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Microwave-Assisted Olefin Metathesis

Yoann Coquerel*[a] and Jean Rodriguez*[a]

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The beneficial effect of microwave irradiation instead of classical thermal conditions in olefin metathesis reactions is illustrated through a series of literature examples of ring-closing-metathesis and cross-metathesis reactions.

Introduction

Following the proposal of the mechanism for the olefin metathesis reaction by Yves Chauvin in the early 1970s,[1] the exponential development of olefin ring-opening metathesis polymerization (ROMP) and ring-closing metathesis (RCM) since the 90s, and more recently of cross-metathesis (CM) reactions, has essentially been due to the discovery of some stable molybdenum[2] (Schrock) and ruthenium[3–5] (Grubbs) carbene catalysts. The 2005 Nobel prize for chemistry was jointly attributed to Yves Chauvin, Richard R. Schrock and Robert H. Grubbs for their determinative contribution to what is now recognized as one of the most efficient, reliable and versatile methods for C=C bond formation.[6] The scope of olefin metathesis in organic chemistry is considerable and the growing number of new and more active/stable metal carbene catalysts continuously made available generates new opportunities.[7]

However, some substrates are still reluctant to undergo efficient metathesis reactions under classical thermal conditions, which translates into prolonged reaction times, low yields and/or large amounts of catalyst. In recent years, microwave (µW) irradiation[8] has been proposed as a complementary activation mode for olefin metathesis. In many cases it has resulted in a dramatic shortening of reaction times and more importantly has allowed otherwise unproductive metathesis reactions. The first report on µW-assisted olefin metathesis appeared in 2000 and the method has gained increasing popularity since then.[9] In this microreview, an exhaustive survey of the literature available on µW-assisted olefin metathesis is detailed (ROMP is excluded) covering the period 2000 to June 2007. Accordingly, the manuscript will be divided into two sections dealing

Yoann Coquerel was born in Rouen (France) in 1975. After studying chemistry at the University Joseph Fourier in Grenoble (France) where he completed his Ph. D. in 2001 under the supervision of Professor Jean-Pierre Deprés, he moved to Florida State University in Tallahassee (USA) to join the group of Robert A. Holton as a post-doctoral associate. Since 2003 he has worked as a CNRS researcher at the University Paul Cézanne in Marseille (France). His research interests include the development of eco-compatible target-oriented synthetic organic strategies, the total synthesis of natural products and the use of transition metals in organic synthesis. In 2002 he was awarded the Fournier – French Chemical Society prize for his Ph. D. Thesis.

Jean Rodriguez was born in Cieza (Murcia, Spain) on 25 June, 1958, and in 1959 his family emigrated to France. After studying chemistry at the University Paul Cézanne in Marseille (France), he completed his Ph. D. as a CNRS researcher with Professors B. Waegell and P. Brun in 1987. He completed his Habilitation in 1992, also at Marseille, where he is currently Professor and Director of the UMR-CNRS-6178-SYMBIO. His research interests include the development of domino and multicomponent reactions, and their application in stereoselective synthesis. In 1998 he was awarded the ACROS prize in Organic Chemistry from the French Chemical Society.

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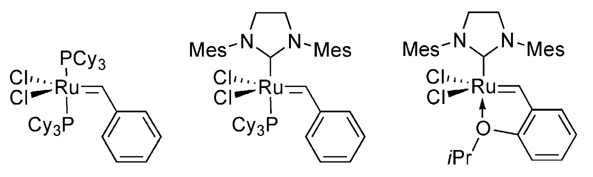
with RCM and CM. The catalysts used are depicted in Figure 1. The results relating to the development of the method will be presented in chronological order and the effective role of µW irradiation in the olefin metathesis reaction will be discussed throughout the manuscript. However, it is not the purpose of this article to introduce and discuss µW-assisted organic chemistry (MAOS) and the interested reader should consult recent reviews and monographs available on MAOS.[8]

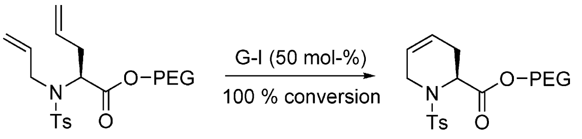


G-I **G-II** **H-G**

Figure 1. Catalysts used in µW-assisted olefin metathesis.

