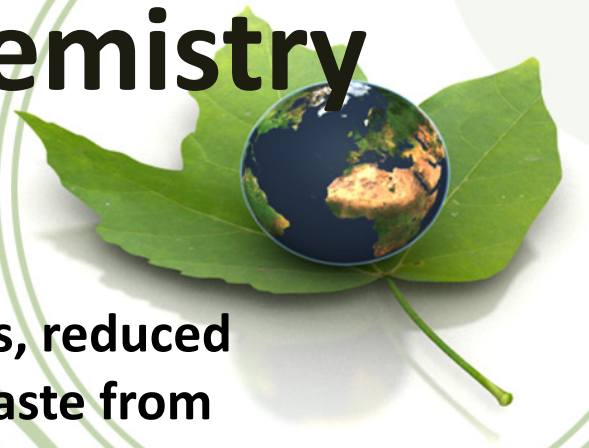
(b)

FIGURE 1.7 Two of the small-scale dedicated microwave units for scientific applications. (a) Anton Paar Monowave (Reproduced with permission from Anton Paar.) (b) CEM Discover SF in open-vessel mode. The Biotage Initiator, equipped with an automated vessel handler, is shown in Figure 1.9. (Reproduced with permission from CEM Corp.)

Small-Scale Equipment



Microwaves vs Green Chemistry



- **Waste Prevention. By enabling faster, cleaner reactions, reduced quantities of reaction by-product waste and solvent waste from purification are reduced.**
- **Design for Energy Efficiency. Microwave chemistry uses a smaller total amount of energy to promote chemical reactions, when compared with more conventional heating techniques, such as oil baths and heating mantles. This is so primarily due to the reduced reaction time required.**
- **Catalysis. In many cases, microwave heating enhances catalytic reactions, such as to further encourage the application of catalytic chemistry.**
- **Inherently Safer Chemistry for Accident Prevention. Since these instruments provide safe microwave irradiation and are able to achieve high pressures and temperatures in a well-controlled manner, worker safety is improved while improving reaction outcomes.**

Microwaves vs Green Chemistry

- **Faster reactions, due to the higher reaction temperatures achievable.**
- **Increased yield; this is probably because it is easier to reach the endpoint of a reaction that is heated to high temperatures for a short period, compared to waiting for an uncertain end point at more modest temperatures over a prolonged period.**
- **Reduced impurities, which are usually attributed to reduced “wall effects”; fewer impurities also mean more product and, hence, higher yields.**

Microwaves vs Green Chemistry

- **Enlarged reaction space through the use of superheated solvents in sealed-vessel systems (i.e., autoclave-type conditions); this may allow for new chemistries to be accessed, such as reactions in near-critical water.**
- **Linear reproducibility on scale-up, potentially avoiding traditional scale-up problems.**
- **Possible energy savings.**

Microwave Heating as a Tool for Organic Synthesis

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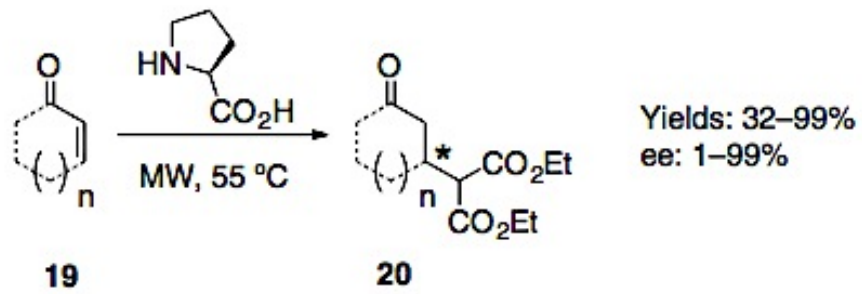
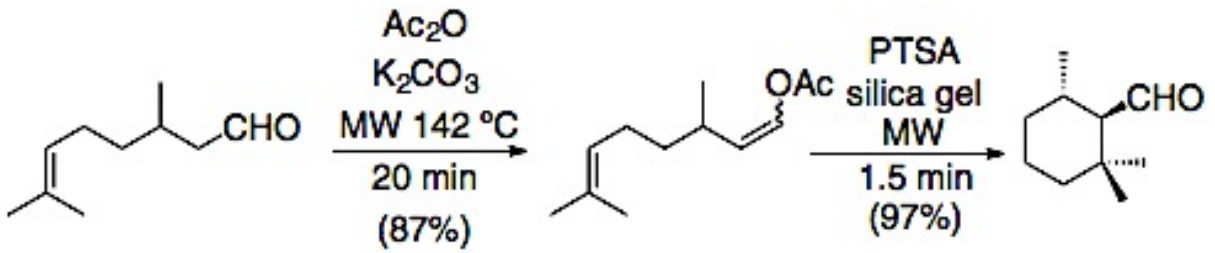
Solvent-free Reactions



19 **20**

Scheme 12.3 *An enantioselective Michael addition under solvent-free conditions.*



21 **22** **23**

Scheme 12.4 *An enantioselective microwave preparation of dihydrocyclocitral.*

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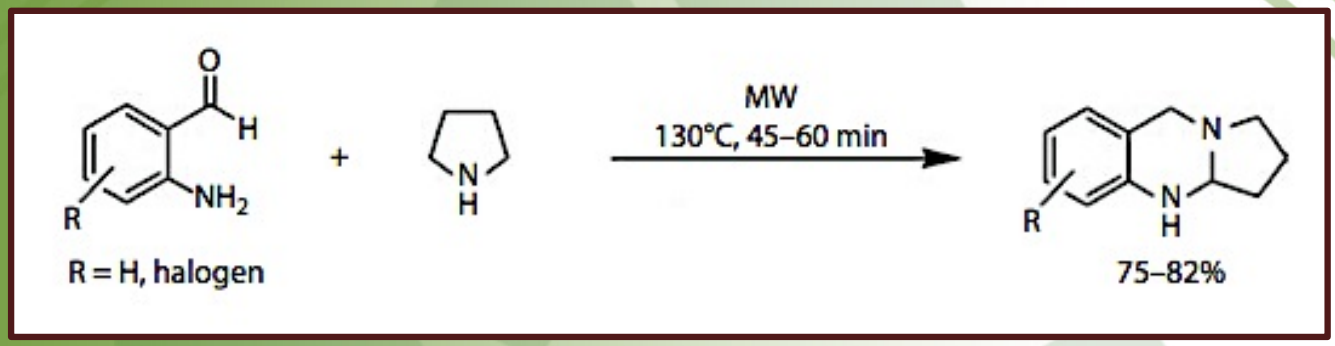
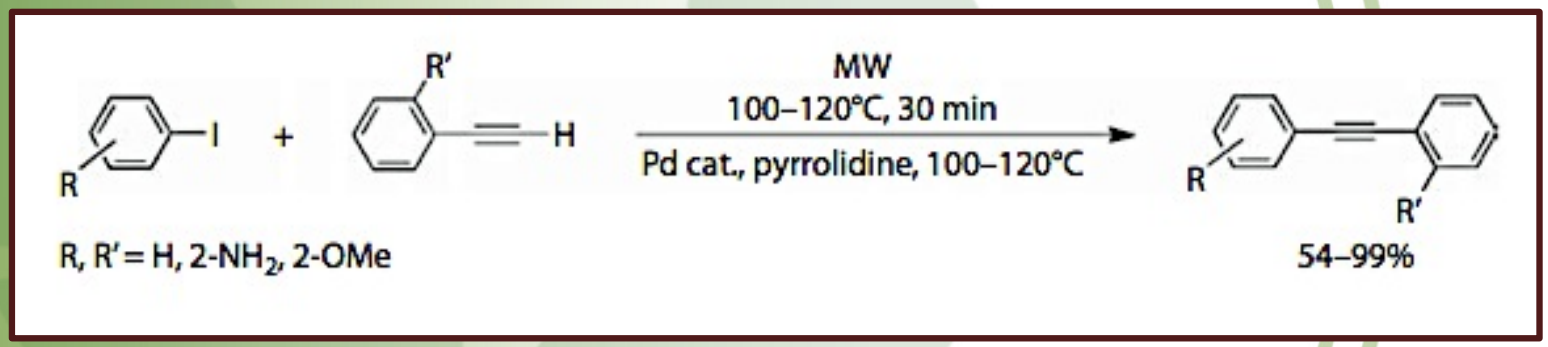
Solvent-free Reactions





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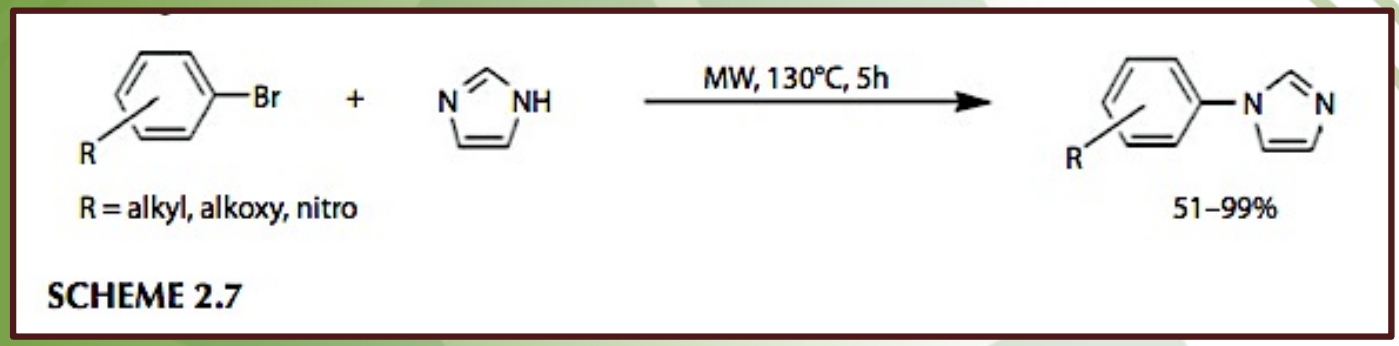
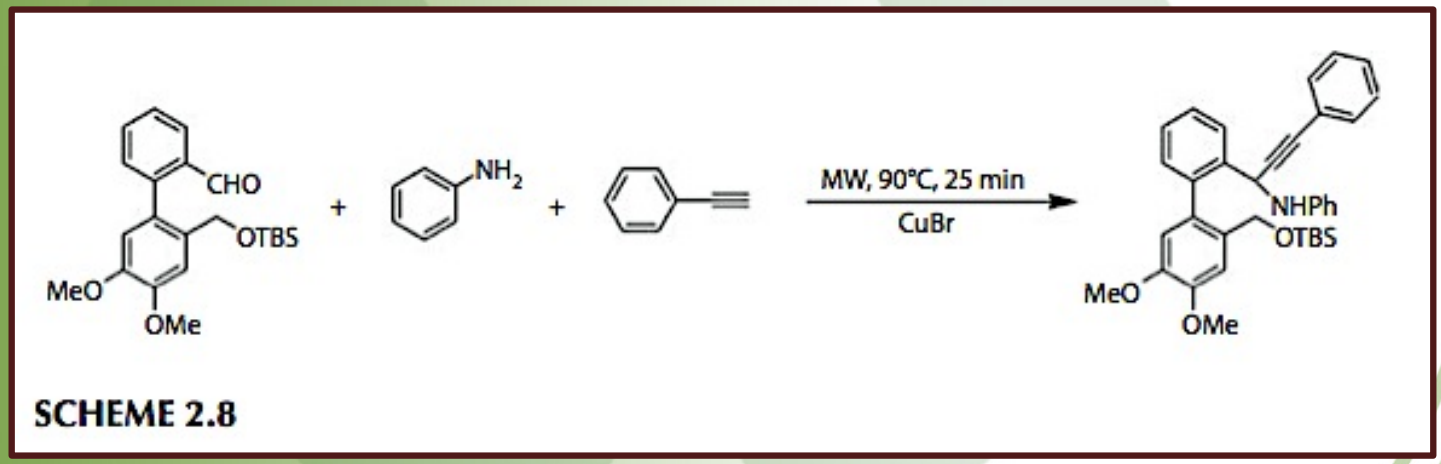
Solvent-free Reactions



SCHEME 2.7



SCHEME 2.8

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Poorly Absorbing Organic Solvents

Heating 2 mL of pure hexane at 200 W in a monomode microwave unit resulted in a temperature rise of only 20 °C after 10 s.
Adding a small amount of the ionic liquid (10–50 mg) resulted in a temperature of 217 °C under the same conditions.
In addition to ionic liquids, disks made of silicon carbide can act as passive heating elements.
In a control study, heating neat hexane (150 W, 77 s) resulted in a final temperature of 42 °C.
Adding a silicon carbide disk to the hexane solution and performing the same study resulted in a temperature of 158 °C.

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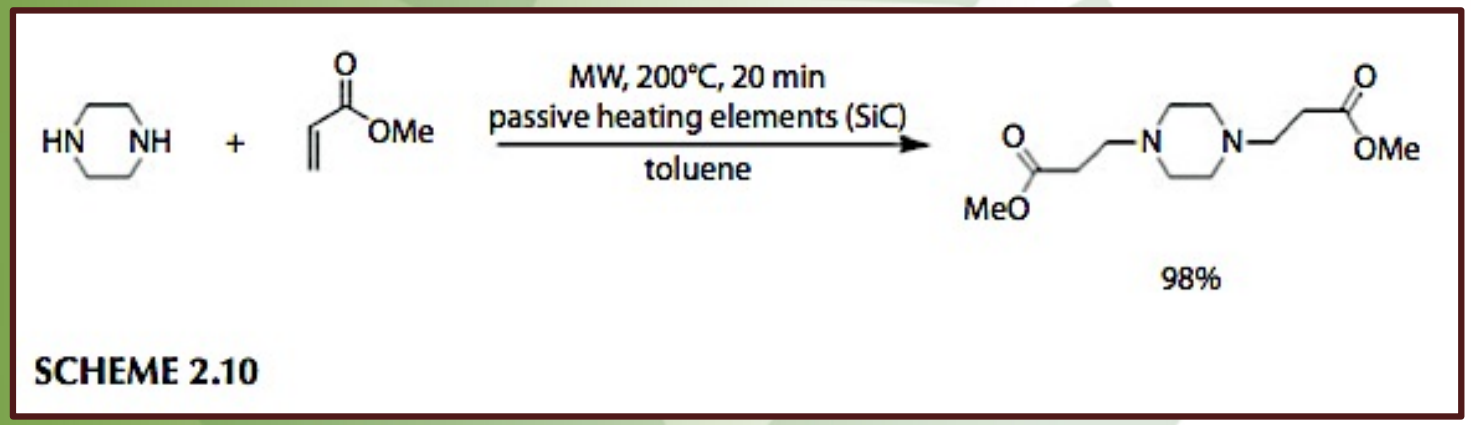
Poorly Absorbing Organic Solvents



