Unravelling the olefin cross metathesis on solid support. Factors affecting the reaction outcome†

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Olefin cross metathesis on solid support under a variety of conditions is described. A comprehensive analysis considering diverse factors governing the reaction outcome gives a series of patterns for the application of this useful methodology in organic synthesis. If the intrasite reaction is not possible, homodimerization of the soluble olefin is crucial. When the homodimer is less reactive than its monomer, reaction outcome depends on the homodimerization rate, which, in turn, depends on the precatalyst used and the reaction conditions. If the site–site interaction is a feasible process, the cross metathesis product is obtained exclusively when the newly-formed double bond is resilient to further metathetic events. Taking into account these considerations, we have demonstrated that excellent results in terms of cross metathesis coupling can be obtained under the optimized conditions, and that microwave irradiation is also an interesting alternative for the development of a practical and energy-efficient cross metathesis on solid support.

Introduction

Due to their central role in modern organic synthesis, organometallic chemistry has been a logical target for the development of solid-phase chemistry, and its synthetic applications have grown substantially in the last decade.[1] However, such development is still far from being completed.

Ruthenium catalyzed cross metathesis has become a powerful synthetic tool in modern organic and polymer synthesis,[2] representing a very interesting alternative to more traditional carbon–carbon bond forming reactions. Cross metathesis (CM) has an advantage over Stille, Heck and Suzuki reactions since alkenes are easier to prepare compared to stannanes, halides and boronates, or they can be obtained from many natural products. On the other hand, CM is particularly helpful in stepwise syntheses since the olefin metathesis precatalysts (**1–3**) (Fig. 1) ensure mild reaction conditions, together with high functional group tolerance, activity and stability.

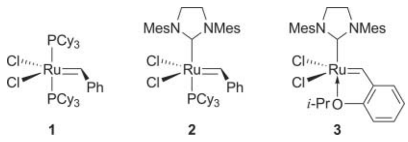
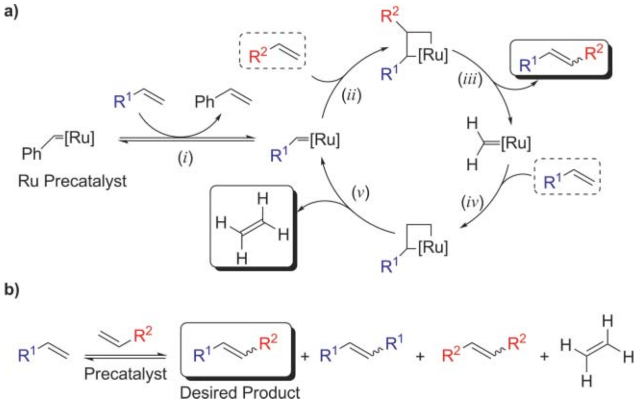


Fig. 1 Most commonly employed commercially available metathesis precatalysts.

The commonly accepted mechanism for olefin metathesis has been proposed by Hérisson and Chauvin[3] and it involves the cycloaddition reaction between a metal–carbene complex and an olefin to form a metallocyclobutane (Scheme 1a, step *ii*), which go back to generate a new metal–carbene complex and a new olefin (step *iii*). This is a reversible process that eventually reaches equilibrium and a statistical mixture of olefins is obtained (Scheme 1b).



Scheme 1 Catalytic cycle proposed by Chauvin for olefin cross metathesis. (a) After an initiation step (*i*), the catalytic process proceeds through cycloaddition (*ii* and *iv*) and cycloreversion (*iii* and *v*) reactions between olefins and ruthenium–carbene complexes. (b) Cross metathesis process, a mixture of compounds can be obtained.

Recently, Grubbs *et al.* reported an olefin classification in order to understand and predict the olefin cross metathesis selectivity.[4] Four categories of olefins were determined: type-I olefins are those that undergo fast homodimerization and secondary metathesis on the homodimers, type-II go through a slow homodimerization and homodimers are sparingly reactive, type-III do not undergo homodimerization while type-IV are just spectators to CM. Which olefin belongs to which category depends on the precatalyst used. According to this empirical approach, product selectivity can

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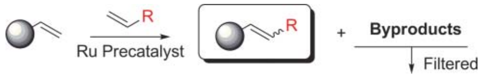
be achieved by using olefins from two different types, in order to suppress the rate of homodimerization of one component and controlling the rate of secondary metathesis on the desired cross product. However, avoiding the formation of unwanted homodimeric products is not always an easy task[5] and, in many of the cases, addition of an excess of one of the olefin is necessary to ensure high yield,[4] compelling to a careful chromatographic purification.

Comparing to its homogeneous-phase counterpart, the olefin cross metathesis on solid-phase has several potential advantages. Immobilization of one of the olefin substrates makes, under certain conditions, its homodimerization a less favorable process due to the site isolation, while the olefin that remains in solution can be eliminated by a simple filtration (Scheme 2). Ruthenium contamination of synthetic products is another less important issue in solid-phase metathesis.[6] Furthermore, solid-supported organic synthesis permits easier purification, automation, and parallelization, for the rapid generation of compound libraries.[7]



Scheme 2 Solid-supported version of olefin cross metathesis. Potentially, most of the olefin by-products generated during the reaction can be eliminated by filtration.

