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Microreview

Solid-phase synthesis

Cross-Metathesis on Immobilized Substrates – Application to the Generation of Synthetically and Biologically Relevant Structures

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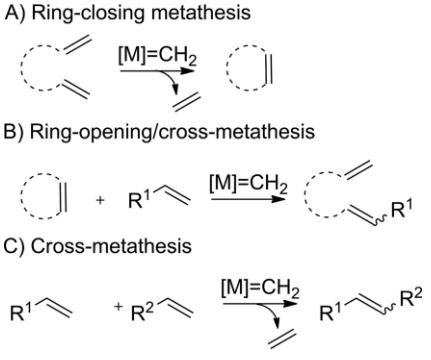
Abstract: Olefin metathesis constitutes a seemingly endless area of research that has had an enormous impact on several branches of chemistry, both in industry and in academia. Once the potential of this reaction as a carbon–carbon bond-forming tool was widely recognized, its adaptation to solid-phase chemistry naturally followed. This review documents the applications and possibilities that polymer-bound alkenes have provided in the challenging cross-version of olefin metathesis, through efforts that are far from exhausted.

1. Introduction

Alkene metathesis is the exchange of an alkylidene group between two olefins catalyzed by a transition-metal carbene complex. In the art of synthetic organic chemistry this reaction has become one of the most valuable tools for carbon–carbon bond formation, especially in the last two decades.[1–4] This is not surprising in view of the large amount of important compounds, including several pharmaceutical agents, that either contain an olefin moiety or can be synthesized by use of alkenes as intermediates.

Basically, alkene metathesis can be classified into three main categories: ring-closing metathesis (RCM), ring-opening metathesis (ROM), and cross-metathesis (CM, Scheme 1).



Scheme 1. Types of olefin metathesis.

After the initial success of commercially available, reliable, well-defined metathesis catalysts, it did not take long for chemists to recognize how beneficial it would be to carry out all types of metathesis reactions on solid support.[5] The reasons

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Martín J. Riveira graduated with a bachelor's degree in chemistry from the National University of Rosario (UNR) in 2009 and then worked on the development of domino reactions of polyunsaturated carbonyl compounds under the supervision of Prof. Mirta P. Mischne. After earning his Ph.D. degree in 2014, he joined the group of Prof. Ernesto G. Mata as a postdoctoral fellow working on the application of transition-metal-catalyzed reactions to SP organic synthesis.

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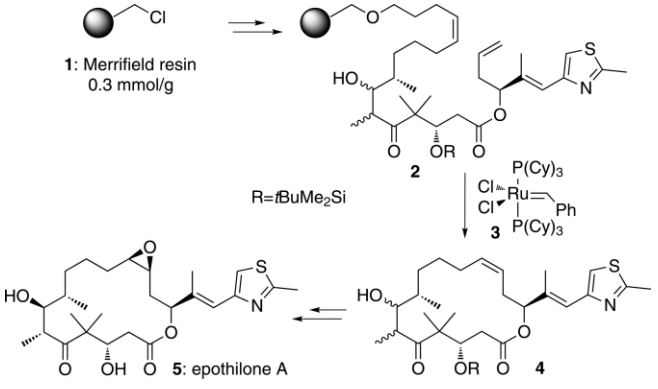
for this are: (1) solid-phase (SP) synthesis is amenable to automation, (2) purification is facilitated by simple filtration, which in some cases also helps to remove metal impurities, (3) self-CM of resin-bound olefins should be discouraged, (4) macrocycle construction through RCM of immobilized olefins should benefit from pseudo-dilution effects on resins, circumventing the need for large volumes of solvent, and (5) soluble olefins can be added in excess to drive CM reactions to completion.

One of the first notable applications of olefin metathesis in SP organic synthesis was achieved by Nicolaou and co-workers during the total synthesis of the anticancer natural product epothilone A (**5**).[6] Alkene metathesis of resin-bound diene **2** in the presence of the first-generation Grubbs precatalyst **3**[7,8] allowed not only the formation of the macrocycle but also the simultaneous release of endocyclic alkene intermediate **4** from the solid support (Scheme 2).



Scheme 2. Solid-phase synthesis of epothilone A through ring-closing metathesis.

Like in this pioneering example, most of the work done so far on the application of metathesis to solid-phase organic synthesis has been focused on the entropically favored ring-closing type of olefin metathesis.[9] Conformationally constrained peptides prepared by this methodology on solid supports are one of the glorious fruits of such recent efforts.[10,11] The purpose of this review, however, is to provide a survey of the applications of the less-explored CM reactions in solid-phase organic synthesis, including our own contributions to this field.