SCHEME 2.10

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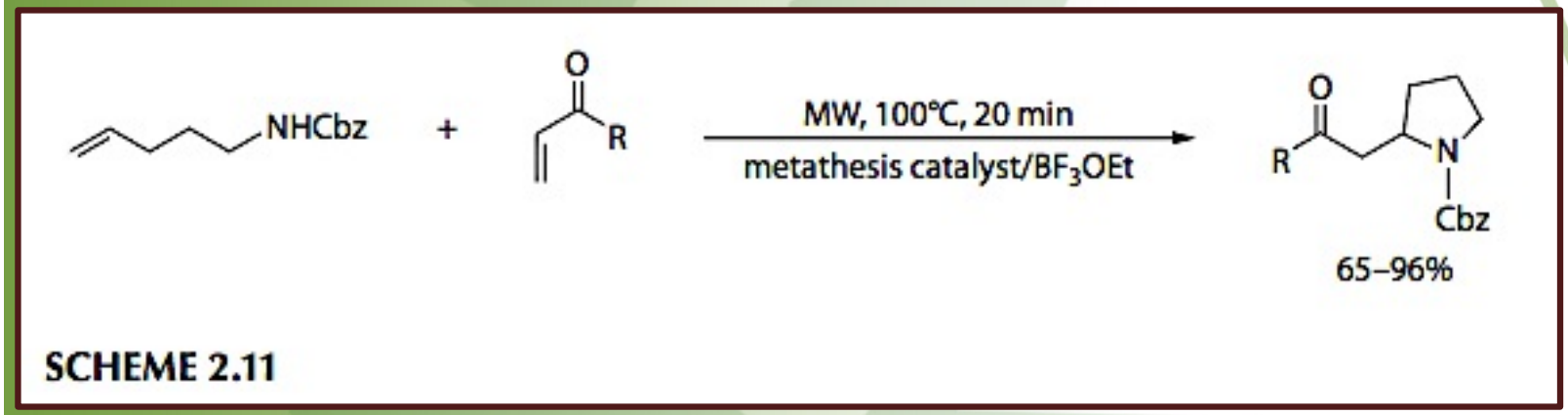
Tandem Metathesis/Michael Addition



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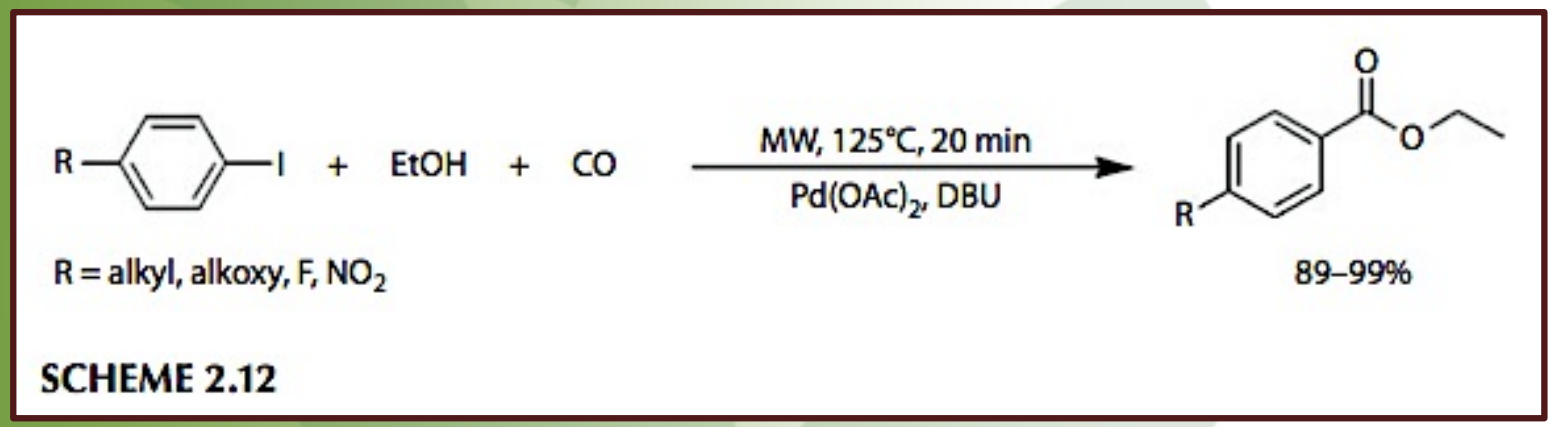
Metal-Catalyzed Carbonylation



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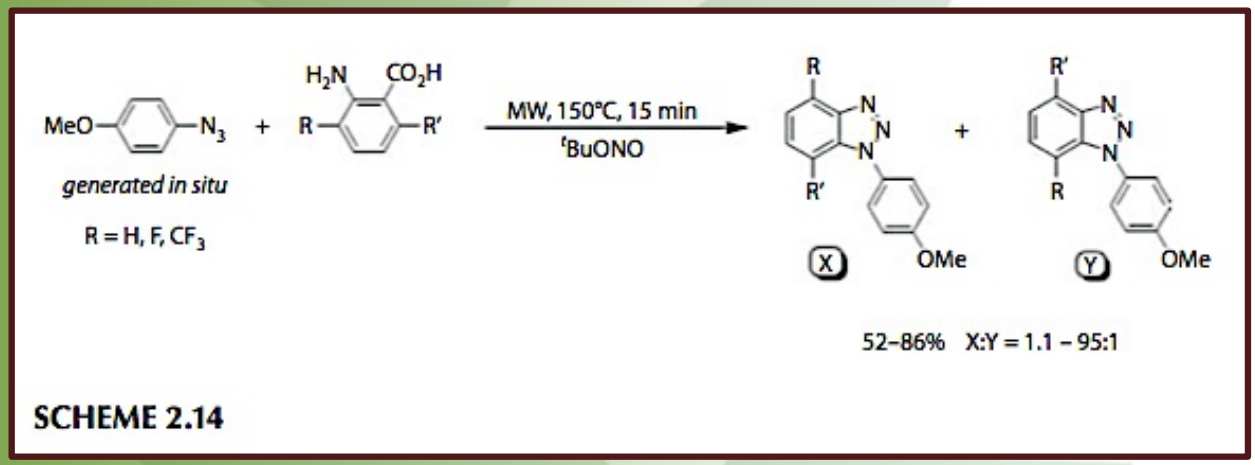
Cycloaddition Reactions



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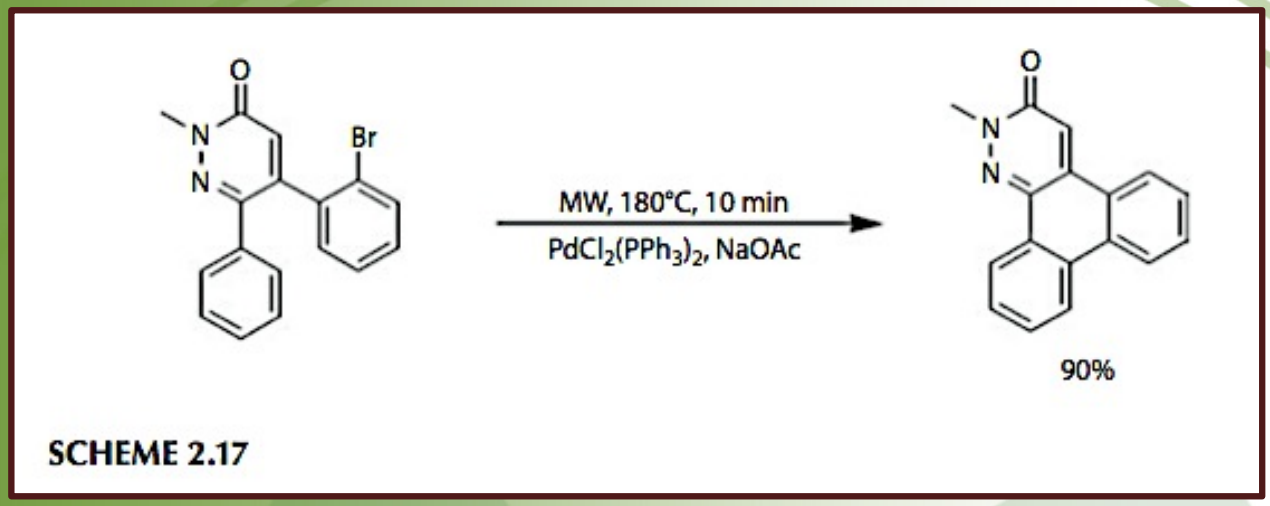
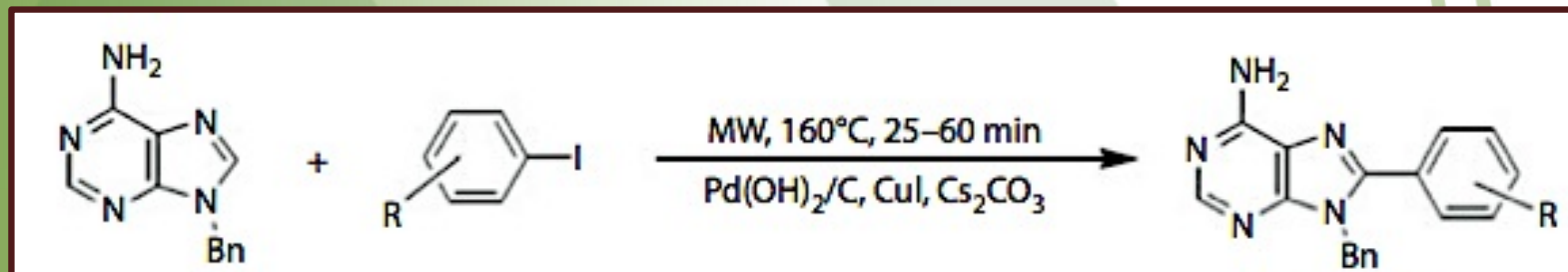
C–H Activation



SCHEME 2.17



R = alkyl, aryl, alkoxy, NH_2, CN

SCHEME 2.19

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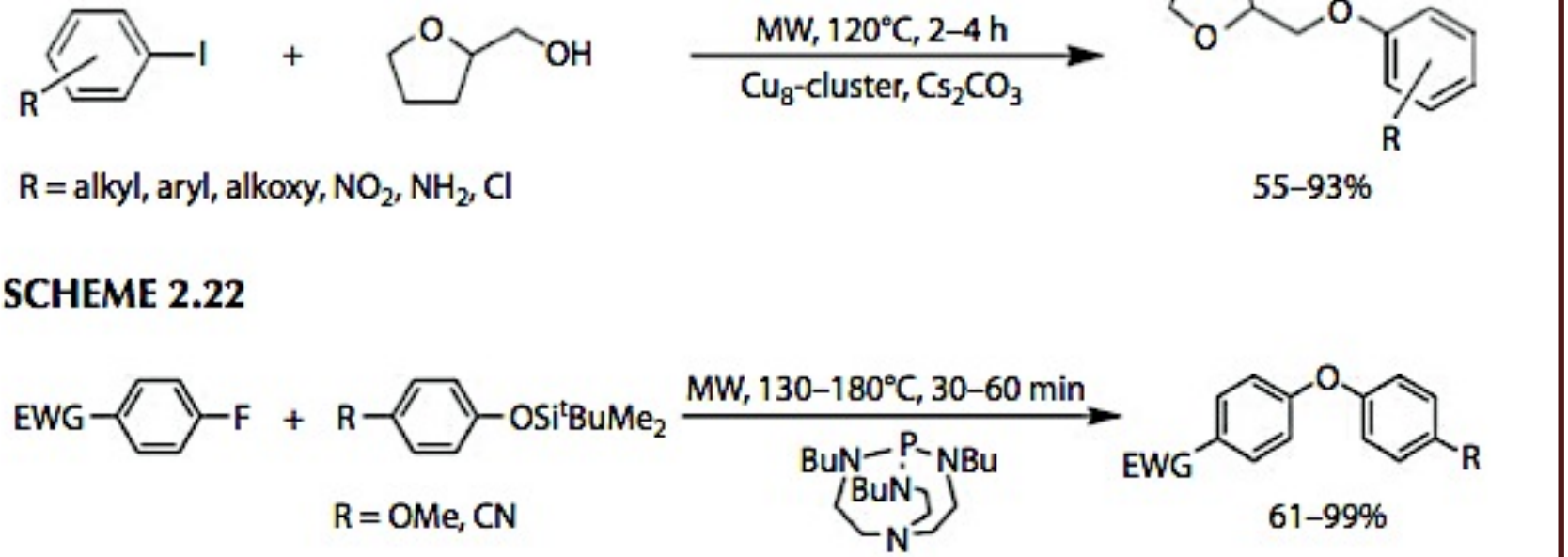
Ullmann Couplings



SCHEME 2.22

SCHEME 2.23

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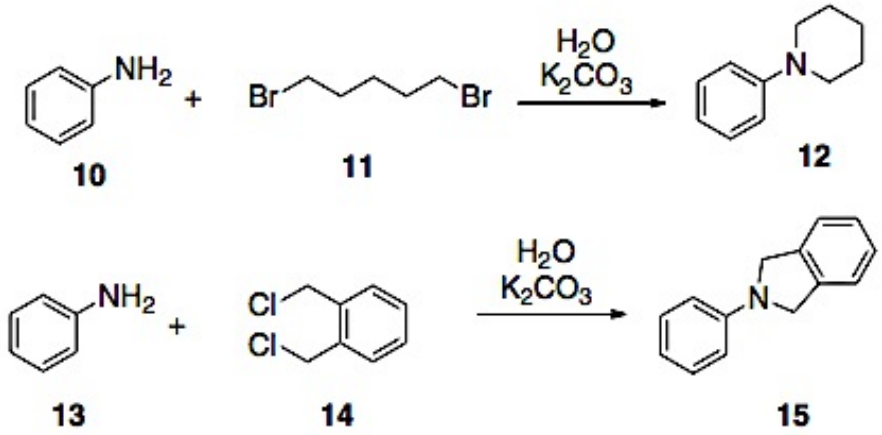
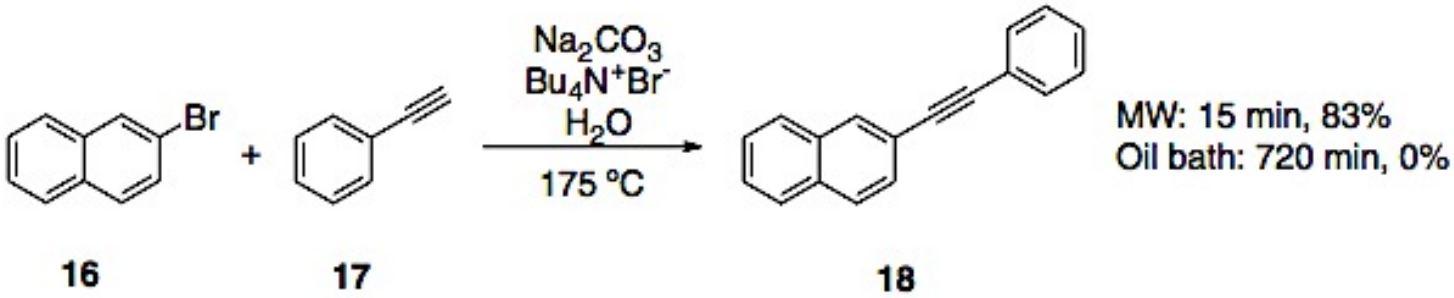
Reaction in Water