Despite these advantages, the alkene solid-phase cross metathesis field has not been well explored to date and it is far below its maximum potential. While there is a considerable number of examples of metathesis reactions where a substrate has been immobilized to a solid support, most of them refer to the ring closing version of the coupling.[8] Probably the limited success of first generation Grubbs precatalyst **1**[9] in solid-phase cross metathesis could be blamed for the delayed development of this methodology.[10] Only recently, this subject has been addressed again by us and others,[11] exploring the application of a new generation of precatalysts, such as second-generation Grubbs precatalyst (**2**)[12] and Hoveyda–Grubbs precatalyst (**3**),[13] to the preparation of biologically promising molecules. Although preliminary, these reports have offered the promise of a more general application of solid-supported olefin cross metathesis for the generation of libraries of complex organic structures.

Now, a comprehensive study of this methodology is provided with an emphasis on the many effects involved in the reaction outcome, and on the combined used of solid-supported chemistry and microwave irradiation.

Results and discussion

From the beginning, it was clear that solid-supported olefin cross metathesis was a complex reaction system in terms of the many factors affecting the reaction outcome. Along with those factors related to the nature of the polymer, such as the effect of the resin loading, linker's length and flexibility; the reactivity of the immobilized olefin, the role of the soluble olefin and the effect of the precatalyst have to be studied in depth.

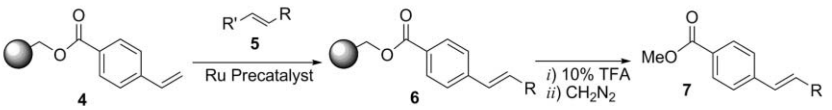
In order to understand the influence of the soluble olefin reactivity on the reaction outcome, the Wang resin-immobilized olefin (**4**) was used for the coupling with different olefin partners (**5a–f**) (Table 1). When an excess of allyl benzene (**5a**) reacted with the resin-bound olefin **4**, in the presence of second-generation Grubbs precatalyst (**2**), methyl 4-(3-phenyl-propenyl)benzoate (**7a**) was obtained in excellent isolated yield (86%) (entry 1, column 6), after releasing into solution with 10% TFA/DCM followed by esterification with diazomethane. Here, as in most of the cases under scrutiny, complete *E* selectivity was obtained. When analyzing this successful coupling outcome, it has to be taken into account that a number of metathesis events can occur when a type I non-immobilized olefin, such as **5a**, reacts under precatalyst **2** with an also very reactive resin-bound olefin, like **4**. Since solid-phase reactions are usually considered as proceeding at a lower rate than their homogeneous-phase counterparts,[14] and the non-immobilized olefin is added in excess, coupling between two of these molecules is statistically more probable and the corresponding homodimer is actually the omnipresent olefin. To confirm this assumption, the homodimer **5′a** was prepared and treated with resin **4** and precatalyst **2** under the optimized conditions to give the expected product **7a** in an almost similar yield to that obtained starting from olefin **5a** (entries 1 and 2). The same rationale can be applied to explain the reaction outcome using 4-methyl styrene (**5b**), which gave the CM product, methyl 4-(4-methylstyryl)benzoate (**7b**), only in 31% yield (entry 3). The corresponding homodimer **5′b** was unreactive to resin-bound olefin **4** under our solid-phase conditions (entry 4) indicating that, despite the high reactivity of 4-methyl styrene (**5b**) the low yield was due to the rapid formation of the unreactive dimer **5′b**. On the other hand, if the homodimerization is very slow, such as in the case of the 4-vinylbenzyl chloride (**5c**) (entry 5), the heterocoupling prevails and the active monomer contributes largely to the formation of the CM product (**7c**) (80% yield). In this case, the use of the homodimer **5′c** as substrate made the CM coupling a less efficient process, since olefin **7c** was obtained in 58% yield (entry 6).

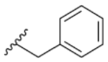
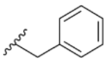
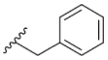
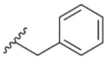
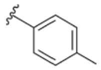
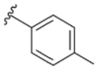
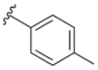
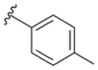
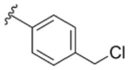
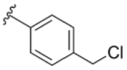
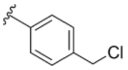
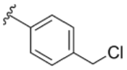
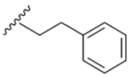
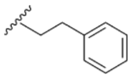
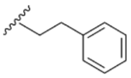
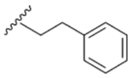
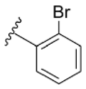
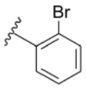
Interestingly, an electron-deficient olefin, such as crotonic acid (**5e**), gave the coupling product (**7e**) in a 97% yield (entry 9). While homodimerization was negligible, metathesis between resin **4** and crotonic acid (**5e**) was favored by the forced conditions (reflux, large excess of olefin) leading to a product (**7e**) which is, in turn, reluctant to further metathetic events. In the case of 2-bromo styrene (**5f**), that also behaves as a type-II olefin when using precatalyst **2**, the expected CM product (**7f**) was obtained in lower yield (43%) (entry 10). The additional steric hindrance of the bromine atom can be the reason for this yield by affecting the approach to the polymer matrix.

From these results it is clear that the solid-supported olefin cross metathesis can go through two pathways (Scheme 3), and system reactivity is modulated by the differential reactivity between monomer and homodimer, and the velocity of dimerization. When the soluble olefin does not dimerize, or dimerizes, but monomer and dimer are equally reactive, the effect of the homodimerization of this olefin is negligible. The problem arises when monomer is significantly more reactive than the homodimer; then, the more rapid the dimerization is, the worse the yield of the CM product is.