2. Towards Solid-Phase Cross-Metathesis

As a transition-metal-catalyzed C–C bond-forming synthetic tool,[12] there are several advantages of performing CM reactions over other traditional olefination and cross-coupling techniques:

(1) Mild reaction conditions, together with relatively short reaction times required, can lead to high yields of olefin products.

(2) Generally low catalyst loadings (1–5 mol-%) are sufficient.

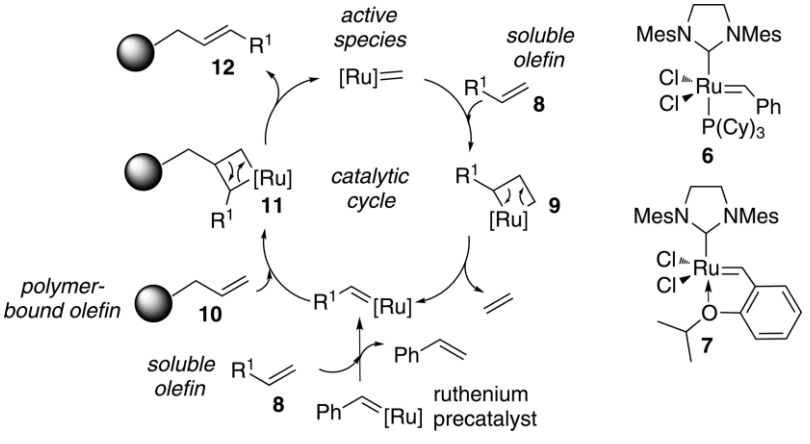
(3) These reactions show excellent tolerance to a wide range of functional groups, circumventing the need for protecting groups.

(4) Many olefin starting materials are either commercially available or relatively easy and inexpensive to prepare.

(5) Ruthenium precatalysts are user-friendly and tolerant to oxygen and moisture, and no substrate activation is needed.

A simplified general mechanism for solid-phase cross-metathesis (SPCM), consistent with Chauvin's well-established proposal,[4] is depicted in Scheme 3 along with the structures of two common second-generation *N*-heterocyclic carbene precatalysts – **6**[13] and **7**[14] – that followed the first-generation Grubbs carbene complex **3**. If an active carbene-Ru catalyst has a preference for soluble olefin **8**, then coordination followed by [2+2] cycloaddition should yield metallacyclobutane **9**. Retro [2+2] cycloaddition with concomitant release of ethylene, followed by complexation to the metal by the resin-bound olefin **10**, should yield new metallacycle **11**, which, after bond cleavage, should liberate the CM product **12** and deliver the active catalyst for another catalytic cycle.

From an inspection of the mechanism depicted in Scheme 3, it is reasonable to consider whether each olefinic substrate could undergo self-CM. Indeed they can: controlling product selectivity to avoid statistical mixtures in solution-phase CM has been a major difficulty that naturally triggered its birth on polymer-supported chemistry with the promise that resin-bound



Scheme 3. General mechanism for the SPCM of olefins, together with common second-generation Ru-based precatalysts (Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl).

olefins would only react with the soluble partner, the homodimers of which would be easily removed by simple filtration.

Another important issue with CM, as well as with other variants of the reaction, is stereoselectivity. Because metathesis is a reversible process, product distribution is time-dependent and governed by thermodynamics, in some cases providing olefinic products with undesired *E*/*Z* ratios, and, above all, hard to predict.

Evolution in metathesis has partially addressed all these limitations, with the elaboration of prediction models[15] and the development of more stable, reactive, chemoselective, and stereoselective precatalysts.[16–21] The second-generation Grubbs precatalyst **6** and the Hoveyda–Grubbs variant **7** were the first achievements in this regard.

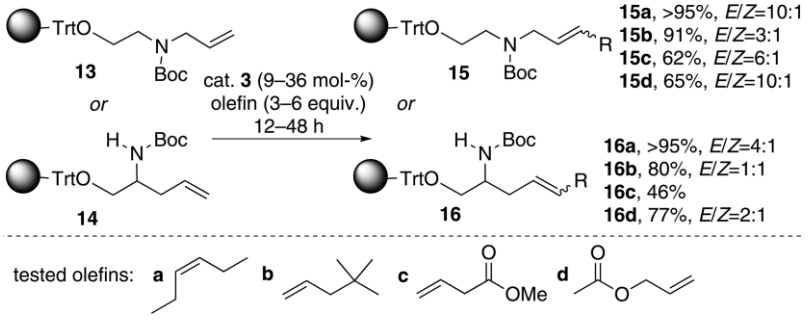
In this minireview we present an exhaustive overview of the literature precedents in the field of SPCM since its beginning. These have been organized into five sections and, for the sake of clarity, each section is disclosed in chronological order.