Scheme 12.1 *A green isolation of products from aqueous reaction mixtures.*



Scheme 12.2 *An aqueous, metal-free Sonogashira-type coupling reaction.*

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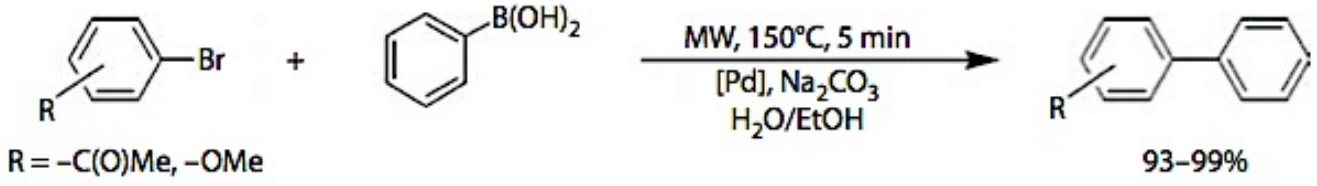
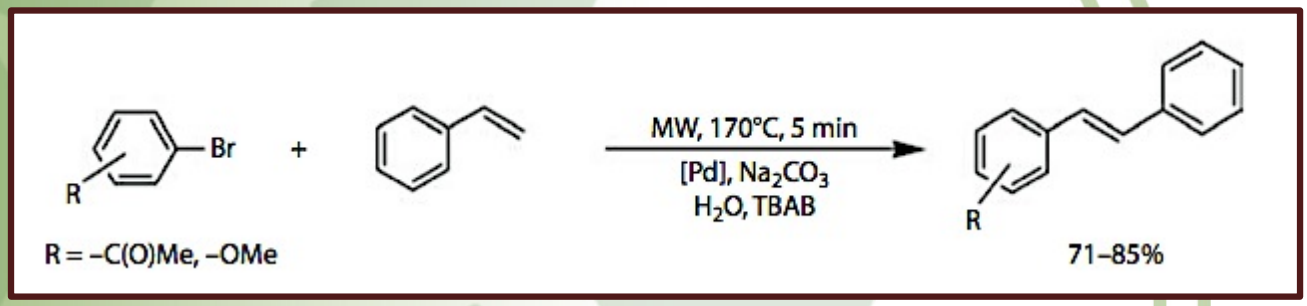
Reaction in Water

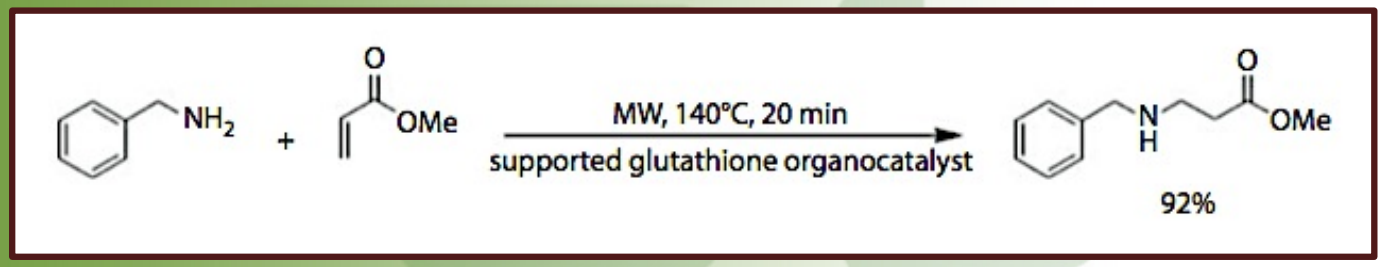
Suzuki Couplings Using Ultra-low Catalyst Loading



Heck Reactions Using Ultra-low Catalyst Loading



Organocatalysis



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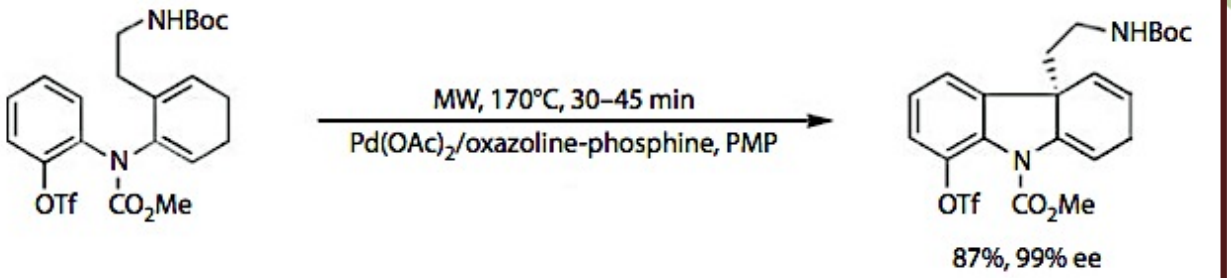
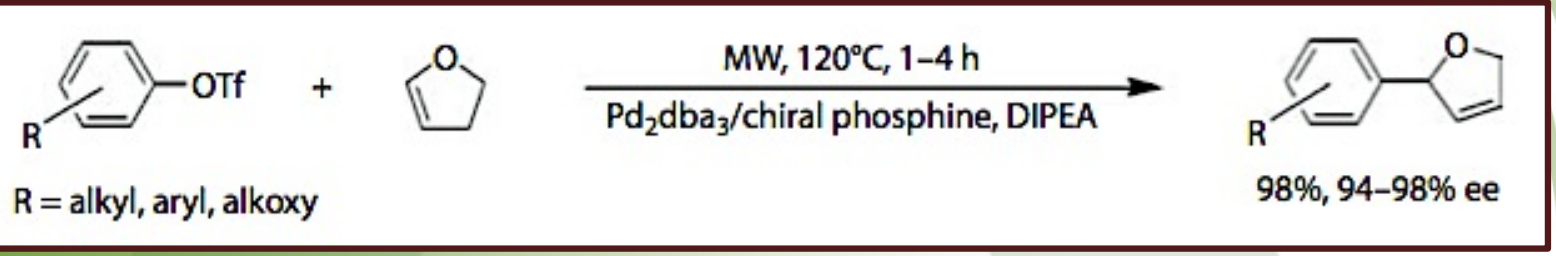
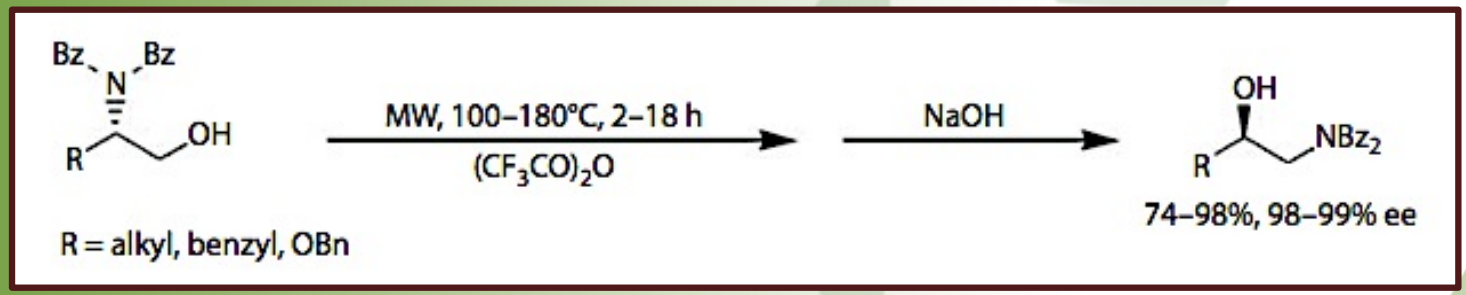
Asymmetric Transformations

Heck Coupling Reactions





Preparation Of Amino Alcohols



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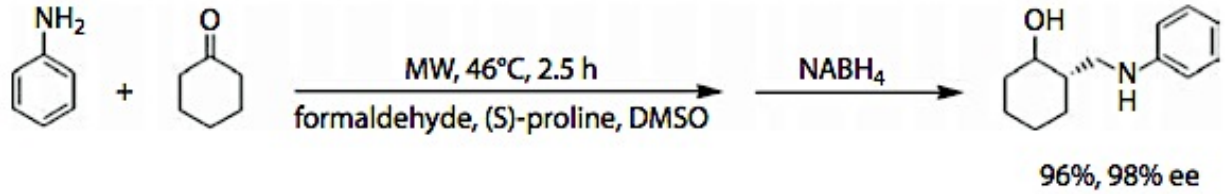
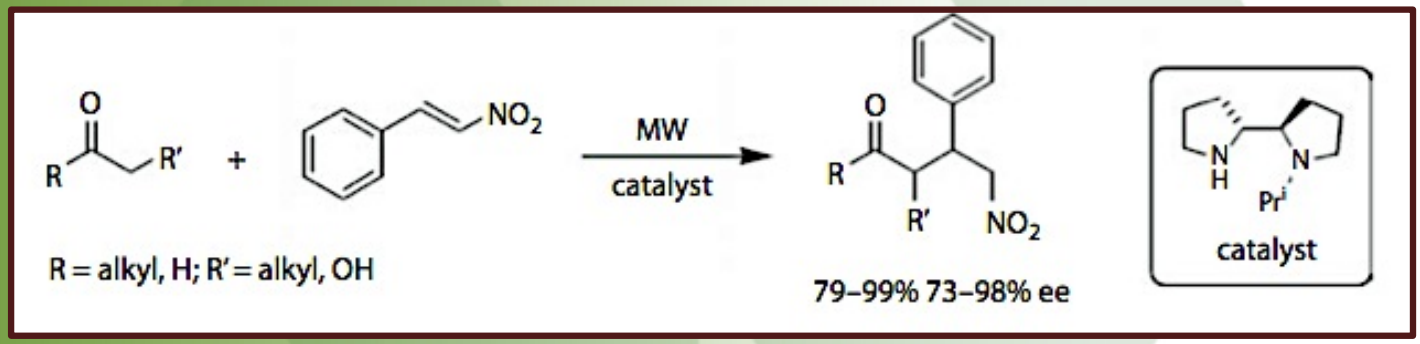
Asymmetric Transformations

Mannich Reactions



Michael Additions



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Microwave Heating as a Tool for Sustainable Polymer Synthesis

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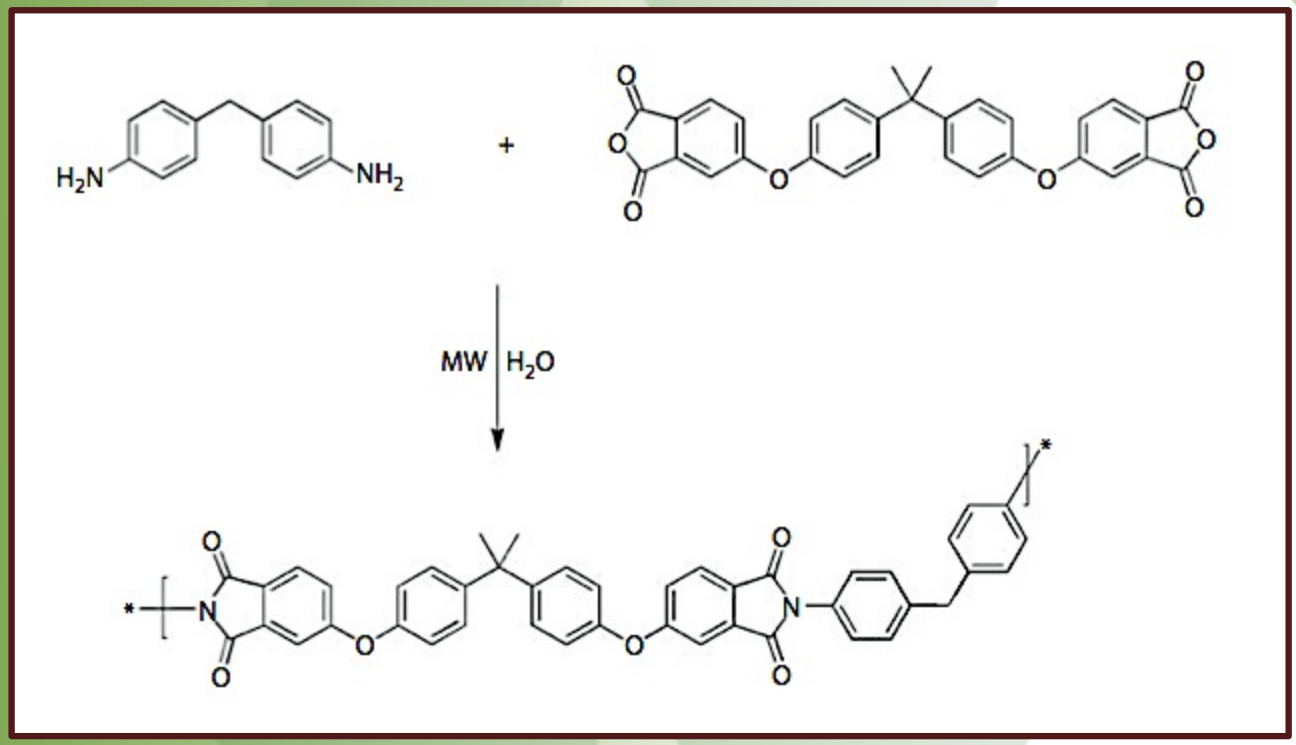
Polymer Synthesis in Water



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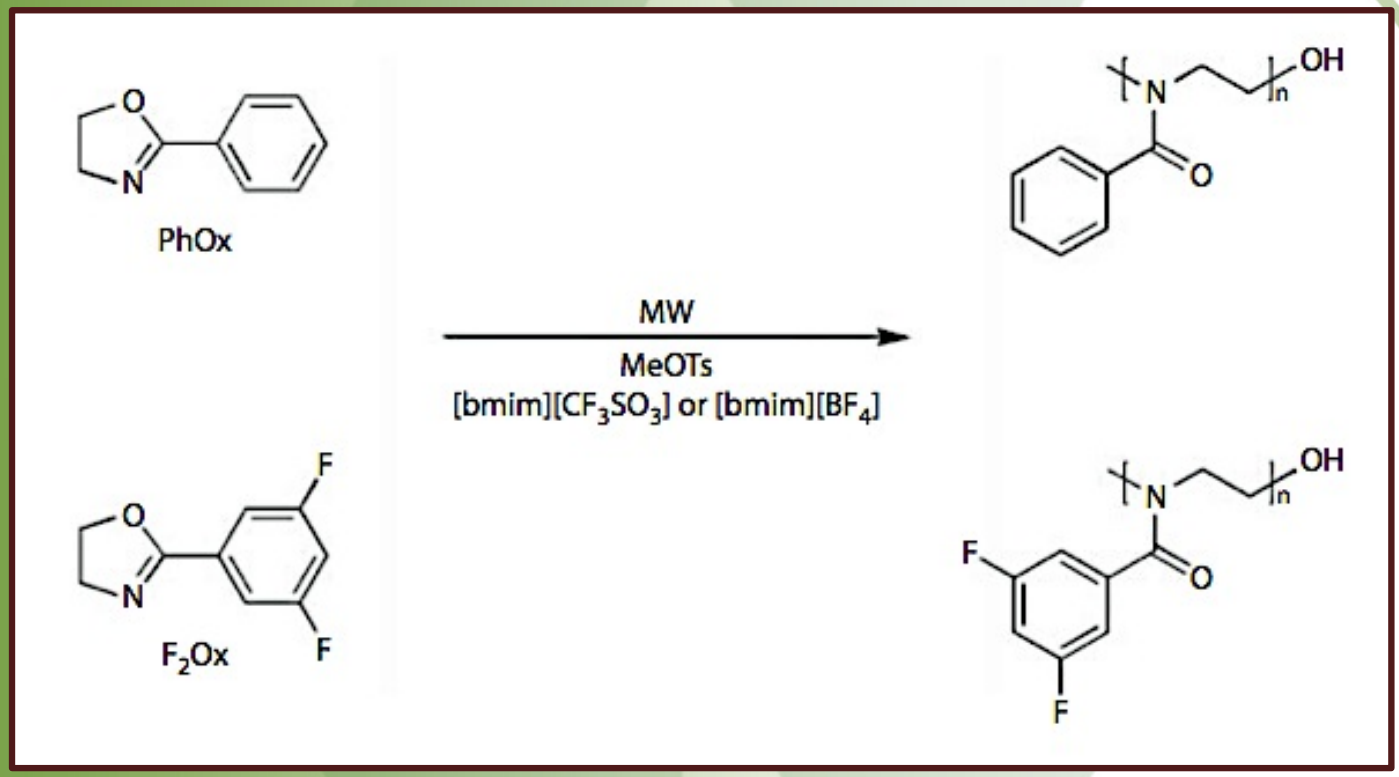
Polymer Synthesis in RTILs