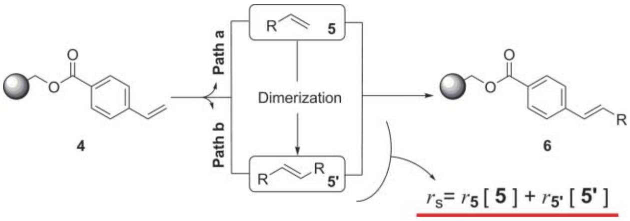
Regarding the precatalyst's nature, as in conventional solution-phase synthesis, the less reactive first generation Grubbs precatalyst (**1**) gave a much lower yield than second-generation Grubbs precatalyst (**2**). Thus, under a similar protocol to that

Table 1 Cross-metathesis by ruthenium carbene complexes on the resin-bound 4-vinyl benzoic acid (**4**)[a]



	Soluble olefin	Homo-dimerization[b]	Product	Yield (%)[c]		
				Precatalyst **1**	Precatalyst **2**	Precatalyst **3**
1	**5a** R′ = H, R = 	Yes, in 15 min	**7a** R = 	22[d]	86	84
2	**5′a** R′ = R = 	—	**7a** R = 		72	
3	**5b** R′ = H, R = 	Yes, in 2 h	**7b** R = 		31	32
4	**5′b** R′ = R = 	—	**7b** R = 		NR	
5	**5c** R′ = H, R = 	Yes, in 20 h	**7c** R = 		80	28[e]
6	**5′c** R′ = R = 	—	**7c** R = 		58	
7	**5d** R′ = H, R = 	Yes, in 5 h	**7d** R = 		57	
8	**5′d** R′ = R = 	—	**7d** R = 		39	
9	**5e** R′ = CH_3, R = –CO_2H	No	**7e** R = –CO_2Me	NR[f]	97	
10	**5f** R′ = H, R = 	No	**7f** R = 		43	43

[a] Conditions: (*i*) olefin **5**(**5′**) (5 eq), Ru precatalyst (5 mol%), DCM, reflux 20 h. (*ii*) 10% TFA in DCM at r.t. for 1 h, (*iii*) CH_2N_2 in DCM at 0 °C for 30 min. [b] Time for total dimerization employing precatalyst **2**. [c] Overall isolated yield after flash column chromatography. *E* isomer exclusively, by ^{1}H NMR. [d] 44% staring material recovered. [e] Homodimerization of the soluble olefin occurs in 5h. [f] No reaction, starting material recovered.



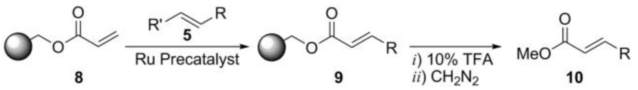
Scheme 3 System variation depending on soluble olefin homodimerization. Metathesis reaction proceeds through either pathway a, b or both of them. Reactivity of the system (rs) depends on the monomer and dimer reactivity (r5 and r5′ respectively), and their concentration in the system.

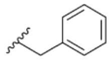
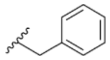
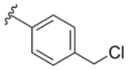
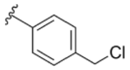
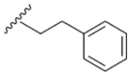
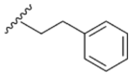
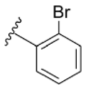
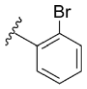
used with precatalyst **2**, the immobilized olefin **4** reacted with excess of allyl benzene (**5a**) in the presence of precatalyst **1** to afford, after separation and methylation, the methyl 4-(3-phenylpropenyl)benzoate (**7a**) in only 22% yield with 44% of recovered starting material (Table 1, entry 1, column 5). In the case of using the moderately reactive crotonic acid (**5e**) as the non-immobilized olefin, precatalyst **1** gave no reaction at all, while a quantitative yield was obtained with precatalyst **2** (entry 9, columns 5 and 6). On the other hand, the Hoveyda–Grubbs precatalyst (**3**), seems to have a similar reactivity than precatalyst **2** (entries 1, 3 and 10, columns 6 and 7), except in the case of **7c**, where the isolated yield decreased from 80 to 28% by changing from precatalyst **2** to **3** (entry 5, columns 6 and 7). This result can be attributed to a faster formation of the homodimer **5′c** (5 h instead of 20 h), which is less reactive than its corresponding monomer **5c**.

Changing the immobilized component to a "type II" olefin, such as **8**, cross metathesis in the presence of precatalyst **2** mostly resulted in slower reaction rates, with yields up to 35% (Table 2, column 5). However, precatalyst **3** generally increased those yields (Table 2, column 6). In the case of type-I soluble olefins, such as allyl benzene (**5a**), 4-vinylbenzyl chloride (**5c**) and 4-phenyl-1-butene (**5d**) yields were increased at least two-fold (entries 1–3, columns 5 and 6). These results are in agreement with literature data on solution-phase chemistry, where precatalyst **3** is considered the best for cross metathesis involving α,β-unsaturated carbonyl derivatives.[15]

When immobilized pentenoic acid (**11**) was used, we noted that this resin-bound olefin was able to undergo site–site interference

Table 2 Cross-metathesis by ruthenium carbene complexes on an immobilized α,β-unsaturated carbonyl olefin (**8**)[a]



Entry	Soluble olefin	Homo-dimerization[b]	Product	Yield (%)[c] Precatalyst **2**	Precatalyst **3**
1	**5a** R′ = H, R = 	Yes, in 15 min	**10a** R = 	35	59
2	**5c** R′ = H, R = 	Yes, in 20 h	**10c** R = 	11	23
3	**5d** R′ = H, R = 	Yes, in 5 h	**10d** R = 	26	68
4	**5f** R′ = H, R = 	No	**10f** R = 	10	16

[a] Conditions: (*i*) olefin **5** (5 eq), Ru precatalyst (5 mol%), DCM, reflux 20 h. (*ii*) 10% TFA in DCM at r.t. for 1 h, (*iii*) CH_2N_2 in DCM at 0 °C for 30 min. [b] Time for total dimerization employing precatalyst **2**. [c] Overall isolated yield after flash column chromatography. *E* isomer exclusively, by ^1H NMR.