Microwave-Assisted Ring-Closing Metathesis

The first report on µW-assisted olefin metathesis appeared in 2000 and described the preparation of poly(ethylene glycol) (PEG)-supported cyclic amino acid derivative **2** (Scheme 1).[10] In this case the µW irradiation allowed the reaction time to be reduced from 24 hours under thermal conditions to 10 minutes. In this initial study, a domestic multimode µW oven was used and the temperature of the irradiated reaction mixture was not measured. It should also be noted that a large amount (50 mol-%) of the G-I catalyst was used under both classical and µW conditions. However, this pioneering work has set the stage for the developments presented in this microreview.

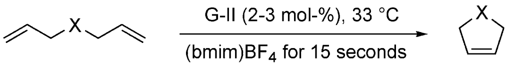


1 **2**

Thermal conditions: water, 20 °C, 24 h
µW conditions: neat, domestic µW oven at 850 W, *T* not measured, 10 min

Scheme 1.

To further study the effect of µW irradiation during RCM reactions, Kiddle and co-workers reported a series of comparative RCM reactions for the formation of five-membered rings **4** under thermal and µW conditions.[11] They studied the reaction in both the ionic liquid (bmim)BF$_4$ and in dichloromethane. Ionic liquids are indeed excellent solvents (or additives, see below) for µW-assisted chemistry as they couple with microwaves through a dielectric heating mechanism. A spectacular accelerating effect was observed under µW conditions with both solvents (Scheme 2). From this study the authors concluded that the µW energy produces non-thermal effects that may involve direct coupling to one of the two or both reactants in this transformation. Here again, a domestic µW oven was used and these results should be taken with precaution. Indeed, a subsequent study by Kappe and co-workers, who investigated the exact same substrate/catalyst/solvent system albeit in a dedicated monomode µW apparatus, led to the opposite conclusion.[12] In this study, the involvement of a non-thermal µW effect was specifically addressed and the authors could not find any evidence for a significant effect as there was a close correlation between the results obtained under thermal and µW superheating. Interestingly, comparison of the µW heating profiles of dichloromethane in a domestic[11] and a dedicated[12] µW oven showed that dichloromethane is not microwave-transparent and will heat up significantly in a single-mode cavity although this heating effect is also caused in part by the heating of the borosilicate glass vessel which is not completely transparent to µW irradiation either. It was also reported that doping the solvent with small amounts of an ionic liquid such as (bmim)PF$_6$ is enough to increase significantly the dielectric constant of the medium and speed up the metathesis reaction by a thermal effect under µW irradiation.



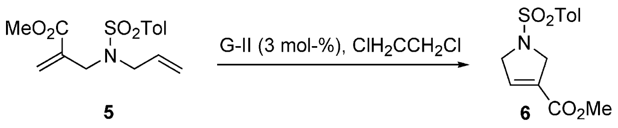
3 **4**

	Substrate	µW conditions (110 W)	thermal conditions
bmim	X = C(CO$_2$Et)$_2$	100%	3%
	X = N-Ts	100%	0%
CD$_2$Cl$_2$	X = C(CO$_2$Et)$_2$	100%	21%
	X = N-Ts	91%	45%

Scheme 2.

The introduction of an electron-withdrawing substituent onto the olefin usually requires a relatively large amount of catalyst and a prolonged reaction time and/or results in a low conversion and yield of the expected cyclized product. Wilson and co-workers evidenced that they were observing a rate acceleration and an increase in catalyst efficiency for the RCM of substrate **5** bearing a methoxycarbonyl substituent (Scheme 3).[13] They rationalized their results by invoking a higher catalyst turnover or slower catalyst decomposition under µW irradiation. The method allowed the efficient formation of methoxycarbonyl-substituted dihydropyrroles, dihydrofurans and cyclopentenes. *N*-Allylated aza-Baylis–Hillman adducts can also serve as good substrates for this µW-assisted RCM leading to dihydropyrroles.[14] A closely related process was reported for the synthesis of dihydropyrroles and tetrahydropyridines which led to a similar drastic reduction in reaction time and reduced catalyst loading (down to 1%).[15]