As is disclosed below, all of the studies in the literature provide evidence that CM with Ru-based catalysts is a viable process for olefins immobilized on standard polystyrene-based resins. However, it is not unusual to find that conditions developed for solution-phase chemistry turn out to be mild when applied to solid-supported olefins and that some adjustments have to be made. In some cases, reactions take longer or require a change of solvent, the use of higher temperatures, or higher loadings of catalysts (maybe addition in more than one portion), or just need to be run more than once.

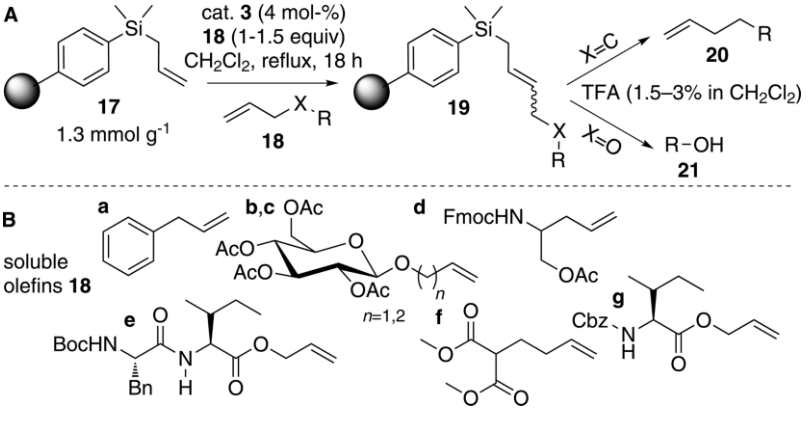
2.1. Solid-Phase Cross-Metathesis Reactions

SPCM was first validated by Blechert and co-workers, who used a chlorotritylpolystyrene resin as solid support (Scheme 4).[22] Initial attempts either with supported allyl alcohol or with supported pent-4-enol were unsuccessful because intraresin dimerization occurred. After some experimentation, it was found that resin-bound *N*-Boc-*N*-allylglycinol (**13**) and *N*-Boc-*C*-allylglycinol (**14**) underwent CM with a variety of soluble olefins provided that low loadings of resins (0.2 mmol g^{-1}) were used. As shown, first-generation precatalyst **3** (9–36 mol-%) allowed the formation of cross-olefin products **15** and **16** in good yields, with, in some cases, useful *E*/*Z* ratios being obtained.

Shortly afterwards, the same research group developed another strategy for the immobilization of olefins, based on **17**, an allylsilyl linker attached to a 1 % divinylbenzene-crosslinked polystyrene resin.[23] CM of **17** with a variety of terminal olefins was performed with use of a lower catalyst loading of **3** (Scheme 5). Interestingly, two different patterns of cleavage were observed. For olefins lacking an oxygen attached to the allylic position [**18a**, **18c** (*n* = 2), **18d**, and **18f**], protodesilylation occurred under mild acidic conditions with concomitant release of the homologated terminal olefins **20**. Additionally, olefins **18b** (*n* = 1), **18e**, and **18g** underwent a modified protodesilylation mechanism, releasing alcohols **21** after loss of buta-1,3-diene. The yields of product formation (**20** or **21**, CM and cleavage) ranged from 40 to 60 % with the exception of compound **20d**, for which the CM was not successful.



Scheme 4. First examples of SPCM reactions (Boc = *tert*-butoxycarbonyl, Trt = trityl).

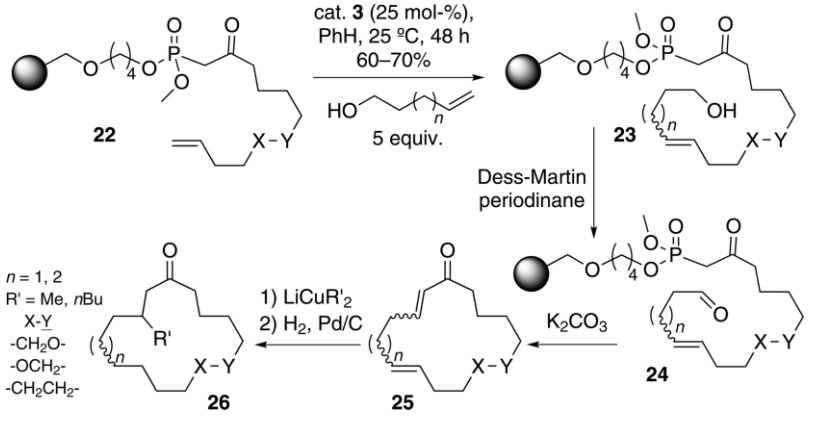


Scheme 5. SPCM of an allylsilyl linker (Cbz = benzyloxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl).