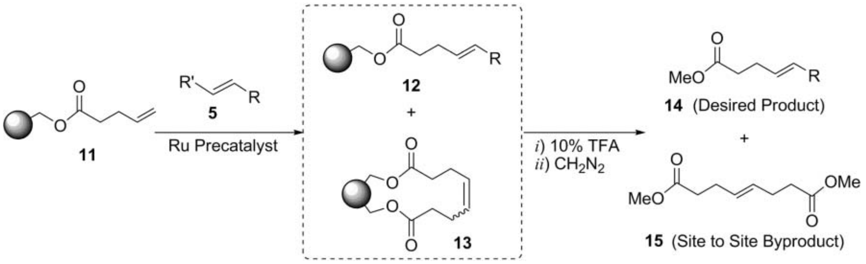
(Table 3). A unique property of solid-phase organic synthesis is the pseudo-dilution effect. When a reactive group is attached to a polymer support, intermolecular reaction between those groups is, in theory, a less favorable process, leading to a virtually infinite dilution.[16] Although this site–site isolation is achieved in most of the cases, under determined circumstances intrasite interactions can occur affecting the reaction outcome. There are some ways to reduce site–site interactions, such as increase cross-linking and decrease resin loading; however, these actions would lead to lower reaction rates[17] and lower resin throughput, respectively. A more generally accepted idea to minimize those interactions is the use of a large excess of the soluble substrate (normally 5 equivalents). Because of that excess, most of the active sites in the polymer react with the molecules in solution instead of reacting with each other. Nevertheless, linker's length and flexibility can be factors that make intrasite reactions difficult to avoid; this is the case of resin **11**. We have performed a series of experiments to understand the influence of different factors on such interference.

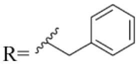
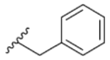
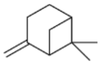
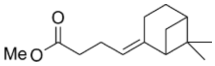
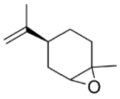
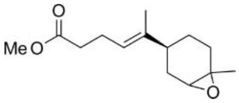
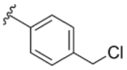
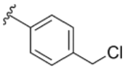
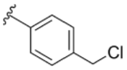
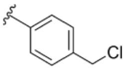
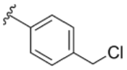
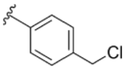
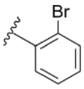
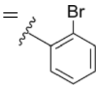
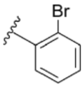
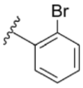
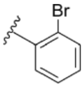
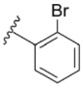
As already mentioned, a large number of metathetic events occur when a very reactive non-immobilized olefin reacts with an also very reactive immobilized olefin, and a new player enters in the game if the site–site interaction is a feasible process. Thus, when the resin-bound pentenoic acid (**11**) was treated under CM conditions with a soluble olefin (**5**) many possible processes could take place (Scheme 4). Since ethylene departs from the system, the fate of the reaction depends on **12** and **13**, one leading to the desired CM product while the other lead to the site–site by-product.

When excess of allyl benzene (**5a**) was subjected to cross metathesis with resin **11** and precatalyst **2**, only the expected heterodimer **14a** was obtained in low yield (18%), after releasing from the resin and esterification with diazomethane (Table 3, entry 1). This result was due to the extensive formation the intrasite CM product, which was isolated as the 4-octenedioic acid dimethyl ester (**15**) in 70% yield. In fact, in the absence of any soluble olefin, similar reaction led to the homodimeric ester **15** in 85% yield (entry 2).[18] However, a significantly different result was obtained when less active type-II, non-immobilized olefins were used. For instance, in the case of crotonic acid (**5e**), the desired CM product was afforded in excellent yield (entry 3) and no intrasite-derived product was observed. More predictable results were obtained with even less reactive type-III olefins, such as β-pinene (**5g**) and linonene oxide (**5h**) (entries 4 and 5). These olefins are very resilient to cross metathesis compared with the olefin linked to the polymer so, in both cases, the intrasite homodimer **15** was the only detected product in very high yield (85%). These results suggest that highly reactive olefins, such as **5a**, are capable to participate in all the pathways showed in Scheme 4, indicating their tendency to give a product equilibration. The intrasite product **13** is the major component in equilibrium, probably due to that the immobilized olefin **11** may be considered as highly concentrated and unable to be diluted. When going down in reactivity, using non-homodimerizable olefins, such as **5e**, coupling product **12e** was essentially inactive to further CM events, preventing any return from **12e** to **13** (path d, Scheme 4). For this reason the CM product was formed exclusively. Inactive olefins such as **5g** and **5h**, gave place to the site–site product since all the paths but path b are blocked.