The domino RCM reaction (internal alkyne–olefin RCM, then bis-olefin RCM) of the Schiff base **7** (Scheme 4) could not be performed efficiently with the G-I catalyst and required 30 mol-% of the G-II catalyst added in three portions over 6 hours to go to completion under classical ther-



Conditions	Time	Conversion (yield)
Thermal, 50 °C	5 min	62 %
Thermal, 50 °C	20 min	75 %
Thermal, 50 °C	5 h	75 %
µW, 0–10 W, 1 psi, 50 °C	5 min	85 %
µW, 60–80 W, 60 psi, 150 °C	5 min	97 % (82 %)

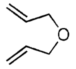
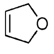
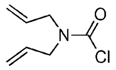
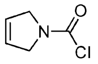
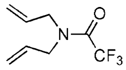
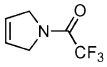
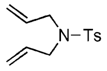
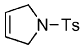
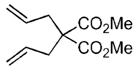
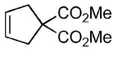
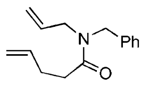
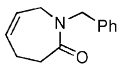
Scheme 3.

mal conditions (toluene, 85 °C). These results were attributed to the fact that a relatively high temperature was used for several hours causing a gradual decomposition of the catalyst. This problem has been overcome by exposure of the reaction mixture to µW heating at a high temperature (160 °C) for a short time.[16] The authors argued that µW energy leads to extremely rapid heating by direct transfer of heat into the reaction medium in contrast to conventional heating in which the energy is transferred via the vessel wall. A thermally unstable catalyst may be expected to deteriorate more rapidly next to the hot vessel walls under conventional reaction conditions than in the uniformly heated interior of the µW-irradiated solution. However, in these experiments, the vessels used were glass tubes (Duran™) which are not totally transparent to µW irradiation, and the reactions were not performed at the same temperature. Another example of enyne µW-assisted RCM is presented in the next section (see Scheme 9). In this latter study the authors realized the RCM of internal alkynes and obtained similar results by heating the reaction mixture in a sealed tube either with µW or in an oil bath at 100 °C.

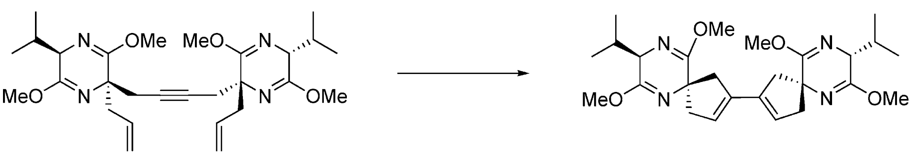
The use of a polystyrene-supported Ru catalyst (G-II based) for RCM reactions under µW irradiation was evaluated in the preparation of eight-membered-ring benzolactams.[17] A related RCM strategy was studied in a continuous-flow microreactor for µW-assisted capillary organic synthesis.[18] Moreover, the beneficial effect of µW-assisted olefin RCM for the formation of eight-membered heterocycles was demonstrated through the synthesis of some buflavine analogues (dibenzazocines).[19]

Contemporaneously to the report by Kappe and coworkers on their study of the absence of a non-thermal µW effect in RCM performed in diluted dichloromethane solutions (superheating),[12] a paper from Thanh and Loupy was accepted for publication relating a non-thermal µW effect in solvent-free RCM (no superheating).[20] A series of solvent-free RCM reactions were performed under identical conditions (time, temperature, vessel, warm-up ramp time) under classical thermal and µW irradiation conditions and a µW effect was revealed in all cases (except when the reactivity of the system was too high, Table 1). According to the authors, this effect can be related to an increase in polarity as the reaction progresses, which is consistent with the mechanism involving a metallacyclobutane with polar carbon–metal bonds. µW irradiation can therefore improve this reaction by enhancing the dipole–dipole stabilization of the transition state relative to the ground state.

Table 1. Classical versus microwave-assisted heating in RCM reactions.