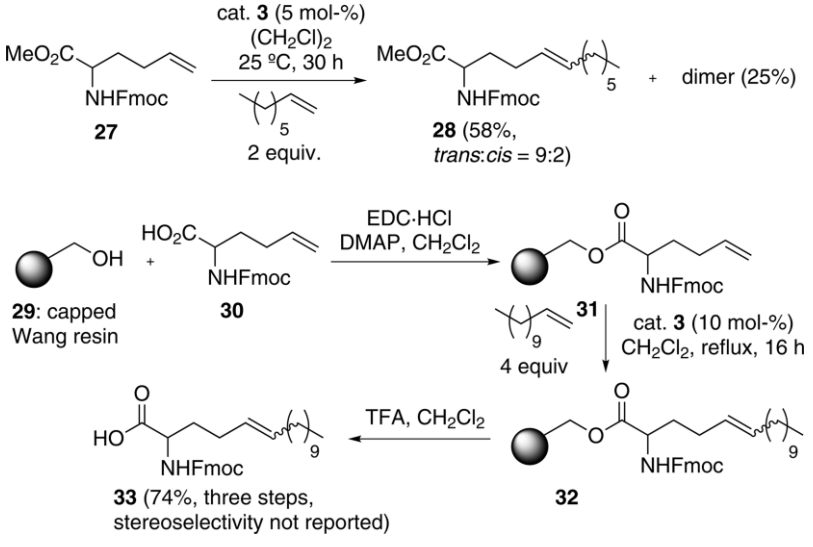
In 1998, Nicolaou and co-workers reported a SP approach to a muscone library that relied on a CM reaction (Scheme 6).[24] Ketophosphonate resins **22** were prepared from Merrifield resin (0.4 mmol g^{-1}) in three steps and subjected to CM with either pent-4-enol or hex-5-enol in the presence of **3** as initiator (5 mol-% with respect to soluble olefins). The obtained resins **23** (60–70 % yield from Merrifield resin) consisted of mixtures of *Z* and *E* isomers. Oxidation of these mixtures allowed an intramolecular Horner–Wadsworth–Emmons process to take place upon treatment with potassium carbonate, thus releasing macrocyclic enones **25** from the solid support (predominantly *E* isomers). Conjugate addition followed by hydrogenation of the remaining olefin moiety completed the sequence, providing DL-muscone (–X–Y– = $–CH_2CH_2–$, *n* = 1, R′ = CH_3) and eleven analogues (compounds **26**). Notably, in this efficient synthetic sequence, apart from the ease of purification and the avoidance of high-dilution conditions, two common undesired solution processes are overcome: self-CM and intermolecular ketophosphonate aldehyde condensation.

In the same year, Gibson et al. reported a study on the CM of unsaturated α-amino acid derivatives with aryl- and alkyl-substituted alkenes.[25] Also in the presence of precatalyst **3** (5 mol-%), homoallylglycine (Hag) derivatives afforded CM products in 43–66 % yields along with the unwanted homodimers in yields ranging from 18 to 48 %. In particular, FmocHagOMe (**27**) and oct-1-ene afforded product **28** and the homodimer of **27** in 58 % and 25 % yield, respectively (Scheme 7). As a proof of concept, the authors attempted a SP version of the reaction. Comparatively, the result was quite promising, with amino acid derivative **33** being obtained in 74 % yield [anchoring of FmocHagOH (**30**) and cleavage of **33** included]. The success of the process relied on the use of **29**, a 90 % capped 0.6–0.8 mmol g^{-1} Wang resin, because initial experiments with higher loadings delivered the product **33** contaminated with its dimer.

To study the scope and limitations of Ru-catalyzed metathesis of alkenes on polystyrene resins, Brown and co-workers evaluated resins **34** and **36**, which were prepared from a high-load-



Scheme 6. SP synthesis of a muscone library through cross-metathesis.



Scheme 7. Solution CM versus SPCM of unsaturated amino acid derivatives [EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide].