In terms of the precatalyst effect on site–site interference, the experimental results indicate that highly active precatalysts tend to displace the reaction outcome to product equilibration while with less active precatalyst that tendency is toward the site–site by-product (Table 3, entries 6 to 11). This pattern is in agreement with the increase in reactivity of the soluble olefin when a more active precatalyst is used. Thus, coupling of **11** with a reactive, non-immobilized alkene such as **5c** in the presence of first generation Grubbs precatalyst (**1**) gave increasing amounts of the intrasite by-product **15** (70%) (entry 6), comparing with similar cross metathesis performed with precatalysts **2** and **3** (entries 7 and 8). These results are in accordance with early literature examples of solid-phase olefin cross metathesis using precatalyst **1**, that showed high influence of site–site interaction on the reaction outcome.[10] As expected, in the case of a less reactive soluble olefin, such

Table 3 Cross-metathesis by ruthenium carbene complexes on immobilized pentenoic acid (**11**)[a]



Entry	Soluble olefin	Homo-dimerization[b]	Precatalyst	CM product	**14** (%)[c]	**15** (%)
1	**5a** R′ = H, R = 	Yes, in 15 min	2	**14a** R = 	18[d]	70
2	None	—	2	—	—	85
3	**5e** R′ = CH_3, R = CO_2H	No	2	**14e** R = $-CO_2Me$	100	0
4	**5g** 	No	2	**14g** 	0	85
5	**5h** 	No	2	**14h** 	0	85
6	**5c** R′ = H, R = 	No	1	**14c** R = 	14	70
7	**5c** R′ = H, R = 	Yes, in 20 h	2	**14c** R = 	45	35
8	**5c** R′ = H, R = 	Yes, in 5 h	3	**14c** R = 	43	33
9	**5f** R′ = H, R = 	No	1	**14f** R = 	6	83
10	**5f** R′ = H, R = 	No	2	**14f** R = 	87	0
11	**5f** R′ = H, R = 	partially	3	**14f** R = 	57	17

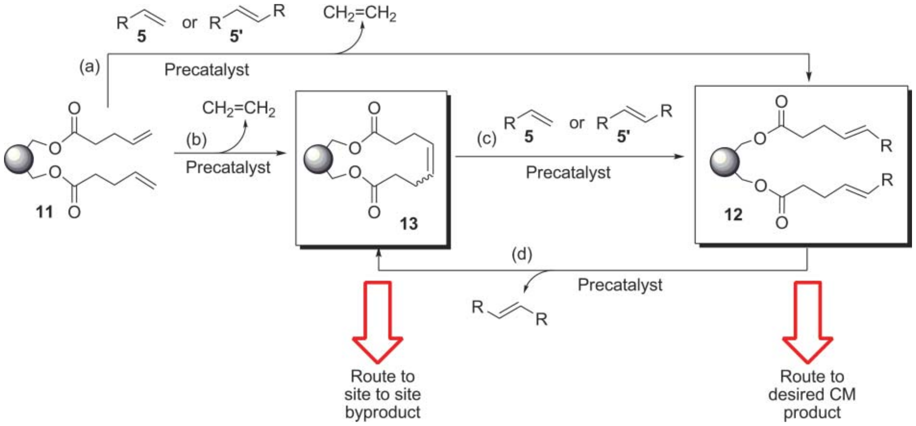
[a] Conditions: (*i*) olefin **5**(**5′**) (5 eq), Ru precatalyst (5 mol%), DCM, reflux 20 h. (*ii*) 10% TFA in DCM at r.t. for 1 h, (*iii*) CH_2N_2 in DCM at 0 °C for 30 min. [b] Time for total dimerization employing precatalyst **2**. [c] Overall isolated yield after flash column chromatography. *E* isomer exclusively, by ^1H NMR. [d] Inseparable mixture of *E*–*Z* isomers [(83 : 17) determined by ^1H NMR].

as 2-bromo styrene (**5f**), precatalyst **1** gave almost exclusively the intrasite homodimer **15** (83%) (entry 9) while precatalyst **2** afforded the cross-coupled product **14f** as the only detectable product (entry 10), due to the unreactivity of the immobilized heterocoupled product **12f**. Conversely, precatalyst **3** gave mixture of **14f** and the by-product **15** (entry 11). This is clearly due to the increase in olefin reactivity by using a more active precatalyst. As a consequence of such reactivity, there is a major tendency to displace the reaction outcome toward product equilibration.

The effect of microwave irradiation

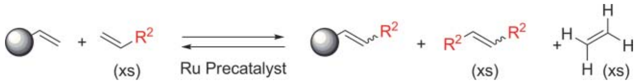
Microwave irradiation offers a promising alternative to conventional heating sources, providing a practical and rapid way to reach high reaction temperatures.[19] Over the last decade, microwave-assisted chemistry has reached a matured state and its importance has been enhanced by the necessity of a sustainable chemistry in terms of a reduction in the amount of solvents and hazardous substances and a more efficient use of energy.[20] On the other hand, microwave-assisted organic synthesis (MAOS) is having substantial impact on drug discovery programs. Reaction times are reduced by orders of magnitude and are readily scalable. Thus, exploratory reactions can be carried out in much shorter time and SAR studies can be dynamized by a rapid synthesis of compound libraries.[21]

While microwave irradiation has been applied to CM reactions, there are no reports on the corresponding solid-phase version.[22] Under this perspective, resin-bound olefin **4**, 4-vinylbenzyl



Scheme 4 Metathetic system for a homodimerizable immobilized olefin.

chloride (**5c**), and precatalyst **2** were used as model for studying the effect of microwave irradiation. First attempted conditions, 60 °C for 10 min. in a sealed tube, gave only 58% of the desired alkene **7c**, and 24% of the recovered starting material in the form of methyl 4-vinylbenzoate. In contrast, conventional heating gave 80% of **7c** as the exclusive product (Table 1, entry 5). In further attempts to improve microwave yields we noticed that, when temperature or time were increased, the reaction reached a stationary point from where no further increase in conversion was possible. We thought that this problem was caused by the presence of ethylene in the closed system. Being a reversible process, ethylene helps to maintain a point of equilibrium and the reaction does not displace to products. This results are in divergence with reports of CM in homogeneous phase, where sealed systems are successfully employed.[23] Analyzing the conditions used in the solid-phase version, it is clear that the effect of the ethylene is much more significant than in the solution-phase counterpart. As a consequence of the excess of the non-immobilized olefin used, the pressure of ethylene generated is such that blocks the reaction progression (Scheme 5).