Entry	Substrate	Product	G-I, temp., time	µW yield (%)	Δ yield (%)
1			4 mol-%, 50 °C, 3 min	94	78
2			4 mol-%, 50 °C, 5 min	67	48
3			4 mol-%, 50 °C, 3 min	90	74
4			4 mol-%, 50 °C, 0.5 min	100	100
5			1 mol-%, 80 °C, 1 min	80	60
6			4 mol-%, 50 °C, 30 min	70	44

Performing RCM under µW irradiation has been particularly helpful for the cyclization of peptides bearing olefinic termination groups. For example, the cyclic peptide **10**



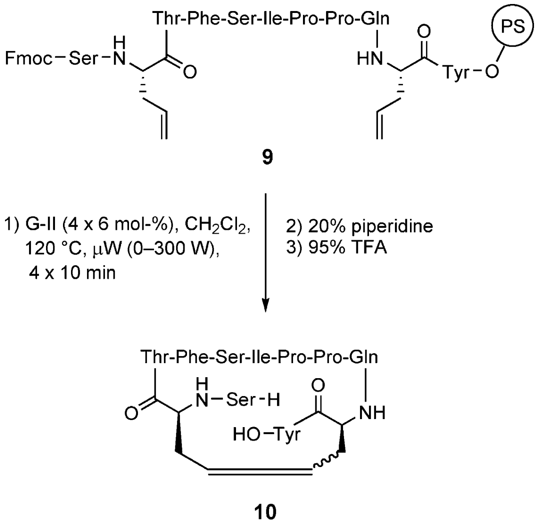
7 **8**

Thermal conditions: G-I (2 x 10 mol-%), toluene, 85 °C, 2 x 5 h; conversion a few %
µW conditions: G-I (14 mol-%), toluene, 160 °C, 45 min; conversion 76 %

Thermal conditions: G-II (3 x 10 mol-%), toluene, 85 °C, 3 x 3 h; conversion 92 %
µW conditions: G-II (5 mol-%), toluene, 160 °C, 10 min; conversion 100 %

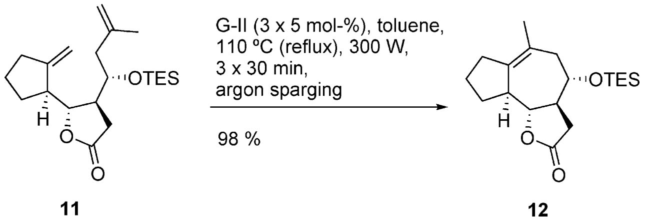
Scheme 4.

was obtained from the acyclic precursor **9** by solid-phase µW-assisted RCM followed by deprotection and cleavage (Scheme 5).[21a,21b] A similar strategy was applied more recently to the synthesis of hydrogen-bonded surrogate-based α-helices and some of their analogues.[21c] In this latter study the authors reported that µW irradiation has a surprising re-energizing effect on the G-II catalyst which catalytically dies when the reaction is performed in an oil bath. However, the reactions were not performed under rigorously comparable conditions. Recently, some 29- to 33-membered bis-pyridinium macrocycles were efficiently assembled by using µW-assisted RCM in the presence of 2% of catalyst G-II[22a] and similar conditions were applied to the RCM macrocyclization of a derivative of the naturally occurring 12-membered macrolide curvularin.[22b]

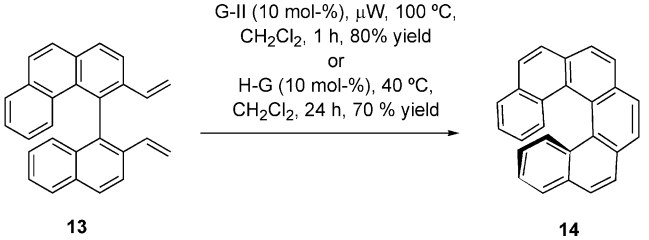


Scheme 5.