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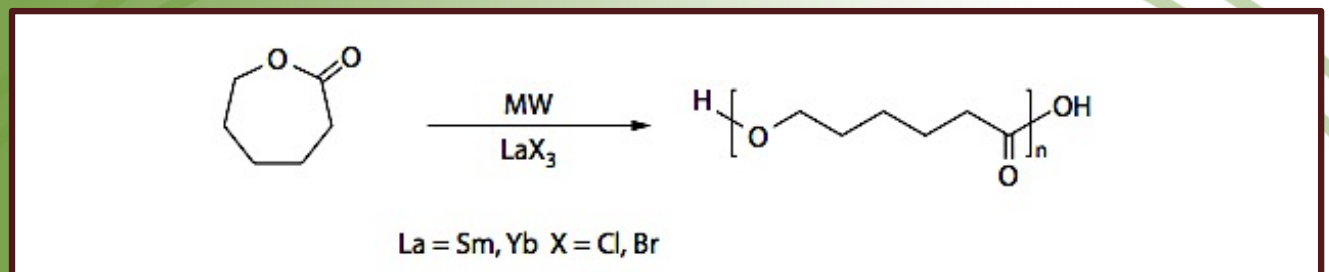
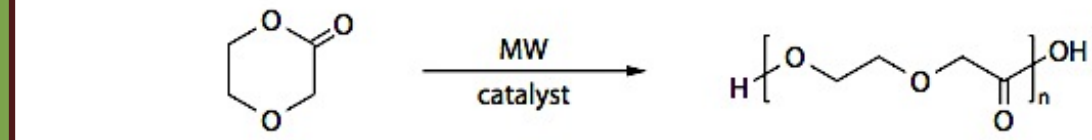
Solvent-Free Polymer Synthesis



SCHEME 3.5



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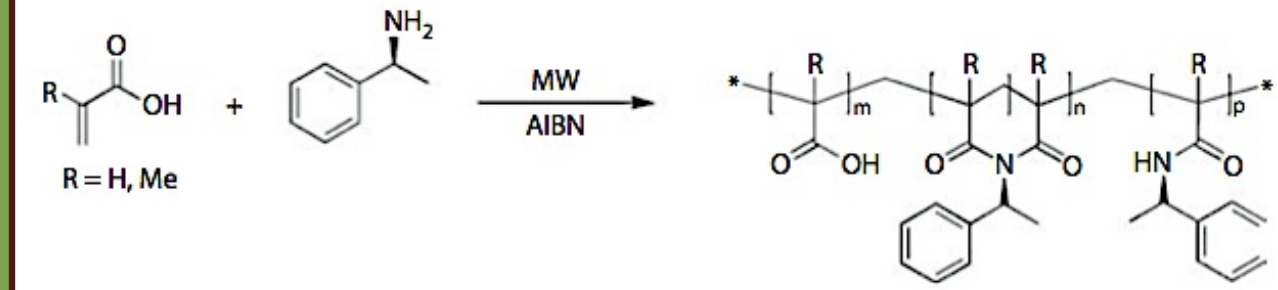

SCHEME 3.7

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Microwave Heating as a Tool for Drug Discovery

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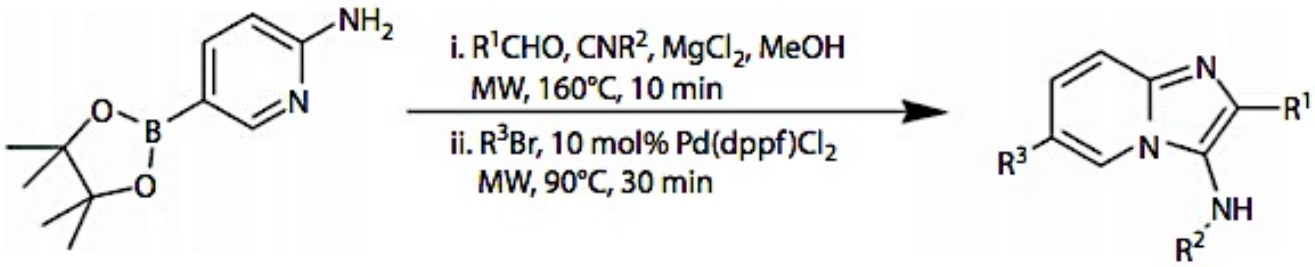
Multicomponent Reactions

Multicomponent Cyclization/Suzuki Coupling Sequence



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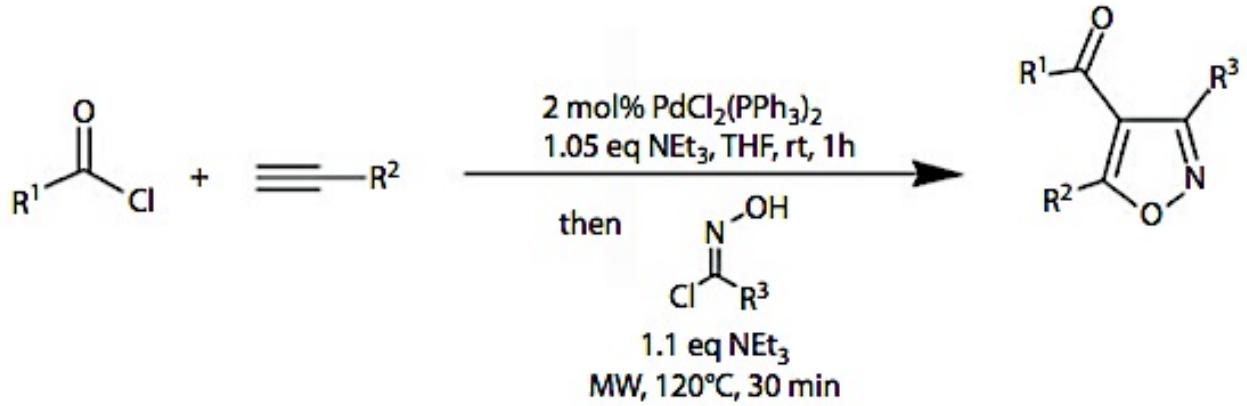

Multicomponent Sonogashira Coupling-Cycloaddition Sequence

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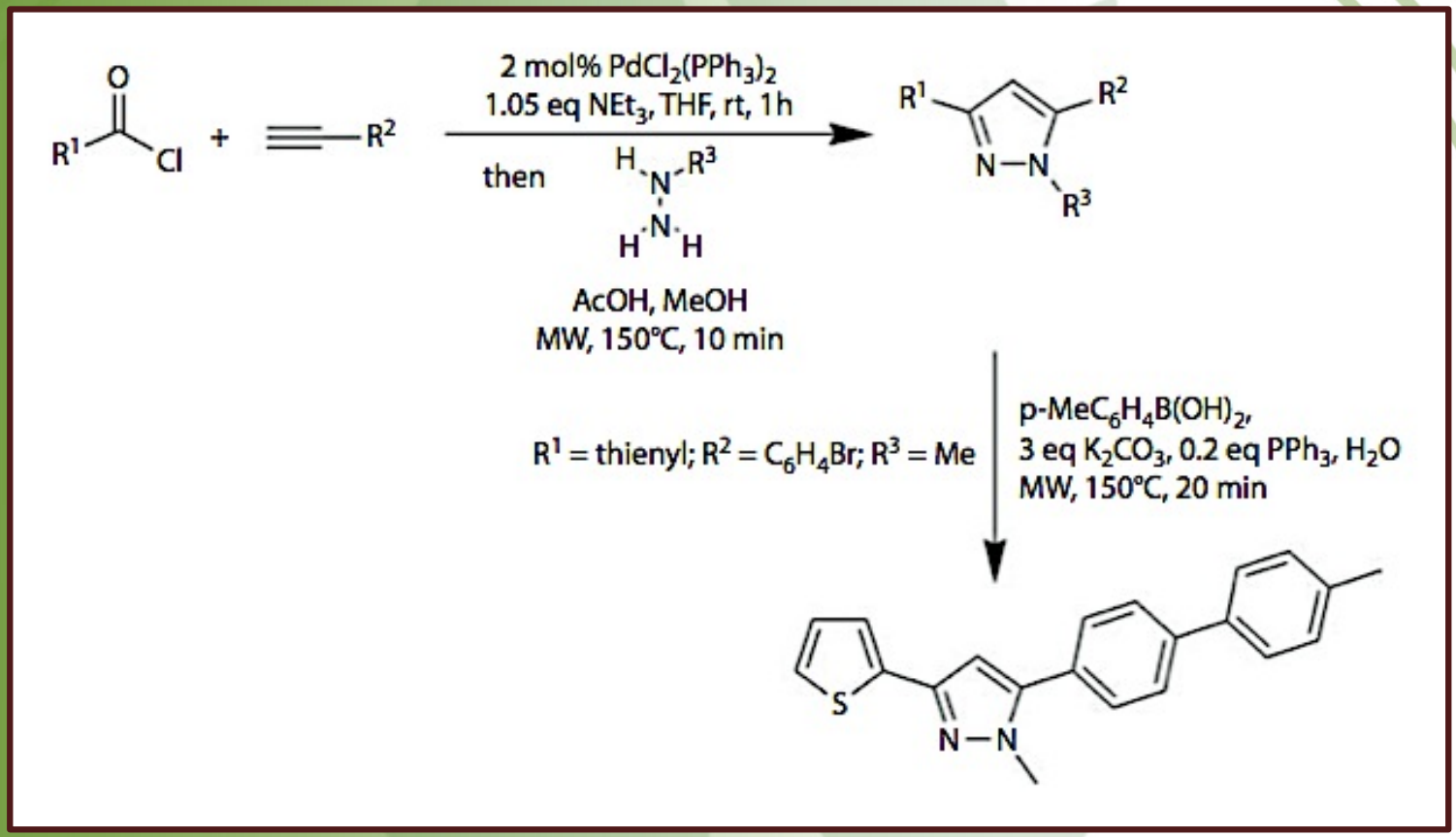
Multicomponent Reactions

Multicomponent Sonogashira Coupling-Cycloaddition Sequence



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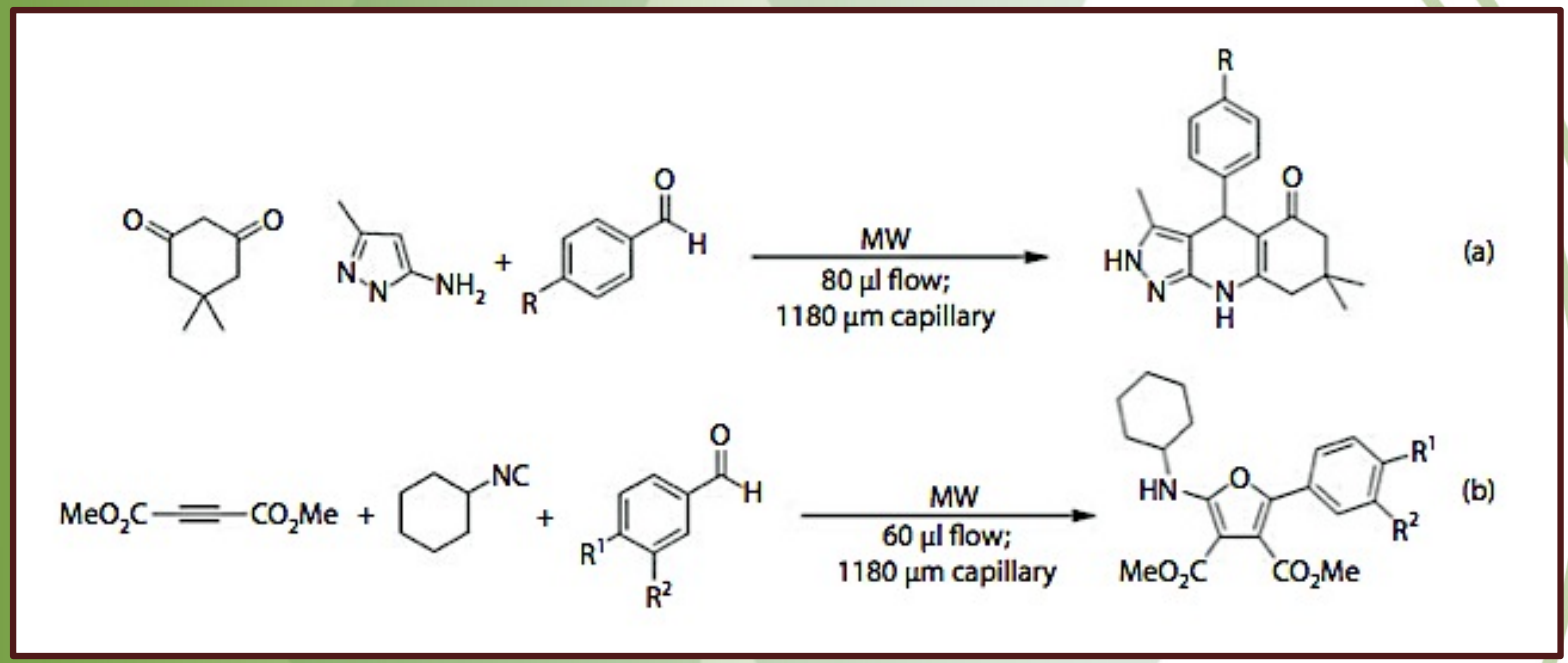
Multicomponent Reactions

Multicomponent Reactions Performed in Continuous Flow



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Domino Reactions

Domino reactions are defined as processes in which a consecutive series of transformations take place, each one taking place at functional groups formed in the preceding reaction. They allow chemists to build a large degree of complexity into one transformation. At the same time, they reduce waste and save time since intermediates are not isolated.