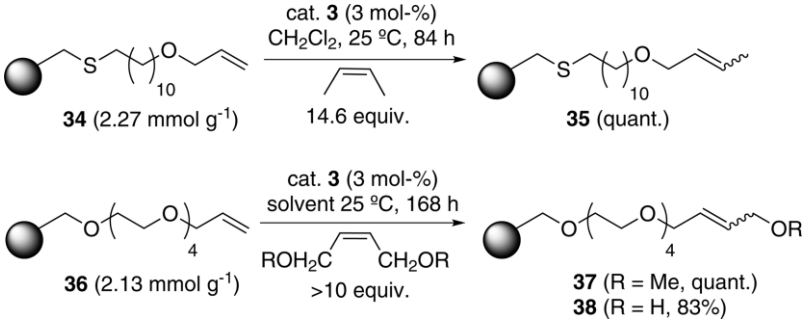
ing Merrifield resin (Scheme 8). The reactions were monitored by ^{13}C NMR (in some cases by the magic angle spinning technique) and diastereoselectivity ratios were not determined.[26] Some evidence of competing interchain metathesis was also obtained.

Hodge et al. also employed olefin metathesis to prepare Merrifield-resin-bound 20-hydroxyicos-10-enoic acid (**40**) during their studies on the synthesis of cyclic oligoesters for applications in macrocyclic lactone synthesis and combinatorial chemistry (Scheme 9).[27] SPCM of **39** with 7 equiv. of undec-10-enol in the presence of 1 mol-% of precatalyst **3** provided the corresponding resin **40** in 36 % yield.

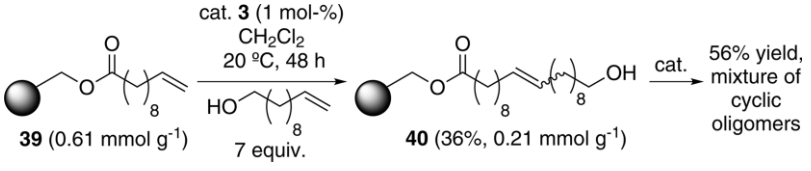
Second-generation Ru *N*-heterocyclic carbene precatalyst **6** was first employed in a SP approach to the synthesis of unsymmetrical (*E*)-hydroxystilbenes (Scheme 10).[28] Thus, treatment of **41** – 4-vinylphenol attached to Merrifield resin – with a series of substituted styrenes provided (*E*)-stilbenoids **42**, related to the natural product resveratrol, in good yields (54–81 %, three steps including anchoring of 4-vinylphenol, CM, and cleavage).

In work based on Blechert's strategy for the immobilization of olefins on an allyldimethylsilyl-functionalized polystyrene support through CM, the Déléris group reported the synthesis of **46**, a 17-mer cyclopeptide expected to have anti-angiogenic properties, in 2005.[29] Peptide **46** was elaborated from **43**, a conveniently functionalized D-tyrosine amino acid derivative loaded onto the corresponding resin with the aid of the Grubbs precatalyst **3** (Scheme 11).

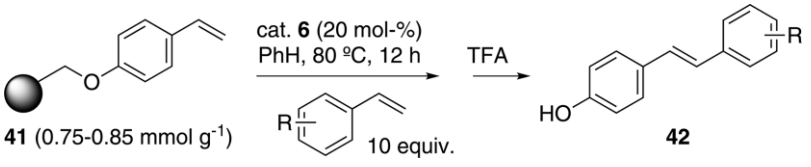
In 2006, during the course of our studies on the SP synthesis of biologically relevant β-lactam derivatives, we reported on the use of Ru-carbene complex **6** in CM reactions.[30] The β-lactam



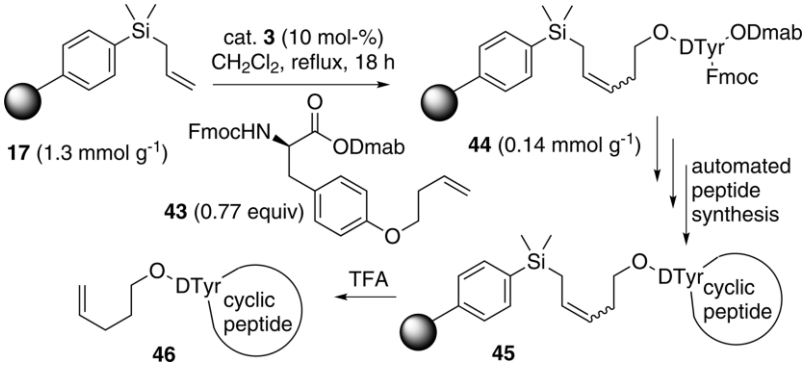
Scheme 8. SPCM of high-loading resins bearing terminal olefins bound through long spacers.