In the course of a study on guaianolide total synthesis, Reiser and co-workers reported a systematic study of RCM to give the tetrasubstituted double bond in **12** (Scheme 6).[23] By combining two techniques, namely, sparging an inert gas through the solution together with dielectric heating by µW irradiation, a high-yielding RCM was achieved in this sterically demanding case. The key aspects seem to be that rapid µW irradiation allows the catalyst a longer lifetime, while sparging with the inert gas purges the evolving ethylene to shift the equilibrium to the product. Noteworthy, attempts to achieve RCM in a closed reaction vessel under µW irradiation failed completely and the starting material could be recovered almost quantitatively, indicating the crucial role played by the inert-gas sparging. Another particularly challenging example concerns some substituted [5]helicenes and [6]- and [7]helicenes which have been synthesized by olefin RCM through classical thermal heating with the H-G catalyst or, advantageously, under µW irradiation with the G-II catalyst, as illustrated for the [6]helicene **14** (Scheme 7).[24] A highlight of this method is the facile formation of various substituted helicenes from readily available binaphthyls or phenanthryls. This ease of functionalization suggests that the method could be of significant interest in the fields of materials science and medicinal chemistry. These two distinct studies reinforce the idea that µW-assisted olefin RCM can be remarkably effective in generating strained molecular architectures.

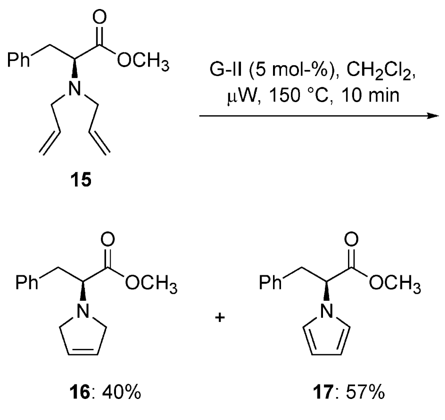


Scheme 6.



Scheme 7.

RCM reactions of olefinic substrates incorporating a free amine function are rather difficult. The amines often have to be deactivated by conversion to amides, carbamates or sulfonamides (see above) or by protonation for the RCM reactions to occur in reasonable yields. Alternatively, the reaction can be conducted in the presence of a catalytic amount of Ti(O*i*Pr)$_4$.[25] The first example of µW-assisted RCM of a basic nitrogen-containing compound was reported by Wilson and co-workers[13] and a more systematic study appeared recently. Several chiral diallylamine substrates such as **15**, which were generated from L-amino acids, were subjected to µW-assisted RCM reactions [without Ti(O*i*Pr)$_4$] and all the substrates cyclized readily with full retention of configuration in substantially less time than by using conventional conditions [with Ti(O*i*Pr)$_4$].[26] However, the reaction gave the pyrrole derivative (e.g., **17**) as the main product in almost all cases (Scheme 8), whereas the dihy-

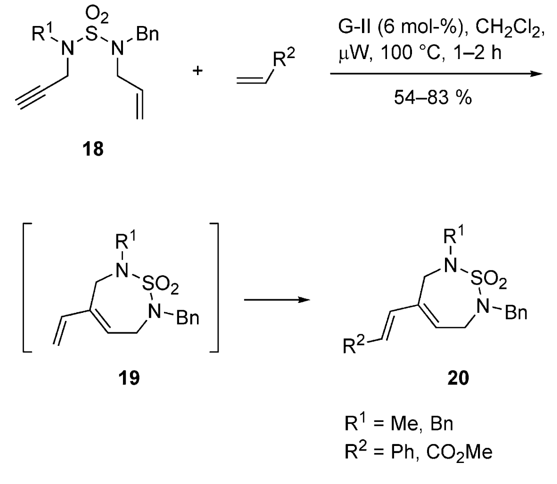


Scheme 8.

dropyrrole (e.g., **16**) was formed in high yield under classical thermal conditions in the presence of $Ti(OiPr)_4$. These results suggest that under µW irradiation, not only RCM took place but also isomerization and dehydrogenation. A series of diallylanilines were also found to produce the corresponding pyrroles in high yields only when subjected to µW-assisted RCM.[26]

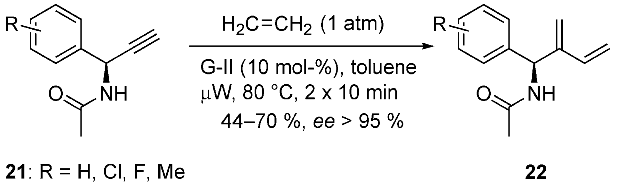
Microwave-Assisted Cross-Metathesis

In 2004, Brown and co-workers reported on an elegant domino RCM/CM reaction involving sulfamide-linked 1,8-enynes and vinylic or acrylic derivatives.[27] When subjected to oil-bath heating (dichloromethane, reflux) in the presence of 10 mol-% of the G-II catalyst, the enyne **18** underwent RCM to give the desired diene **19** (49 and 56%, two examples), but the product was contaminated by some CM overreacted homocoupling dimer (12 and 21%). Under µW irradiation, the enyne **18** readily underwent RCM to give the desired diene **19** in a better yield (60 and 63%) and with a better selectivity (10 and 8% of homodimer). In the presence of either styrene or methyl acrylate in the starting solution, the intermediate diene **19** underwent an additional CM reaction in the same pot to give the substituted (*E*)-**20** in good yield (Scheme 9).