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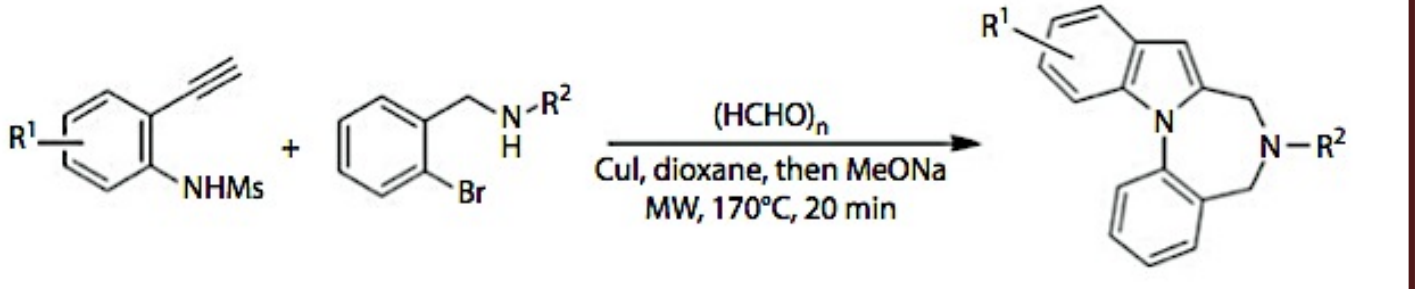
Domino Reactions

Copper-Catalyzed Domino Reactions



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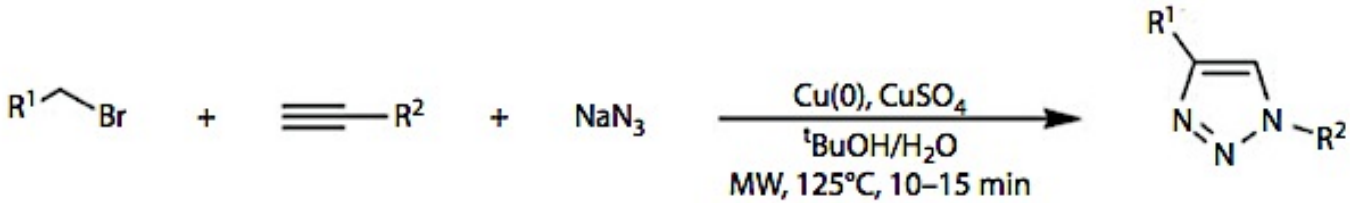

SCHEME 4.7

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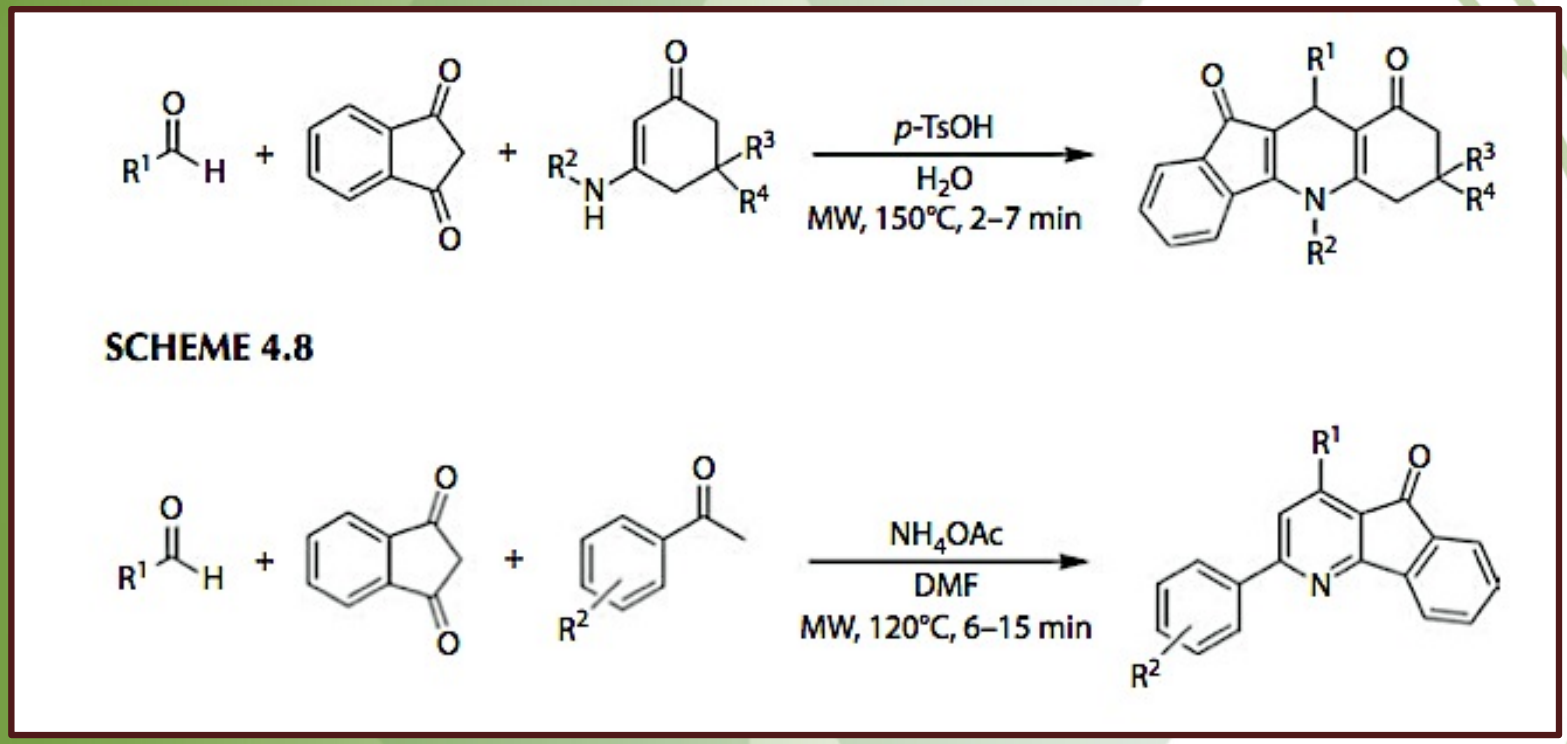
Domino Reactions

Organocatalyzed Domino Reactions



SCHEME 4.8

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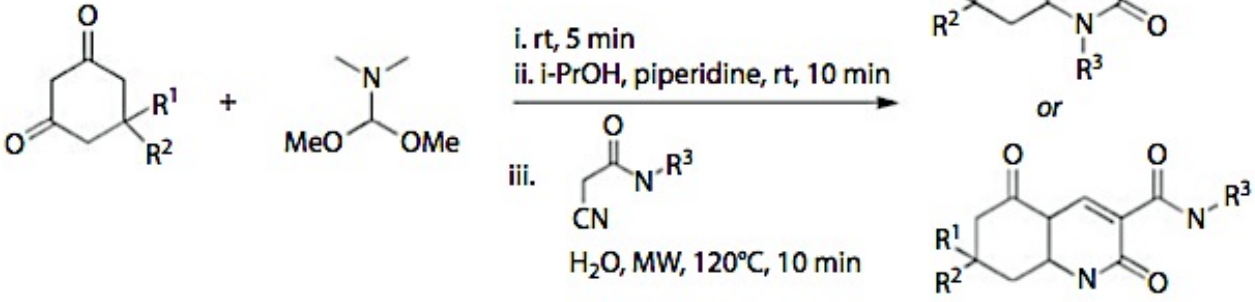
Domino Reactions

Organocatalyzed Domino Reactions



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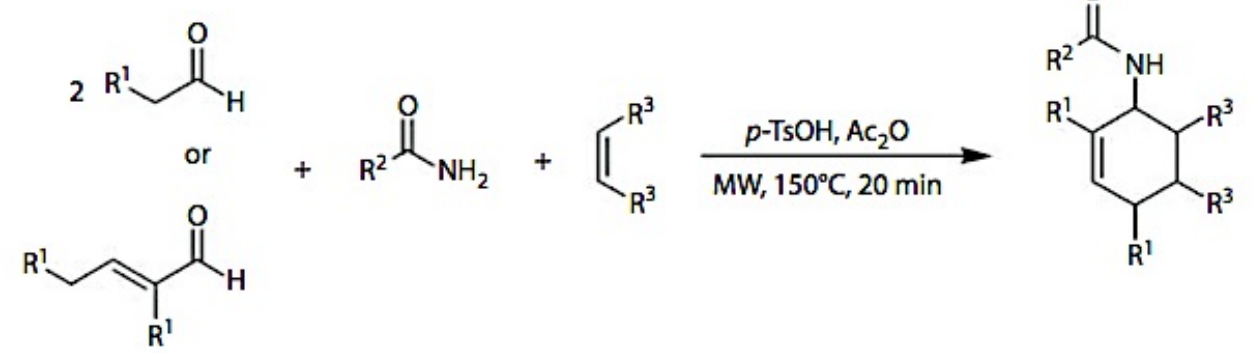

SCHEME 4.11

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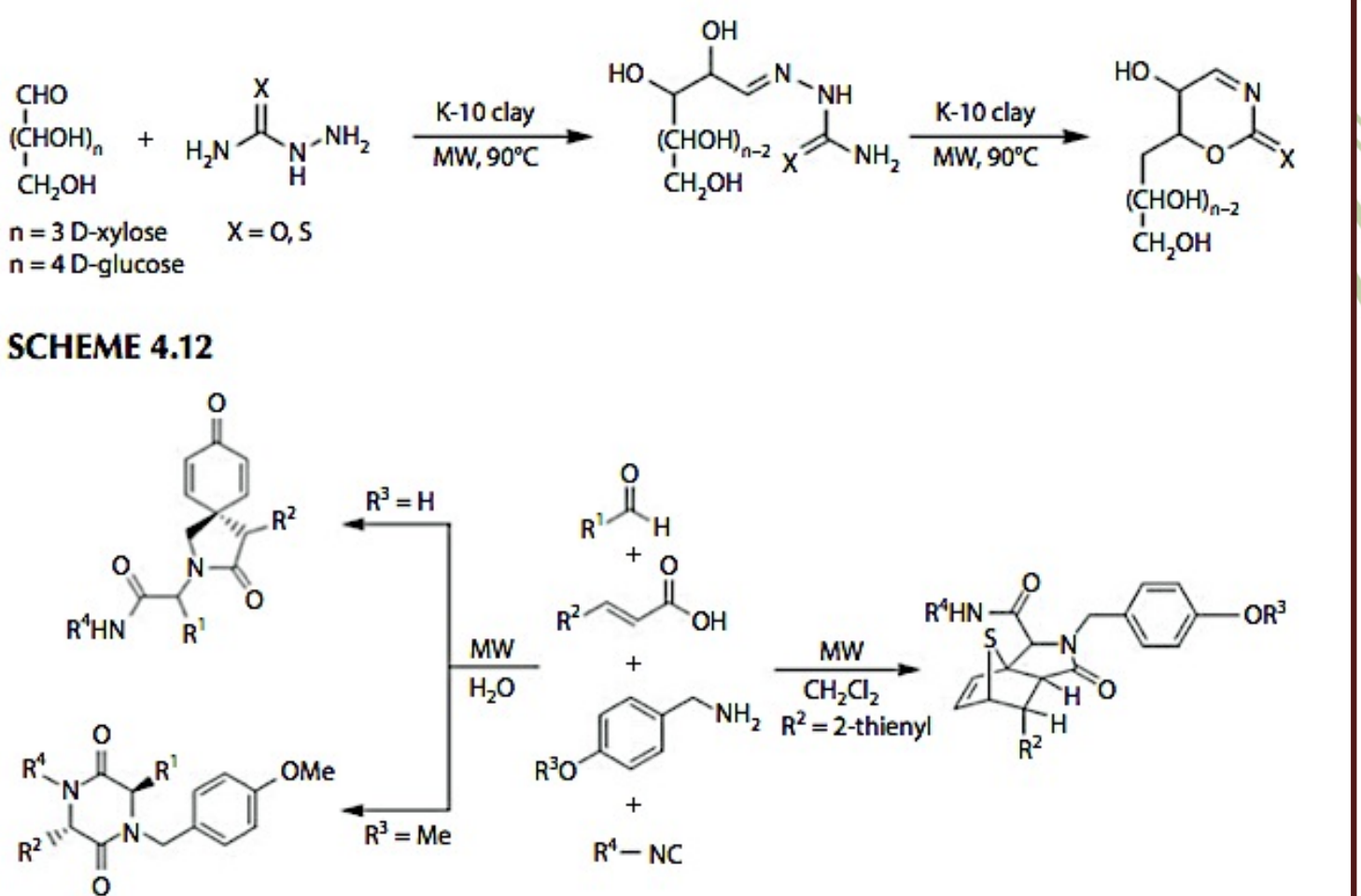
Domino Reactions

Organocatalyzed Domino Reactions



SCHEME 4.12

SCHEME 4.13

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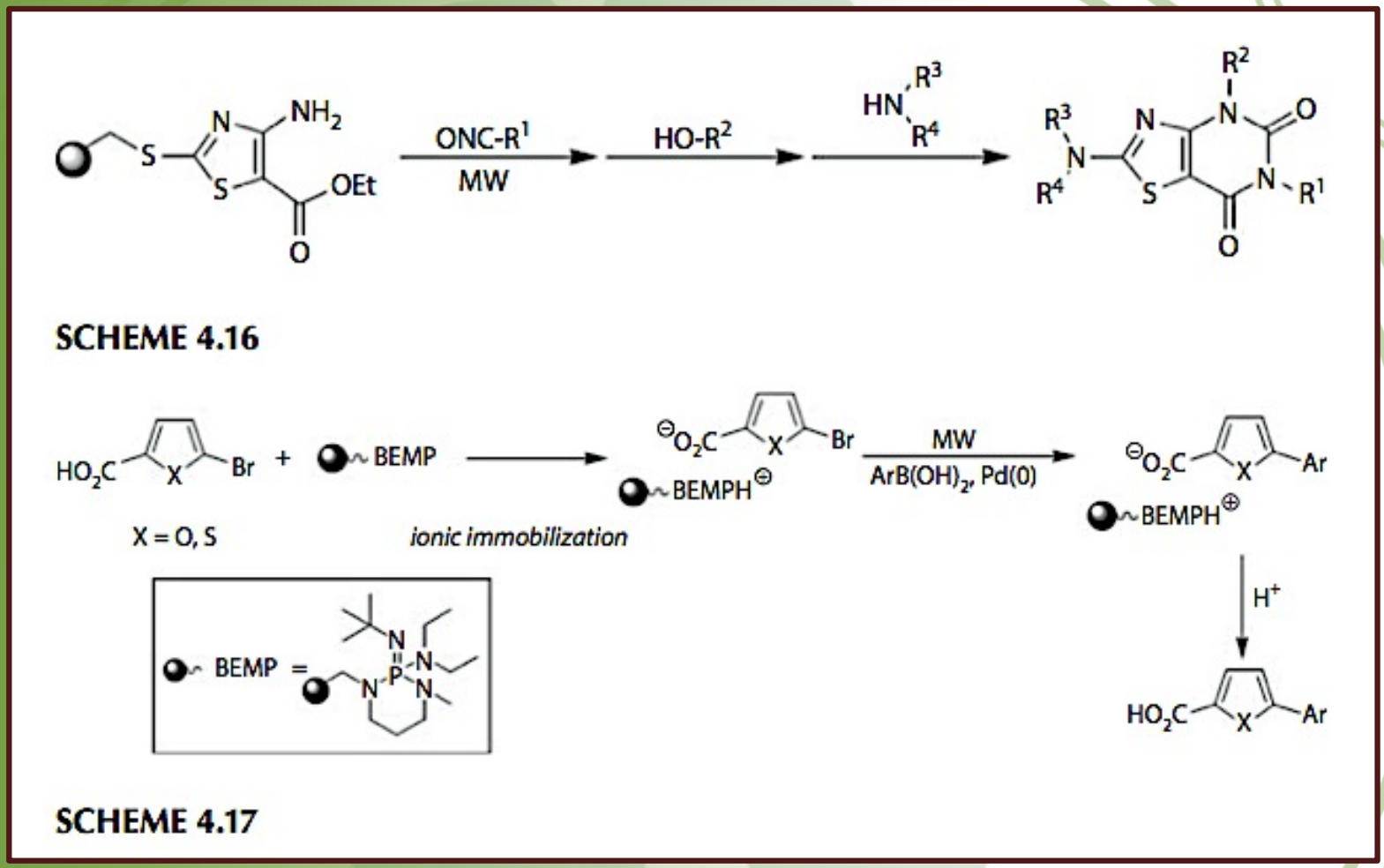
Solid-Supported Synthesis