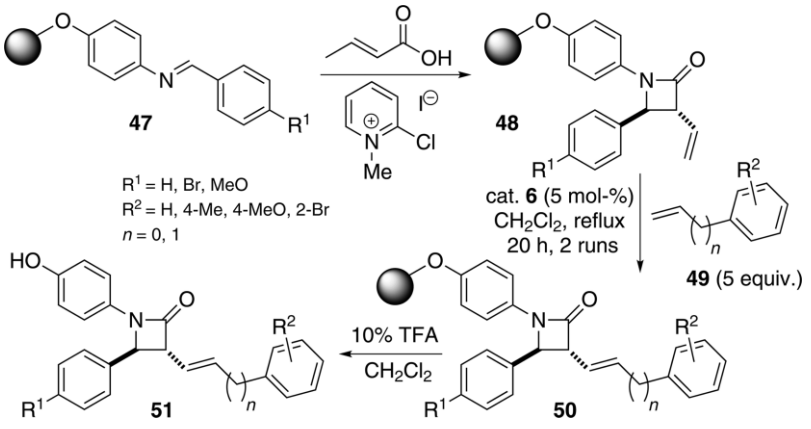
Scheme 9. Preparation of polymer-supported 20-hydroxyicos-10-enoic acid (**40**).



Scheme 10. SP synthesis of (*E*)-hydroxystilbenoids.



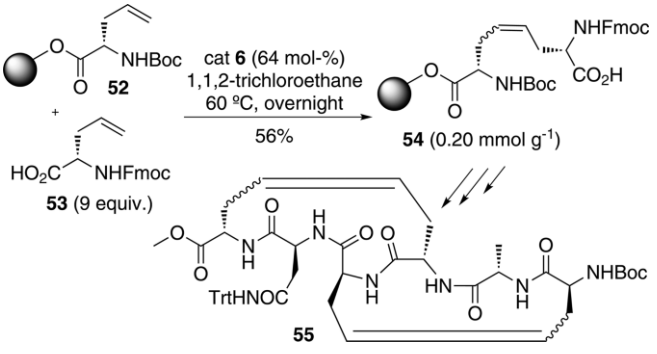
Scheme 11. SP synthesis of a 17-mer cyclopeptide (Dmab = 4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl).



Scheme 12. SP synthesis of biologically relevant β-lactams.

core was first assembled through a SP Staudinger reaction with use of Mukaiyama's reagent as acid-activating agent (Scheme 12). Reaction between imines **47**, supported on Wang resin (0.96 mmol g^{-1}), and crotonic acid then provided the 3-vinyl-β-lactams **48** stereoselectively. CM of olefins **48** with a series of substituted styrenes and allylbenzenes **49**, catalyzed by the Grubbs precatalyst **6**, provided resin-bound β-lactams **50** with complete *E* selectivity. After cleavage under mild conditions, the desired products **51** were obtained in good overall yields (11–25 %, six steps; 35–78 % for CM reactions). In particular, one of the products was further elaborated into a well-known cholesterol absorption inhibitor (two additional steps in solution, 18 % overall yield).

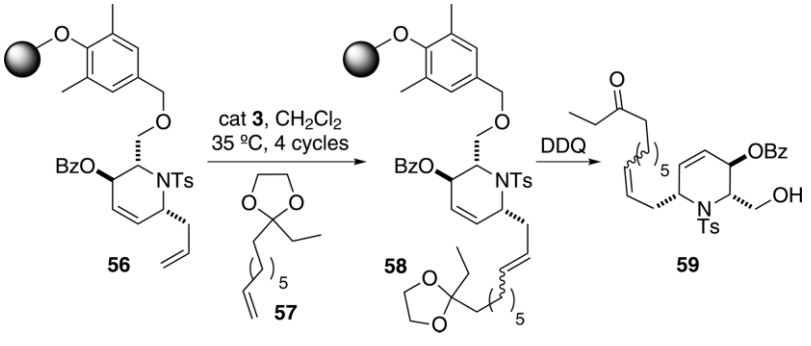
CM was also employed by Liskamp and collaborators to construct an alkene-bridged derivative as a mimic of the thioether moiety of the lanthionine functionality that is present in the DE-fragment of the antimicrobial peptide nisin Z.[31] CM between Boc-protected L-allylglycine bound to ArgoGel-OH resin (**52**, 0.36 mmol g^{-1}) and Fmoc-L-allylglycine (**53**) was catalyzed by precatalyst **6** and provided resin **54** in 56 % yield (Scheme 13). Interestingly, the reaction worked without the need for protecting groups for the carboxylic acid moiety of the soluble CM partner. Further steps featuring a macrolactamization and a RCM in solution provided the desired peptide mimic **55** in an overall yield of 7 % (16 steps).