Scheme 9.

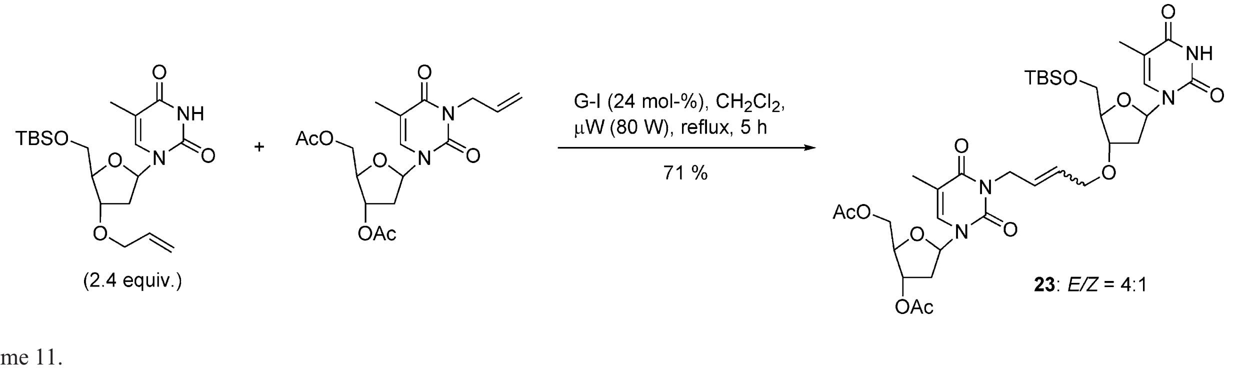
A µW-assisted ethylene/alkyne CM was reported for the preparation of both enantiomers of 2-(1-acetylamino-1-arylmethyl)-1,3-butadienes (Scheme 10).[28] Under 1 atm of ethylene and classical conditions (various temperatures and solvents), no CM diene product **22** could be detected. However, under µW irradiation the reaction proved possible providing at least 10 mol-% of the G-II catalyst was used and the expected dienes could be isolated with complete retention of their optical activity. The authors attributed the success of the reaction to the rapid and uniform heating of the reaction mixture and the increased lifetime of the catalyst, a result of the elimination of wall effects under µW dielectric heating.



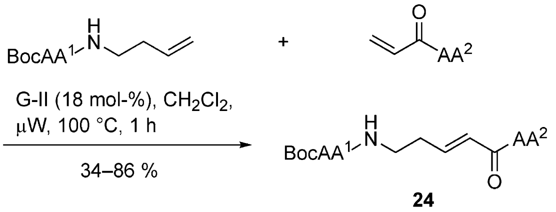
Scheme 10.

Some hetero-dinucleosides derived from thymidine were prepared by CM under µW irradiation (Scheme 11).[29] These reactions are quite difficult as this strategy is often hampered by the formation of two unwanted homodimeric compounds. In this study, µW irradiation did not only result in shorter reaction times, but also allowed much better selectivity for the heterodimer **23** over the homodimer, which is the major product when the CM is performed by classical oil-bath heating. Interestingly, the µW irradiation did not affect at all the stereochemical outcome of the reaction.