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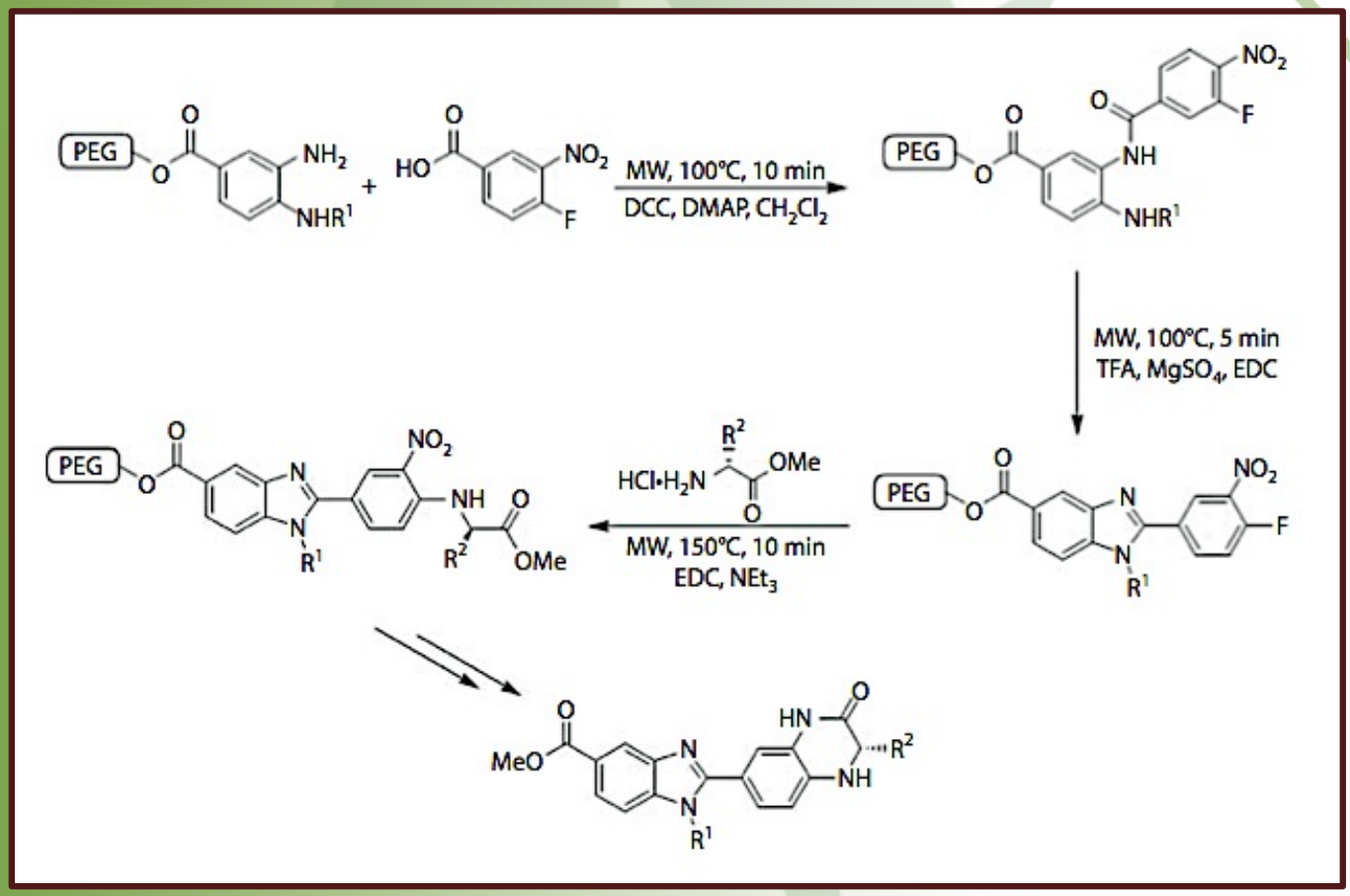
Solid-Supported Synthesis

Parallel Synthesis Using Soluble Polymer-Supported Strategies



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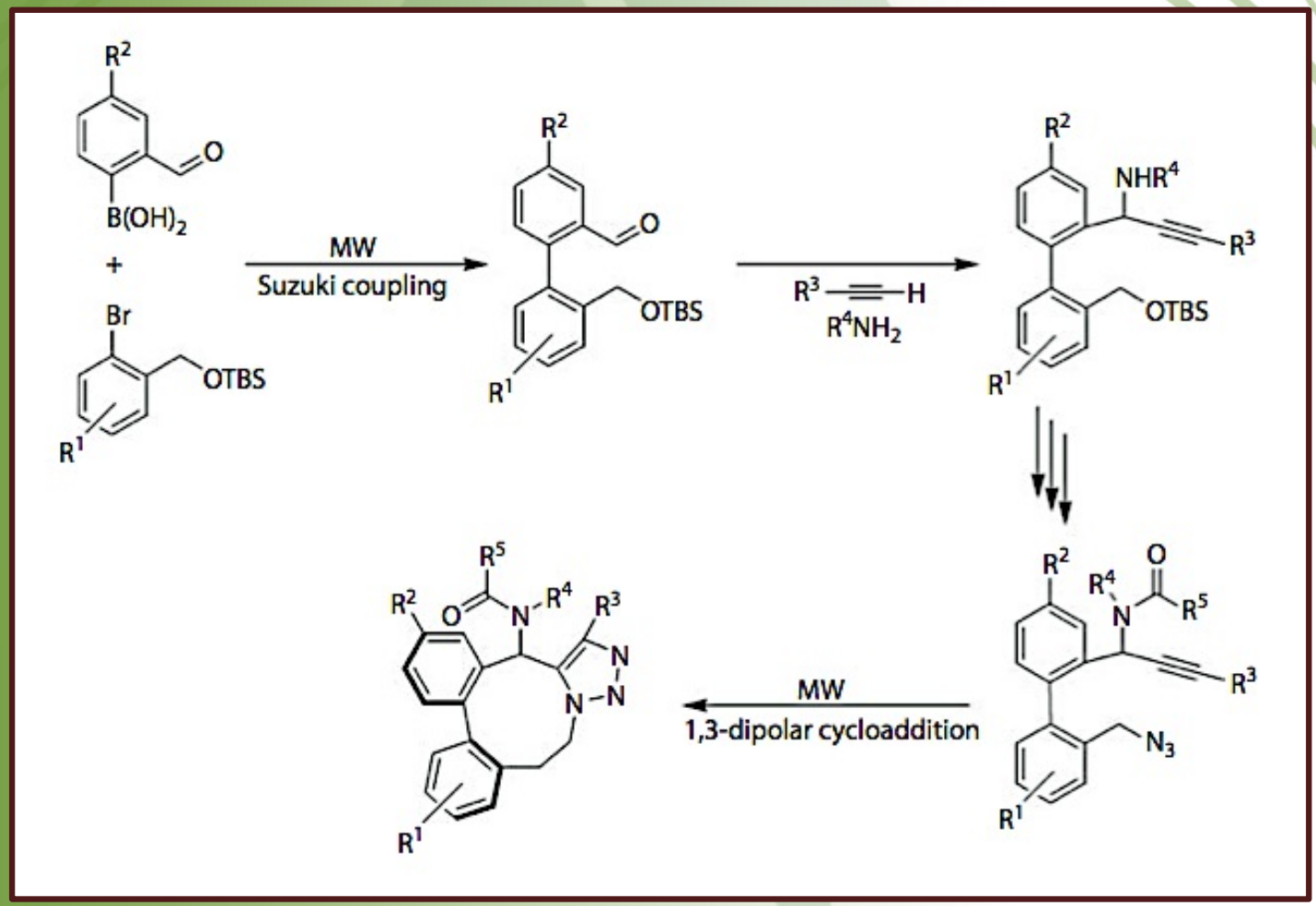
Natural Product-Like Libraries



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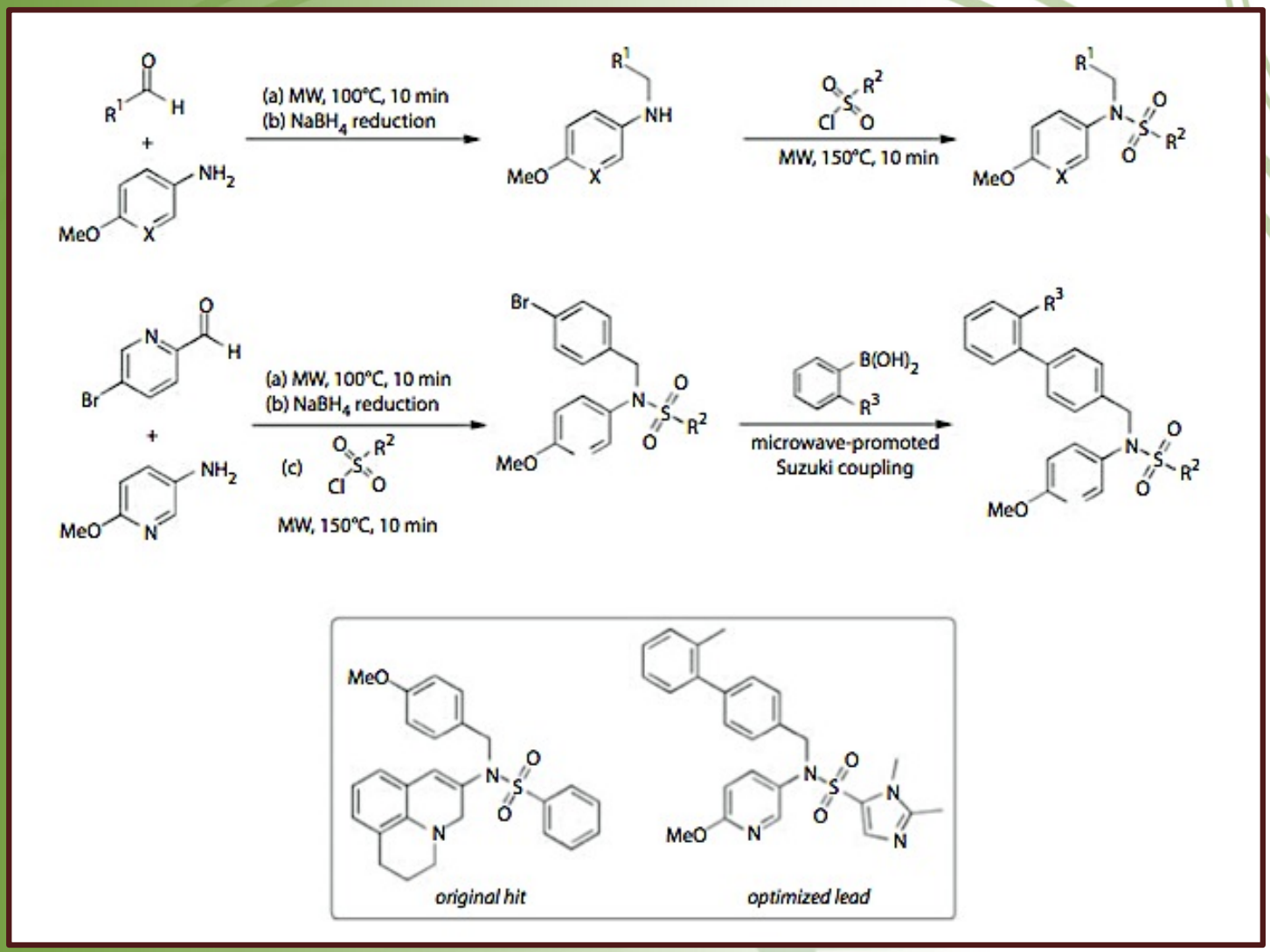
Medicinal Chemistry



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Microwave Heating as a Tool for Process Chemistry

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Introduction

- The examples presented will be drawn mainly from pharmaceutical process chemistry derived from traditional organic synthesis and particularly the chemistry of drug discovery;
- Microwave heating is relatively expensive compared to other types of conventional, conductive heating methods, so to be commercially competitive, it must be applied to high-value products.
- Manufacture of high-value, low-tonnage pharmaceuticals, polymers and peptides (effectively biopolymers).

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Introduction

The key limiting factor is the penetration depth of microwave irradiation, which is only a few centimeters in most solvents at 2.45 GHz.

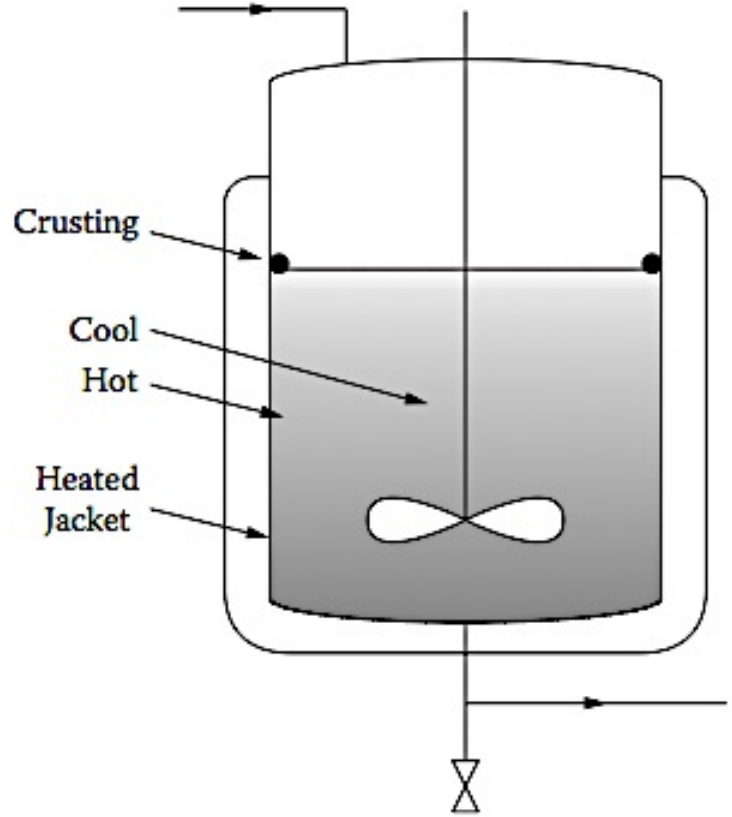

FIGURE 5.1 Heating effects in a conventionally heated large-scale batch reactor.