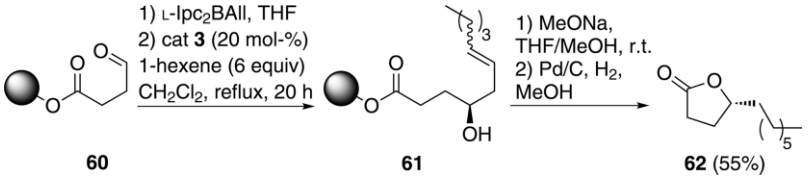
Scheme 13. Synthesis of a crossed alkene-bridged nisin Z DE ring mimic.

In the same year Couladouros et al. reported the synthesis of the piperidine alkaloid (±)-prosophylline by way of a CM reaction as a key step (Scheme 14).[32] Intermediate **56**, loaded on Merrifield resin through an aromatic ether linker, was subjected to a chemoselective CM with terminal olefin **57** in the presence of precatalyst **3**. After four cycles, the obtained resin **58** was treated with the oxidant DDQ (2,3-dichloro-5,6-dicyano-benzo-1,4-quinone). This reagent not only induced cleavage from the resin but also removed the acetal protecting group, affording product **59**, which is an intermediate en route to the natural product sought. The yield of the metathesis step was not specifically reported, but the overall yield for the nine steps carried out on SP was 13 %.

Another natural product synthesis featuring a SPCM reaction was accomplished by Waldmann and collaborators during their studies on the asymmetric allylation and crotylation of alde-



Scheme 14. Key cross-metathesis step en route to (±)-prosophylline.



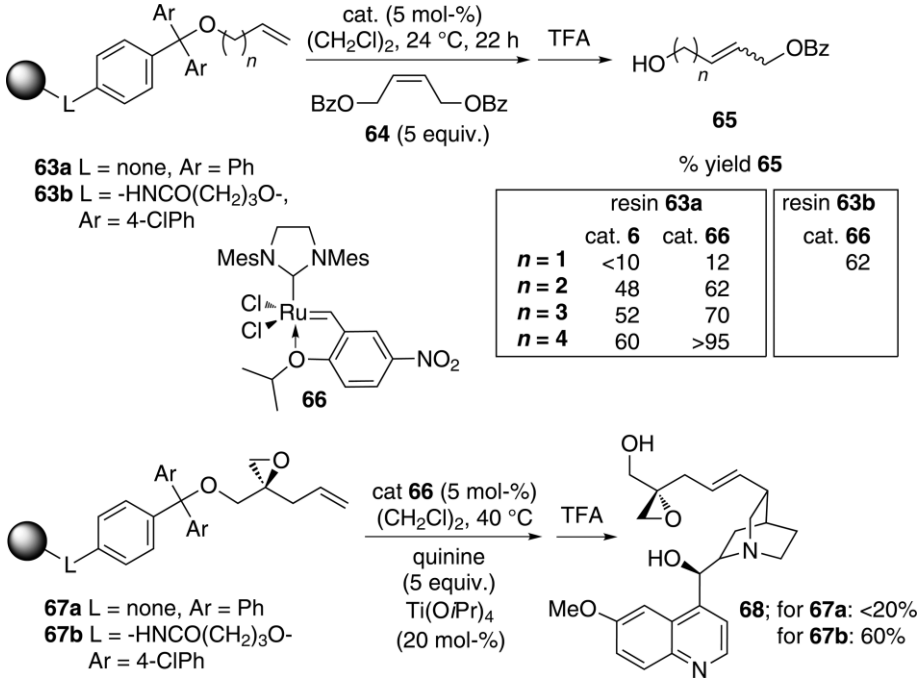
Scheme 15. Synthesis of naturally occurring (*R*)-5-heptyl-dihydrofuran-2-one (**62**) with the aid of a SPCM [LIpc$_2$BAll = L*B*-allyldiisopinocamphenylborane].

hydes on solid support (Scheme 15).[33] Asymmetric allylboration of immobilized aldehyde **60** yielded the corresponding allyl alcohol (*er* 95:5), which, upon CM with hex-1-ene in the presence of **3** as precatalyst, generated polymer-bound olefin **61**. Subsequent cyclorelease from the resin followed by catalytic heterogeneous hydrogenation delivered the natural product **62** in 55 % overall yield.