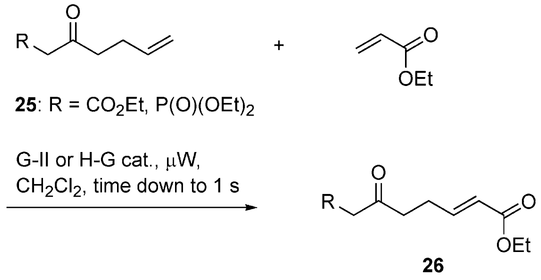
The beneficial effect of µW irradiation has also been illustrated for the CM homocoupling of *N*-allylamino acid substrates.[30] The synthesis of peptidomimetics **24** was realized by CM of amino acids (AA) bearing an olefinic terminal group, and the method has been applied to larger peptides (Scheme 12).[31] The resulting product, which has a linker with a length equivalent to that of two amino acids with the desired configuration [(*E*) isomer] yet lacking the central amide bond, has potential for use in the synthesis of modified proteins. It is worth noting that the G-II catalyst was by far superior to the H-G catalyst in these CM reactions.



Scheme 11.

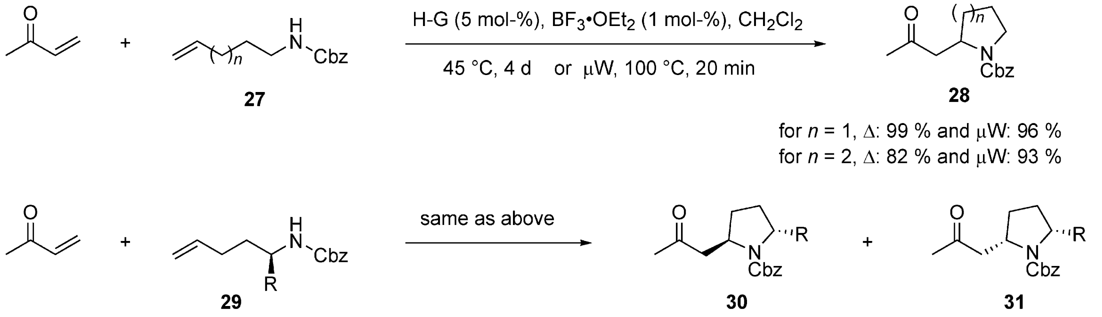


Scheme 12.



Scheme 13.

Bargiggia and Murray systematically examined the CM of ethyl acrylate with various functionalized olefins **25** under µW conditions (Scheme 13).[32a] They studied the same reaction under classical conditions (reflux) and µW irradiation and observed effective acceleration of the CM reactions with both the G-II and H-G catalysts. However, similar results and stereochemistry were obtained by per-

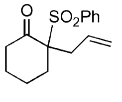
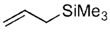
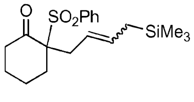
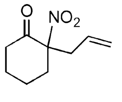
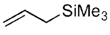
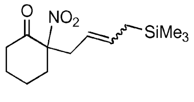
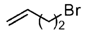
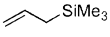
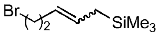
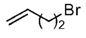
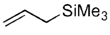
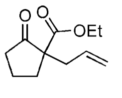
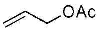
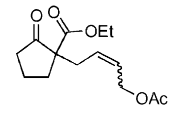
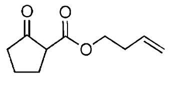
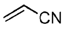
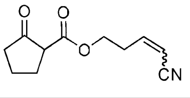


for *n* = 1, Δ: 99 % and µW: 96 %
for *n* = 2, Δ: 82 % and µW: 93 %

for R = *i*Pr, Δ: 97 % (*dr* = 3:1) and µW: 81 % (*dr* = 1:4)
for R = CF_3, Δ: 76 % (*dr* = 5:1) and µW: 97 % (*dr* = 1:3)

Scheme 14.

Table 2. Classical versus microwave-assisted heating in CM reactions.

Substrate	Olefin	Catalyst (mol-%)	Product	Thermal conditions		µW irradiation	
				Conditions	Yield (%); *E*/*Z* ratio	Conditions	Yield (%); *E*/*Z* ratio
		G-II (3)		neat, 90 °C, 24 h	51; 1:1	neat, 60 °C, 35 min	68, 1:1
		G-II (4)		CH_2Cl_2, 40 °C, 15 % $\mathrm{Ti(O}i\mathrm{Pr)_4}$, 16 h	40; 1.8:1	CH_2Cl_2, 60 °C, 15 % $\mathrm{Ti(O}i\mathrm{Pr)_4}$, 40 min	62; 1.8:1
		G-II (0.8)		neat, 90 °C, 8 h	6; ca. 2:1	neat, 60 °C, 40 s	77; 1.9:1
		G-II (0.15)		not tested	–	neat, 60 °C, 3 min	69; 1.9:1
		G-II (3)		CH_2Cl_2, 40 °C, 12 h	41; 1:5.7	CH_2Cl_2, 60 °C, 15 min	78; 1:5.7
		H-G (3+1)		CH_2Cl_2, 100 °C, 20+10 min	79; 1:3.1	CH_2Cl_2, 100 °C, 20+10 min	89; 1:3.3