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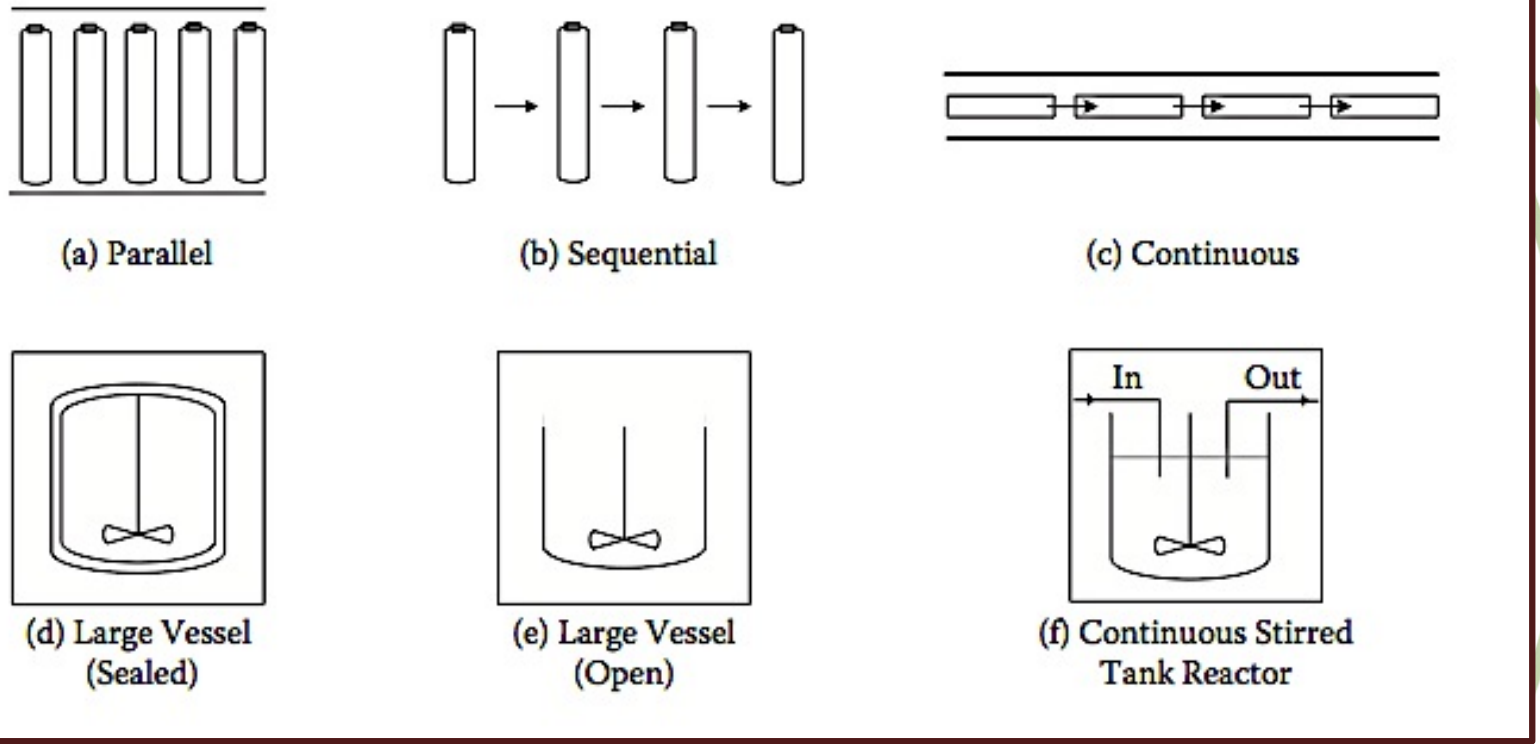
Microwave Scale-Up



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Microwave Scale-Up

TABLE 5.1
Operating Parameters of Commercial-Scale-Up Microwave Reactors

Type	Microwave Reactor	Power (W)	Vessel Size (mL)	Max Fill[a] (mL)	Max Temp (°C)	Max Pressure (bar)	Solid Handling[b]
Parallel	Synthos (HF100)	1400	16 × 100	1000	240	40	(Yes)
	Synthos (XQ80)	1400	8 × 80	400	300	80	(Yes)
	MARS	1600	14 × 75	700	200	40	(Yes)
	MicroSYNTH Q20	1000	20 × 45	600	250	80	(Yes)
	MicroSYNTH SK-10	1000	10 × 100	700	250	80	(Yes)
Single, sealed	Advancer	1200	350	250	250	20	Yes
	BatchSYNTH[c]	1000	1000[d]	700[d]	230[d]	8[d]	(Yes)
	UltraCLAVE[e]	1000	3500	2000[f]	300	200	(Yes)
Single, open	MARS	1600	5000	3000	Solvent bp	1	Yes
	MicroSYNTH	1000	4000	2500	Solvent bp	1	Yes
Sequential	Voyager	300	80	$n \times 50$	250	20	No
	Kilobatch	1200	350	4 × 250[g]	250	20	Yes
Continuous	FlowSYNTH	1000	200	Unlimited	200	30	No

[a] Usable reactor volume per cycle.
[b] (Yes) = solids handled under most conditions dependent on density, loading, and agitation.
[c] Based on MicroSYNTHPlus.
[d] Smaller single vessels possible with different operating parameters.
[e] Multiple parallel vessel configurations also possible.
[f] In single vessel use.
[g] $n \times 250$ if homogeneous reaction mixture.

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Microwave Scale-Up

FIGURE 5.3 The Anton Paar Synthos 3000. (Reproduced with permission fro
Paar.)

FIGURE 5.4 The CEM MARS in sealed-vessel mode. (Reproduced with permission from CEM Corp.)

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Microwave Scale-Up

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Microwave Scale-Up

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Microwave Scale-Up

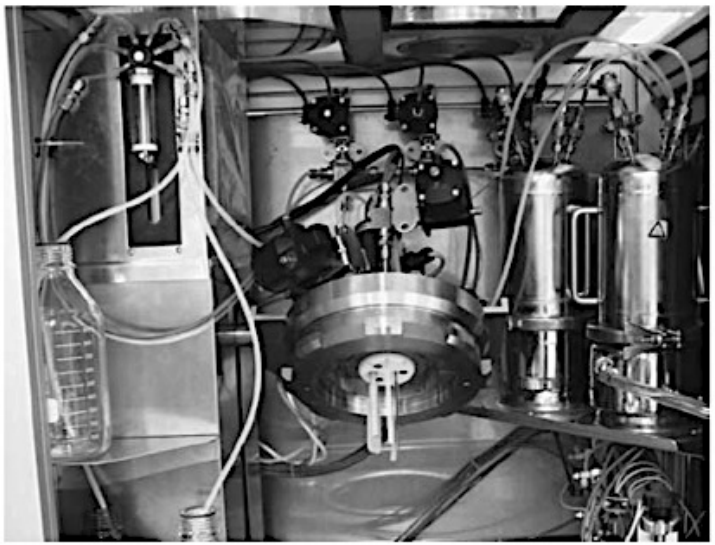

FIGURE 5.11 The Biotage Advancer Kilobatch, showing liquid- and solid-handling functionality together with product collection receptacles. (Reproduced with permission from Biotage.)

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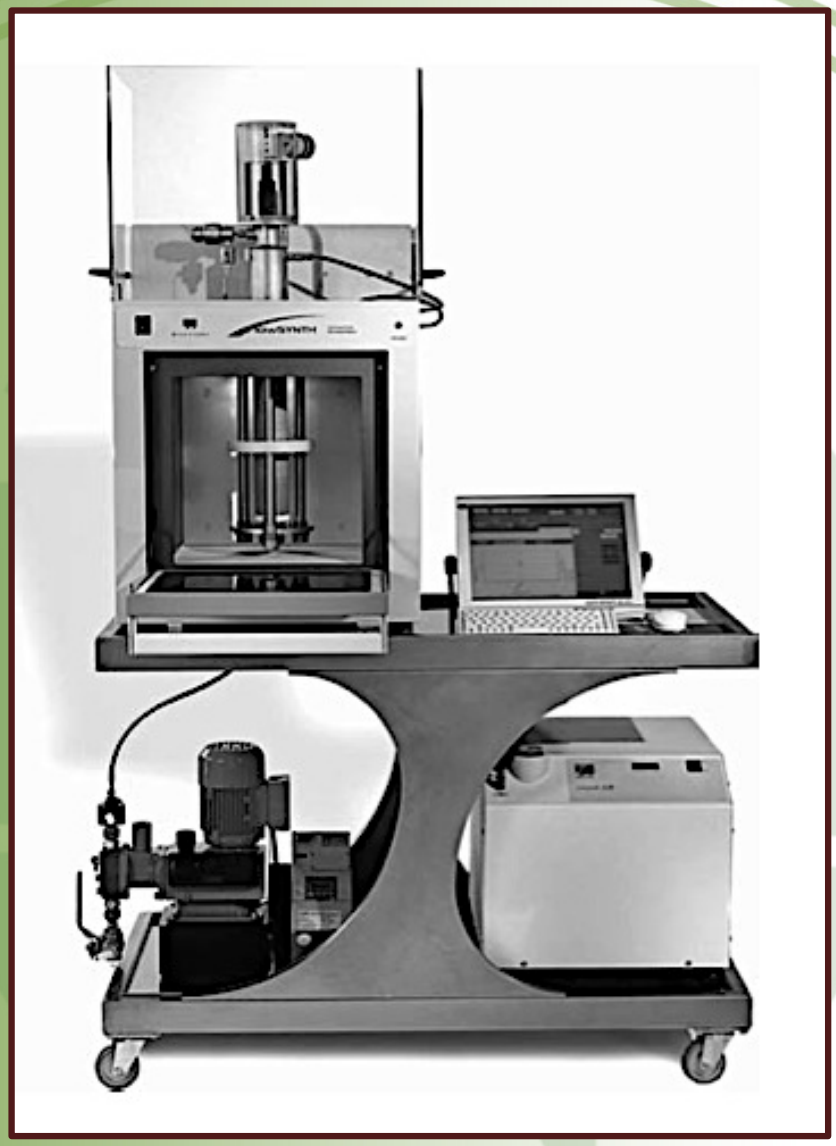
Microwave Scale-Up



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Microwave Scale-Up

TABLE 5.2
Reactor Productivity for a Typical 10% w/v Pharmaceutical Process

Type	Microwave Reactor	Approximate Cycle Time	Typical Throughput (g)	Manual Handling	Achievable Number of Batches Per Day[a]	Typical Daily Throughput (g)
Parallel	Synthos (HF100)	45 min	100	High	2 (4)[b]	250
	Synthos (XQ80)	45 min	40	High	2 (4)[b]	100
	MARS	1 h	70	High	2 (4)[b]	200
	MicroSYNTH[c]	1 h	70	High	2 (4)[b]	200
Single, sealed	Advancer	30 min	25	Low	8–16[d]	300
	BatchSYNTH	1 h	70	Low	4–6	500
	UltraCLAVE	1.5 h	200	Low	4	800
Single, open	MARS	1 h	300	Medium	4–6	1200
	MicroSYNTH	1 h	250	Medium	4–6	1000
Sequential	Voyager	15 min	n × 5	Automated	30 (90)[e]	200 (600)[e]
	Kilobatch	20 min	4 × 25	Automated	32 (90)[e]	800 (2400)[e]
Continuous	FlowSYNTH	2 L/h[f]	200 g/h[f]	Automated	Continuous	1600 (4800)[e,f]

[a] Assuming typical loading, unloading, and cleaning times.
[b] Assumes use of two rotors.
[c] For several vessel configurations.
[d] For heterogeneous reactions; for homogeneous, see Kilobatch below.
[e] With 24 h continuous operation.
[f] Data from Reference 28.

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Synthetic Transformations

TABLE 5.3
General Summary of Reaction Classes Suitable for Microwave Scale-Up

	Beneficial/Suitable	No Benefit/Unsuitable
Major reaction classes	Additions condensations	Amide bond formation
	Alkylations/acylations	Deprotections (excluding hydrogenations)
	Heterocycle formation	Functional group additions
	Hydrogenations	Functional group interconversions
	S_NAr reactions	Protection reactions
Minor reaction classes	Cycloadditions	Grignard reactions
	Friedel–Crafts reactions	Low-temperature organometallic reactions (e.g., lithiation)
	Metal-catalyzed reactions (e.g., Heck and Suzuki couplings)	Oxidations
	[Peptide synthesis][a]	Reductions (metal hydrides, excluding hydrogenations)
	[Polymer synthesis][b]	
	Thermal rearrangements	
Other reaction parameters	Autoclave/pressure reactions	
	Reactions with gases	
	Reactions with solid-support reagents	
	Reactions with water as solvent	
	Where thermodynamic product required	

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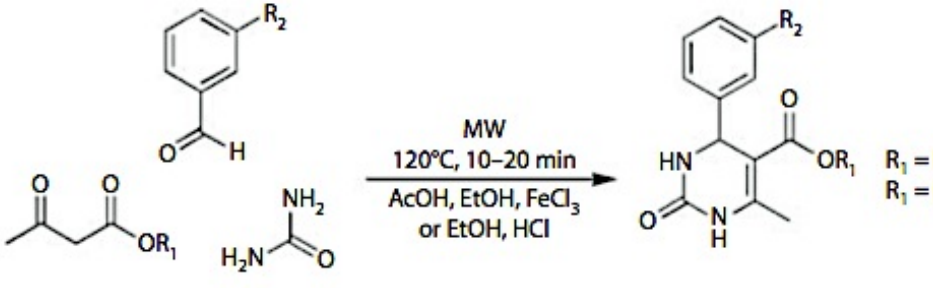
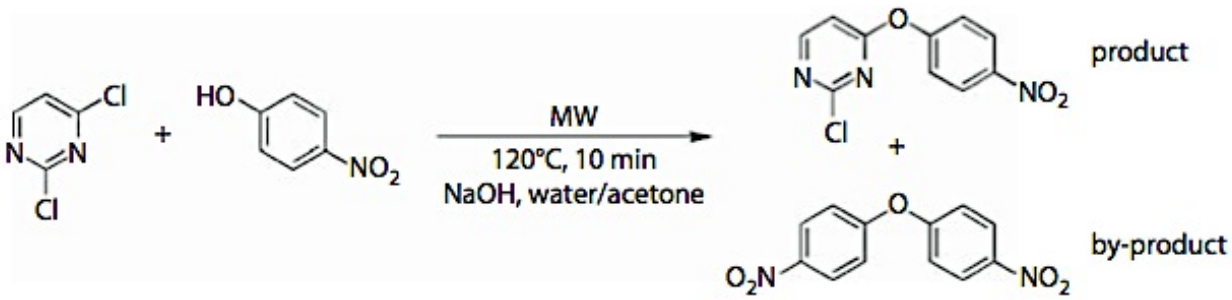
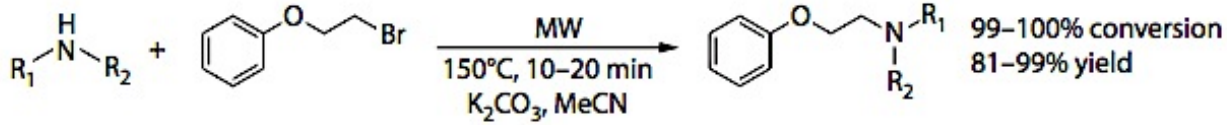
Synthetic Transformations