Scheme 5 Effect of ethylene on solid-phase cross metathesis under a closed microwave system.

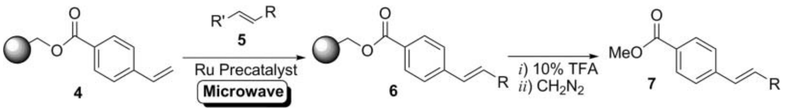
Therefore, it was expected that, under an open-vessel microwave system, the efficiency of the CM would be improved. To our delight, coupling of **4** with **5c** in the presence of **2** under mild conditions (75 °C, 15 min.) gave the desired alkene **7c** in 78% yield and 16% of recovered starting material. Optimized conditions were reached when the time was extended to 25 min, affording product olefin **7c** exclusively in 90% yield (Table 4, entry 4). The generality of this procedure has been demonstrated by a series of examples (Table 4). In almost all the cases, yields were similar or better than the CM coupling under conventional heating. The only notable exception was the metathesis using crotonic acid (**5e**) as soluble substrate, that led to only 35% of the CM product **7e** (entry 6). This unexpected result was firstly attributed to the volatility of the crotonic acid which was evaporated under the open-vessel conditions before the reaction was complete. In fact, this assumption was corroborated by using a less volatile derivative, such as the benzyl crotonate **5i**. CM coupling of immobilized olefin **4** and **5i** in the presence of precatalyst **2** under open-vessel microwave conditions gave the expected CM product **7i** in quantitative yield (entry 8). The role of the homodimerization of the non-immobilized olefin has also to be taking into account under microwave irradiation. Probably, the reason for the lack of yield increase when using 4-methylstyrene (**5b**) (entry 2), is that, although the coupling becomes faster, the homodimerization also goes faster (5 min), and that homodimer (**5′b**) is almost unreactive under microwave conditions (entry 3).

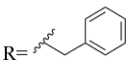
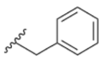
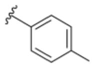
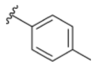
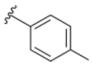
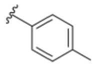
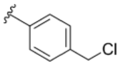
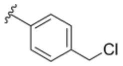
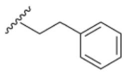
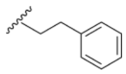
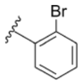
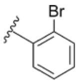
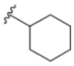
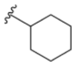
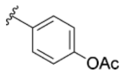
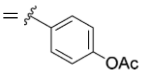
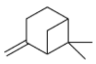
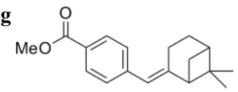
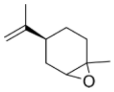
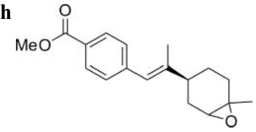
When the “flexible” immobilized resin **11** was used as substrate, CM under open-vessel microwave conditions gave similar results to that of conventional heating. As in the cases shown in Table 3, highly active soluble olefins gave mostly a mixture of the expected CM product and the site–site by-product,[24] while unreactive soluble olefins gave only the intrasite by-product. CM products were only favored when the newly formed olefin was essentially inactive to further CM events, avoiding any equilibration.

Comparison between microwave and conventional heating

Although beneficial effects of microwave irradiation have been reported for more than two decades in the literature, a direct comparison with conventional heating has not been always carried out. Since our microwave conditions were changed during optimization, we decided to perform a direct comparison between conventional and microwave heating by developing some reactions at strictly the same CM conditions. Thus, when resin-bound olefin **4** was reacted with soluble olefin **5c** in the presence of precatalyst **2** by conventional heating, under identical conditions to that used in microwave heating, the CM product **7c** was obtained in virtually the same yield (84%) (Table 5, entry 1). This result demonstrates that 24 h reflux in DCM is excessive in order to obtain a very high yield of the desired coupling product, since the reaction can be complete in just 25 min at 75 °C. More interestingly, a similar comparison using Hoveyda–Grubbs precatalyst (**3**) gave the CM product in 85%, which is about the same yield as obtained by microwave irradiation and implies a great increase comparing to

Table 4 Cross-metathesis by precatalyst **2** on the resin-bound 4-vinyl benzoic acid (**4**), under open-vessel microwave conditions[a]



Entry	Soluble olefin	Product	Yield (%)[b]	
			Microwave	Classical Conditions
1	**5a** R′ = H, R = 	**7a** R = 	79	86[c]
2	**5b** R′ = H, R = 	**7b** R = 	30	31[c]
3	**5b** R′ = R = 	**7b** R = 	15[d]	NR[c,e]
4	**5c** R′ = H, R = 	**7c** R = 	90	80[c]
5	**5d** R′ = H, R = 	**7d** R = 	86	57[c]
6	**5e** R′ = –CH_3, R = –CO_2H	**7e** R = –CO_2Me	35	97[c]
7	**5f** R′ = H, R = 	**7f** R = 	80	43[c]
8	**5i** R′ = –CH_3, R = –CO_2Bn	**7i** R = –CO_2Bn	100	96
9	**5j** R′ = H, R = 	**7j** R = 	82	—
10	**5k** R′ = H, R = 	**7k** R = 	85	—
11	**5g** 	**7g** 	NR	NR
12	**5h** 	**7h** 	NR	NR