forming the reactions in sealed tubes at 100 °C either under oil-bath or μW heating. The authors thus ascribed the observed acceleration to the efficient and rapid μW heating and the increased pressure in the μW apparatus and not to a possible non-thermal μW effect. These conditions were used recently in the total synthesis of naturally occurring alkaloids of the stephacidin and notoamide families.[32b]

Fustero et al. recently reported a domino CM–aza-Michael strategy for the synthesis of substituted pyrrolidines and piperidines.[33] In the presence of the H-G catalyst and a Lewis acid, amine **27**, bearing a terminal olefin, underwent CM with methyl(vinyl)ketone and the resulting ω-amino enone further underwent an aza-Michael addition to finally give the cyclic β-amino carbonyl derivative **28** in quantitative yield. The same results were obtained either by heating the reaction mixture (dichloromethane) at reflux for 4 days or by μW irradiation at 100 °C for 20 minutes (Scheme 14). With α-branched amines of type **29** the reaction could also be performed under both thermal and μW conditions with comparable efficiency, but the stereochemical issue of the reaction was different: thermal conditions (45 °C) favoured the *trans* isomer **30** (thermodynamic product) whereas under μW irradiation (100 °C) the *cis* isomer **31** (kinetic product) was the major product (Scheme 14).

The highly beneficial effect of μW irradiation compared with classical heating in the case of reluctant CM reactions was evidenced very recently through a series of comparative experiments.[34] The reactions were performed with or without solvent and in every case the μW conditions proved superior in terms of efficiency while the *E*/*Z* ratio of the products was not affected (Table 2). For example, the CM between homoallyl bromide and allylsilane is very sluggish under oil-bath heating at 90 °C with 0.8 mol-% of the G-II catalyst, while under μW irradiation at 60 °C with only 0.15 mol-% of the same catalyst the coupling product could be isolated in 69 % yield which corresponds to an exceptionally high TON of 460 for the catalyst G-II in CM (usually 10 to 50). The better yields and conversions observed under μW irradiation appear to result from the rapid and direct heating of the reaction mixture and a faster CM reaction relative to catalyst decomposition.

Conclusions

From the above analysis, it is clear that μW irradiation has a pronounced beneficial impact on olefin metathesis reactions. Not only is a dramatic reduction of reaction times from hours to seconds observed, but it allows side-reactions to be reduced, yields to be increased and also for the catalyst loading to be reduced by ensuring a fast metathesis reaction relative to catalyst decomposition. Most of the authors involved in the science presented herein agree that the reason for the observed rate enhancements in μW-assisted olefin metathesis is a purely thermal/kinetic effect (Arrhenius equation). However, some "μW-specific effects", which are thermal effects that cannot be achieved by conventional heating, such as the elimination of wall effects, must also be considered. This could account for the higher TON observed for the metathesis catalysts under μW irradiation as the catalyst is expected to decompose faster on contact with the hot reaction-vessel wall than in the homogeneously directly heated solution. Some authors have suggested the possibility of "non-thermal μW effects" when the polarity of the transition state of the reaction is higher than the ground-state polarity, which is the case with the olefin metathesis reaction. Microwave effects are the subject of considerable current debate and controversy and it is evident that extensive research efforts will be necessary to truly understand these and related phenomena. An inherent problem in the study of these effects is that the temperature profiles obtained under μW irradiation are very difficult, if not impossible, to reproduce by conventional heating, rendering the comparison of results troublesome.

The bottom line is, although the actual reasons for the beneficial effect of μW irradiation in olefin metathesis reactions (and others) are not well understood, when thermal activation is needed to perform an olefin metathesis, μW irradiation should be the first choice and not last resort.

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