SCHEME 5.3



SCHEME 5.4



SCHEME 5.5

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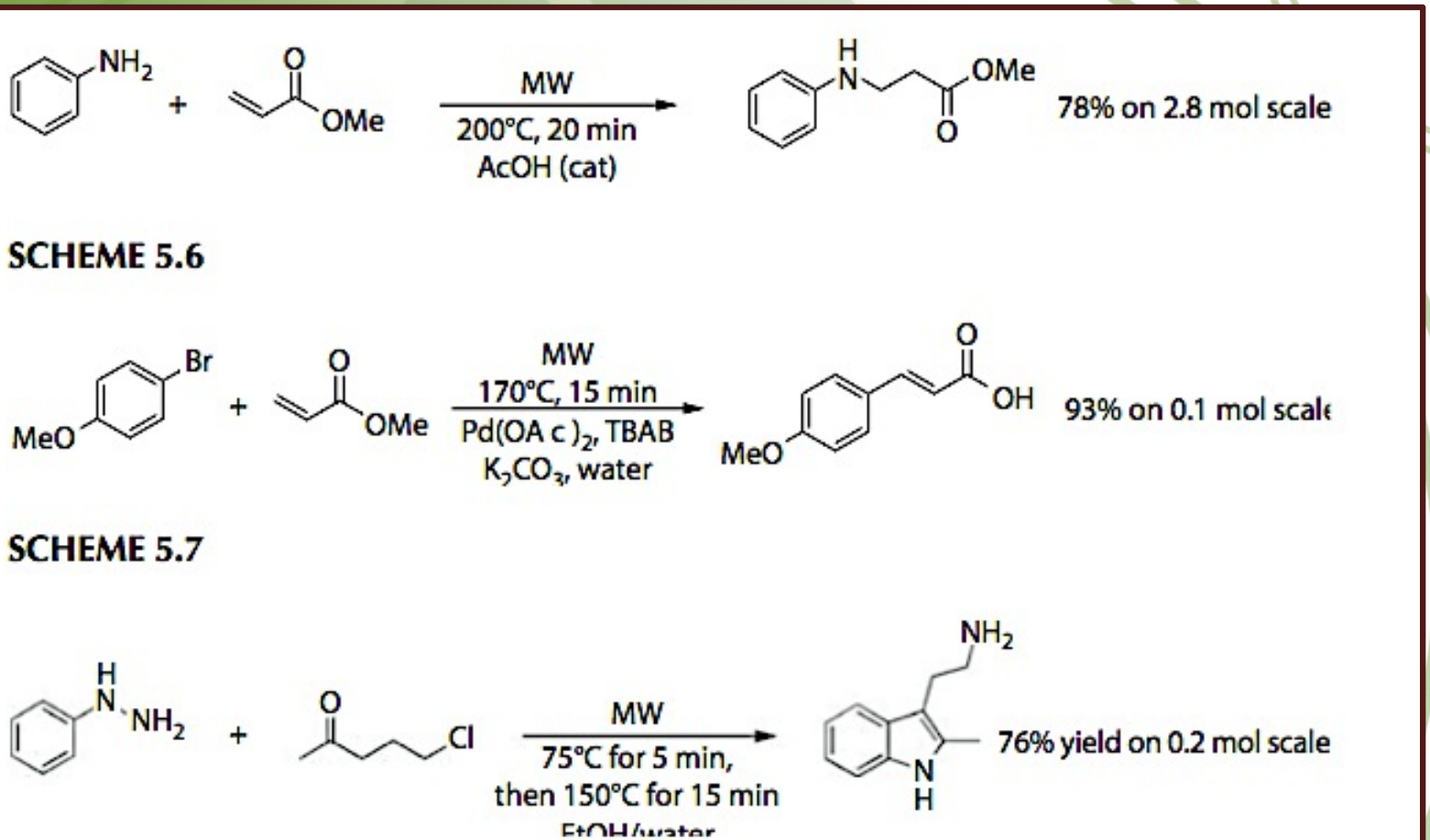
Synthetic Transformations



SCHEME 5.6

SCHEME 5.7

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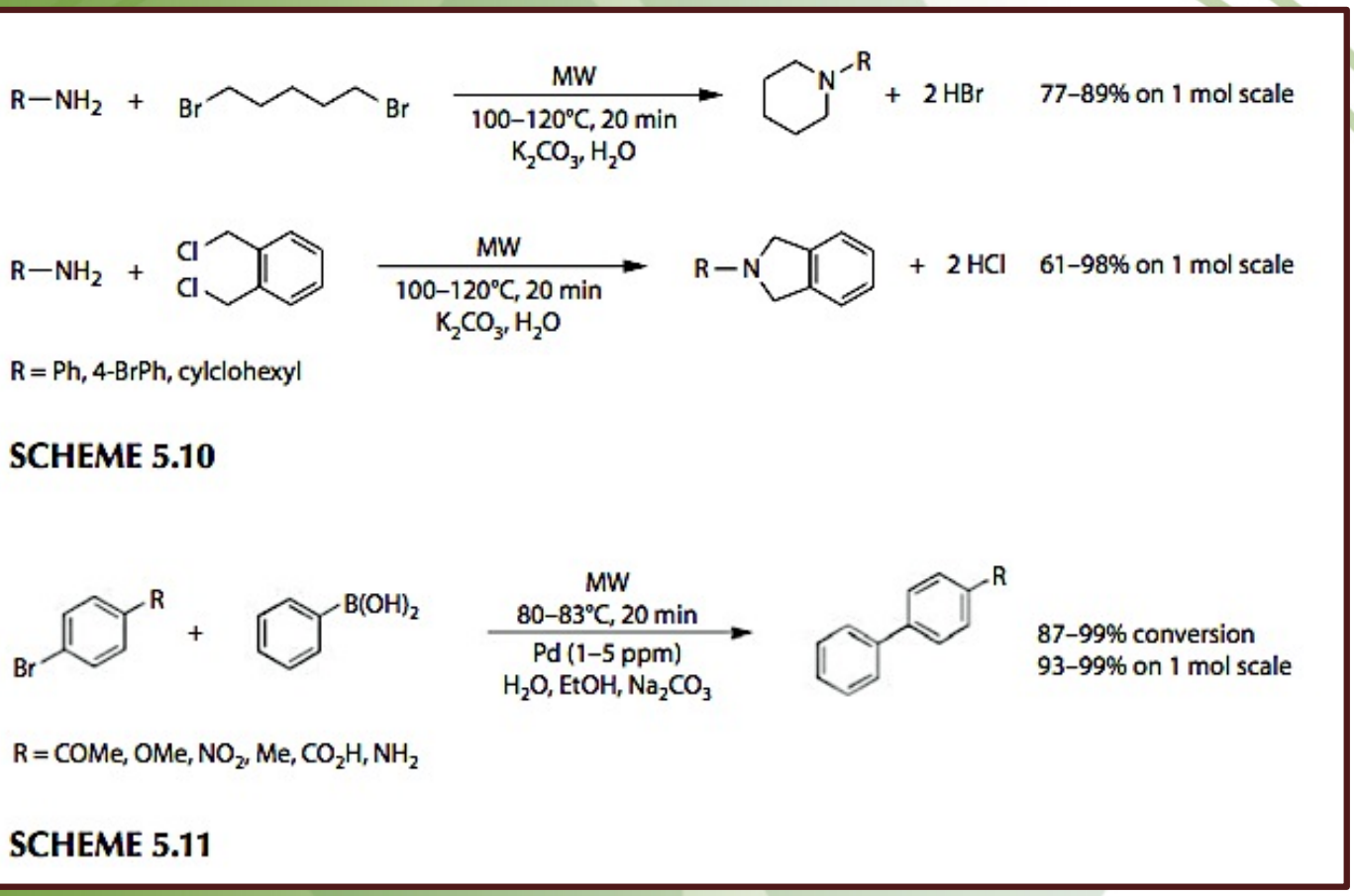
Synthetic Transformations



SCHEME 5.10

SCHEME 5.11

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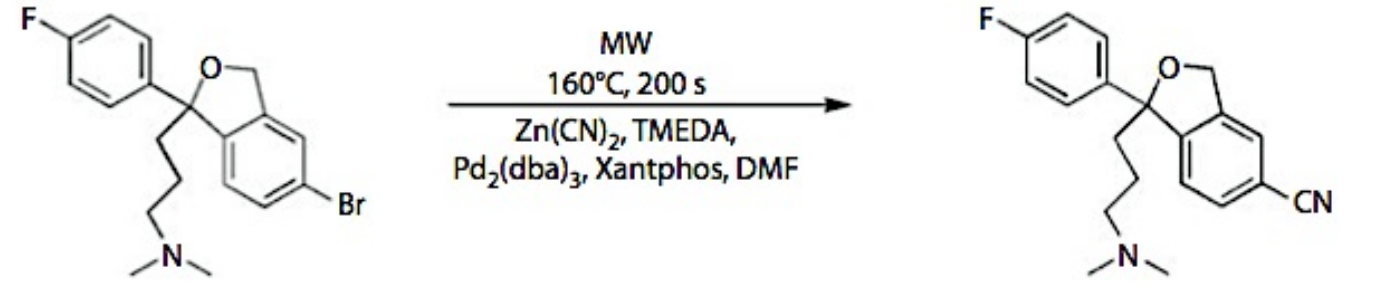
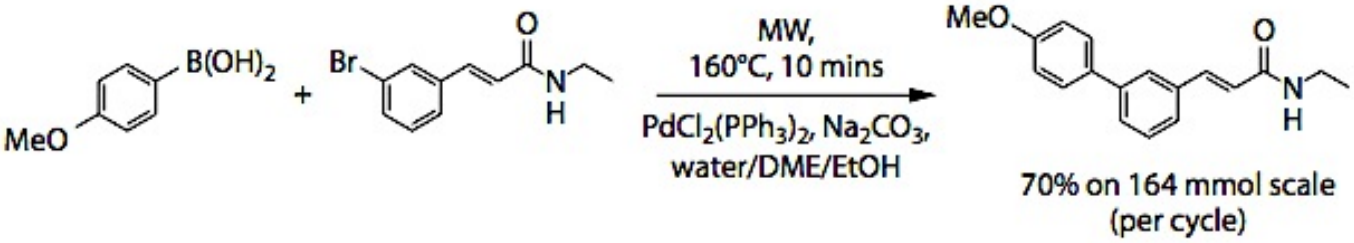
Synthetic Transformations



SCHEME 5.15



SCHEME 5.16

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Synthetic Transformations

Table 12.2 *Continuous flow microwave reactions reported by Bowman* et al. *[32] and Bergamelli* et al. *[33].*

Entry	Reaction type	Reaction	Scale (mol)	Yield (%)
1	Suzuki	$PhB(OH)_2$, 0.038 mol % Pd, NaOH. EtOH, MW, 150 °C, 40 mL min^{-1}	0.25	83
2	Heck	CO_2Me, 0.1 mol % $Pd(OAc)_2$, TBAB, Hunig's base, DMA, MW, 140 °C, 20 mL min^{-1}	1	60
3	Esterification	n-BuOH, H_2SO_4, MW, 150 °C, 200 mL min^{-1}	22	78
4	Heterocycle formation	$H_2N(C=S)NH_2$, EtOH, MW, 140 °C, 34 mL min^{-1}	0.5	97

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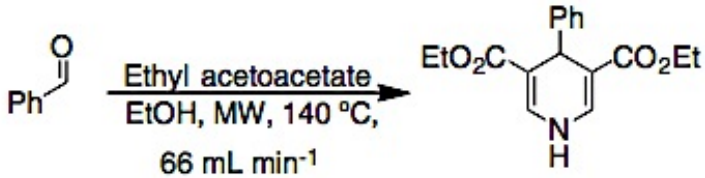
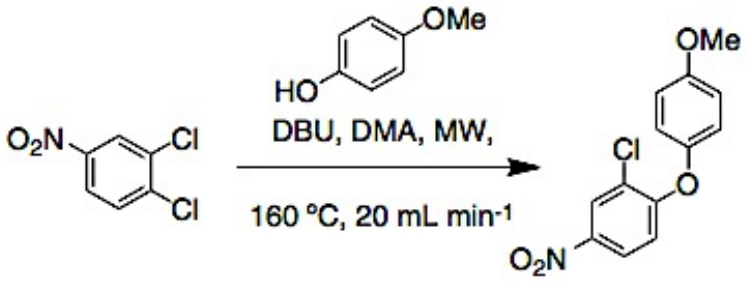
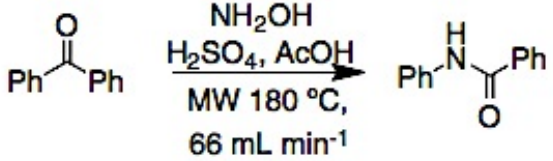
Synthetic Transformations

5	Hantzsch		1	91
6	S_NAr		0.6	95
7	Beckmann		2.7	50

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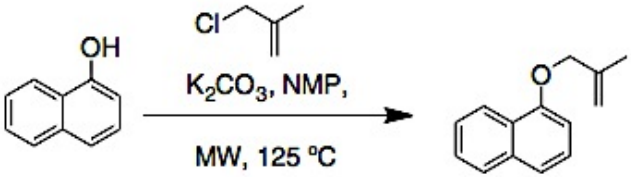
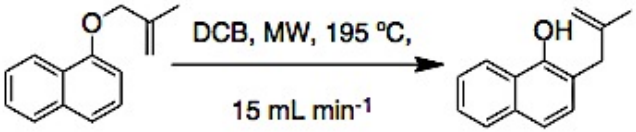
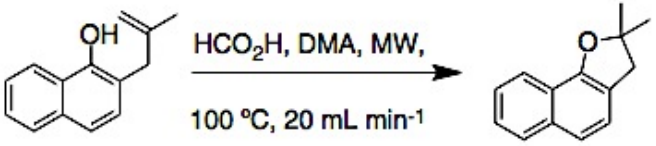
Synthetic Transformations

Table 12.2 *(Continued)*

Entry	Reaction type	Reaction	Scale (mol)	Yield (%)
8	Alkylation		1	0
9	Claisen		1	99
10	Naphthofuran formation		1	84

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