[a] Conditions: (*i*) olefin **5** (5 eq), precatalyst **2** (5 mol%), toluene, open vessel microwave irradiation, 75 °C (120 W) for 25 min. (*ii*) 10% TFA in DCM at r.t. for 1 h, (*iii*) CH_2N_2 in DCM at 0 °C for 30 min [b] Overall isolated yield after flash column chromatography. *E* isomer exclusively, by ^1H NMR. [c] Taken from Table 1. [d] Soluble olefin monomer dimerizes in 5 min. [e] Soluble olefin monomer dimerizes in 2 h.

previous thermal conditions (28%) (entry 2). A similar result was obtained when a less reactive soluble olefin (**5f**) was subjected to CM under precatalyst **2** (entry 3).

Based on the results presented herein, it is clear that the heating effects on the reaction outcome are thermal and not related to any electromagnetic field, which is in agreement with the conclusions recently reported by Kappe and co-workers.[25,26] They have developed a critical analysis of the effects involved in microwave heating, not only in homogeneous-phase,[25] but also in solid-phase chemistry.[26] They have found no evidence of nonthermal effects on microwave irradiation, establishing that, under an efficient agitation of the reaction mixture, nearly identical results in terms of yields, selectivity and racemization rate (in the case of solid-phase peptide synthesis) can be obtained.

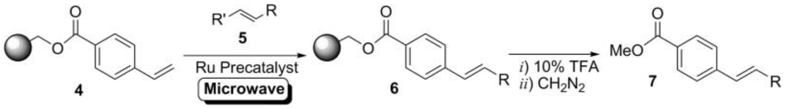
In the case of the solid-phase version of the cross metathesis, the reason for the success of the microwave irradiation approach and the optimized conventional heating conditions can to be found into the short reaction time (25 min against 20 h), which avoids unnecessary metathetic and non-metathetic events that lead to abnormal products.[27]

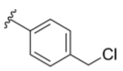
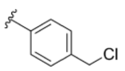
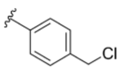
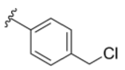
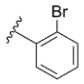
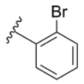
Experimental section

General

Chemical reagents were purchased from commercial sources and were used without further purification unless noted otherwise. Solvents were analytical grade or were purified by standard procedures prior to use. ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$, in the presence of TMS (0.00 ppm) as the internal standard. Conventional and gel-phase ^{13}C NMR spectra were recorded on the same apparatus at 75 MHz with

Table 5 Comparison of solid-phase cross-metathesis under classical and microwave conditions



				Yield (%)[a]		
Entry	Soluble olefin	Product	Precatalyst	Initial thermal conditions[b]	Microwave irradiation[c]	Thermal optimized conditions[d]
1	**5c** R′ = H, R = 	**7c** R = 	**2**	80	90	84
2	**5c** R′ = H, R = 	**7c** R = 	**3**	28	80	85
3	**5f** R′ = H, R = 	**7f** R = 	**2**	43	80	80

[a] Overall isolated yield after flash column chromatography. [b] Conditions: olefin **5** (5 eq), Ru precatalyst (5 mol%), DCM, conventional heating, reflux 20 h. (taken from Table 1) [c] Conditions: olefin **5** (5 eq), Ru precatalyst (5 mol%), toluene, open vessel microwave irradiation, 75 °C (120 W) for 25 min. [d] Conditions: olefin **5** (5 eq), Ru precatalyst (5 mol%), toluene, conventional heating, 75 °C for 25 min.

$CDCl_3$ as solvent and reference (76.9 ppm). Analytical thin-layer chromatography (TLC) was carried out with silica gel 60 F254 pre-coated aluminium sheets. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Microwave irradiations were performed on a CEM Discover LabMate reactor and the reaction temperature was measured with the internal infrared control system from the apparatus. Compounds **5′a**,[28] **5′b–c**,[11d] **5′d**,[29] **7a**,[11d] **7b–d**,[11d] **7e**,[30] **7f**,[31] **10a**,[32] **10c**,[33] **10d**,[32,34] **10f**,[35] **14a**,[36] **14c**,[11f] **14e**,[37] **14f**[11f] and **15**,[38] have been previously reported.

General procedure for the solid-phase cross-metathesis by ruthenium carbene complexes under microwave irradiation

In a 10 mL round-bottomed flask, resin-bound olefin **4** (0.15 mmol) was suspended in anhydrous toluene (3 mL) and the non-immobilized olefin **5** (0.75 mmol, 5.0 eq) was added *via* syringe under a nitrogen atmosphere. The precatalyst **2** (7.5 μmol, 5 mol%) was added and the flask fitted with a straight connecting adapter and a condenser (see the ESI†). A polypropylene cannula was passed through the septum and brought close to the reaction mixture in order to maintain an open vessel system with a dry nitrogen flow and a fast ethylene removal. This apparatus was placed in the microwave reactor and irradiated under a standard heating protocol at 75 °C for 25 min (maximum power = 120 W) with magnetic stirring. The resin was filtered, washed with DCM (3 × 4 mL), MeOH (3 × 4 mL), DCM (1 × 4 mL), and dried under high vacuum. Resin-bound olefin **6** (0.15 mmol) was treated with 5 mL of 10% TFA in DCM for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give crude product. This crude material was dissolved in DCM and treated with diazomethane at 0 °C for 30 min. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (hexane–AcOEt) to provide the desired product **7**.

General procedure for the solid-phase cross-metathesis by ruthenium carbene complexes under thermal optimized conditions

Utilizing the same glassware apparatus described above in the microwave protocol, resin-bound olefin **4** (0.15 mmol) was suspended in anhydrous toluene (3 mL) and the non–immobilized olefin **5** (0.75 mmol, 5.0 eq) was added *via* syringe under a nitrogen atmosphere. Precatalyst **2** (7.5 μmol, 5 mol%) was added and the system was heated in an oil bath at 75 °C for 25 min with magnetic stirring. Resin was washed with DCM, MeOH, DCM, and dried under high vacuum. Resin-bound olefin **6** (0.15 mmol) was treated with 5 mL of 10% TFA in DCM for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. This crude material was dissolved in DCM and treated with diazomethane at 0 °C for 30 min. Desired product **7** was purified by flash column chromatography (hexane–AcOEt).

(*E*)-methyl 4-(3-(benzyloxy)-3-oxoprop-1-enyl)benzoate (7i). Mp: 55–56 °C (from DCM, white needles). IR (film) ν_{max} 3034, 2952, 1720, 1436, 1308, 1280, 1166, 1107. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 8.04 (d, $J = 8.2$ Hz, 2H, ArH), 7.74 (d, $J = 16.1$ Hz, 1H, H5), 7.57 (d, $J = 8.2$ Hz, 2H, ArH), 7.43–7.32 (m, 5H, ArH), 6.56 (d, $J = 16.1$ Hz, 1H, H6), 5.26 (s, 2H, H10), 3.93 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 166.3, 166.2, 143.6, 138.4, 135.7, 131.3, 130.0, 128.5, 128.2, 127.8, 120.2, 66.0, 52.0. HRMS (ESI) *m*/*z* 319.0944 [(M + Na$^+$); calcd for $C_{18}H_{16}O_4$: 319.0940].

(*E*)-methyl 4-(2-cyclohexylvinyl)benzoate (7j). Mp: 60–61 °C (from DCM, colourless needles). IR (film) ν_{max} 2929, 1719, 1284, 1104. ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.95 (dt, $J = 1.8$ Hz, $J = 8.5$ Hz, 2H, ArH), 7.39 (dt, $J = 1.8$ Hz, $J = 8.5$ Hz, 2H, ArH), 6.38 (d, $J = 16.1$ Hz, 1H, H5), 6.30 (dd, $J = 16.1$ Hz, $J = 6.0$ Hz, 1H, H6), 3.90 (s, 3H, CH_3O), 2.21–210 (m, 1H, H7), 1.80–0.80 (m, 10H, H8-10). ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 166.9, 142.6, 139.6, 129.7, 128.1, 126.5, 125.7, 51.9, 41.2, 32.6, 26.0, 25.9. HRMS (ESI) *m*/*z* 267.1349 [(M + Na$^+$); calcd for $C_{16}H_{20}O_2Na$: 267.1355].

(*E*)-methyl 4-(4-acetoxystyryl)benzoate (7k). Mp: 189–190 °C (from DCM, white amorphous solid). IR (film) ν_{max} 3022, 2954, 1761, 1718, 1287, 1112. ^{1}H NMR (CDCl$_3$, 300 MHz): δ_H 8.07–7.99 (m, 2H, H8), 7.61–7.50 (m, 4H, H2–3), 7.19 (d, J = 16.5 Hz, 1H, H5), 7.11 (dt, J = 2.0 Hz, J = 8.8 Hz, 2H, H9), 7.06 (d, J = 16.5 Hz, 1H, H6), 3.92 (s, 3H, CH$_3$O), 2.31 (s, 3H, H12). ^{13}C NMR (CDCl$_3$, 75 MHz): δ_C 169.3, 166.7, 150.4, 141.5, 134.4, 130.0, 129.9, 128.9, 127.6, 126.5, 126.2, 121.8, 52.0, 21.0. HRMS (ESI) m/z 319.0936 [(M + Na$^+$); calcd for $C_{18}H_{16}O_4$: 319.0940].

Conclusions

This study demonstrates that the success of the olefin cross metathesis on solid support depends on many different factors influencing many metathetic events taking part during the reaction. Thus, flexible and long support linkers open the door to the formation of intrasite products. Exclusive obtention of the CM product can only be achieved if the new double bond is resistant to further metathetic events, while highly active non-immobilized olefins gave mostly a mixture of the desired CM product and the site–site by-product. Virtually unreactive soluble olefins gave only the intrasite by-product. If the intrasite reaction is not possible, the role of the homodimerization of the non-immobilized olefin can be crucial. If the homodimer is less reactive than its monomer, reaction outcome depends on the homodimerization rate. But homodimerization rate, of course, depends on the precatalyst used and the reaction conditions. This means that just the use of a more reactive precatalyst or improved reaction conditions does not always give a better yield of the desired product. Aside from that, it is clear that optimized conditions give excellent results in short reaction time (25 min) and, particularly, microwave irradiation offers an interesting alternative to achieve good results in a very practical way and with a more efficient use of the energy. In summary, we think that this comprehensive analysis expands our knowledge on the solid-phase cross metathesis, an underdeveloped methodology, in order to exploit its undoubted potential.

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