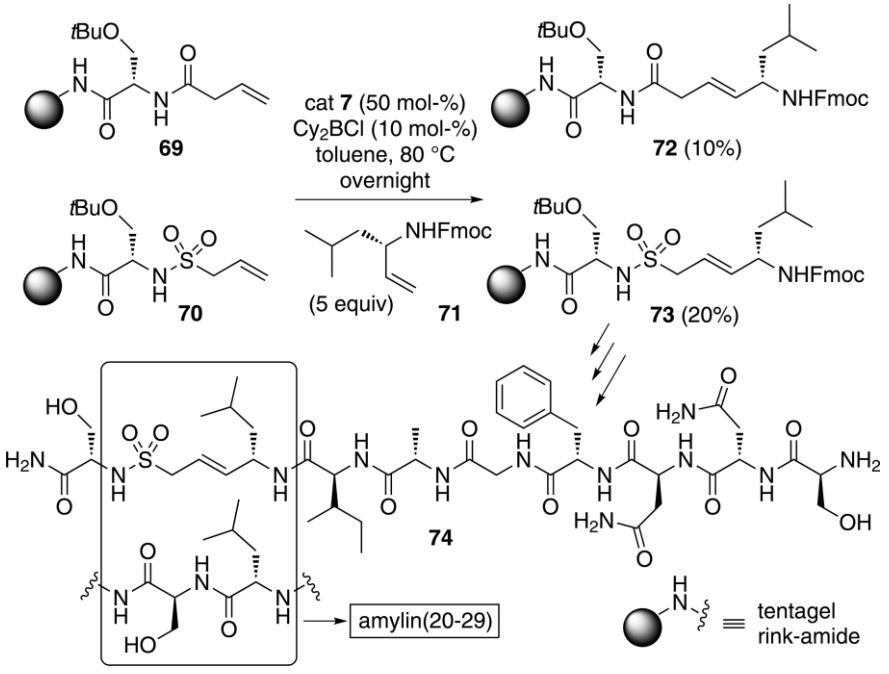
In particular, the effect of the distance between the polymer matrix and the alkene moiety of a supported olefin on CM reactions was studied by Koide and Garner.[34] Whereas attachment of an olefin through a long carbon chain could, in principle, facilitate intrabead homodimerization, use of a short carbon chain could also impact metathesis efficiency because of steric hindrance. To study this proximity effect they evaluated CM between alkenes **63a**, bound to a trityl chloride resin (0.94–0.98 mmol g^{-1}), and non-terminal olefin **64** (Scheme 16). Apart from the fact that no intrabead dimerization was observed in these experiments, the reactions were indeed influenced by the carbon chain length. A gradual increase in yields of corresponding products **65** was found on going from supported allyl alcohol to supported hex-5-enol (n = 1 → 4). Similar reactivity profiles were observed on changing the solid support from chlorotritylpolystyrene to Merrifield resin or an alkylsilyl resin. Interestingly, the best results were obtained with the advanced Ru reagent **66**,[35] a nitro-substituted derivative of the phosphine-free Hoveyda–Grubbs precatalyst **7**.

The influence of the chain length was also observed when resin **63b**, with a linker incorporating a 4-hydroxybutanamide moiety, was used. In this case, CM product **65** (n = 1) was obtained in 62 % yield instead of the previous 12 % yield obtained with **63a** (Scheme 16). Additionally, whereas epoxyalcohol trityl ether resin **67a** provided the immobilized quinine **68** in less than 20 % yield when subjected to CM, resin **67b**, incorporating the linker discussed above, gave the same product in 60 % yield. In both cases, catalytic amounts of Ti(O*i*Pr)$_4$ were necessary to prevent chelation between the epoxide moiety and Ru-carbene complex, thus enabling catalyst turnover.

After their research on peptidomimetics, Liskamp and coworkers also evaluated the use of a Lewis acid to assist SPCM reactions.[36] The alkene dipeptide isostere **72** and the alkene dipeptidosulfonamide isostere **73** were developed in this way with **7** as catalyst and Cy$_2$BCl as Lewis acid, albeit in low unoptimized yields (Scheme 17). These amide-bond surrogates **72** and **73** were then incorporated into derivatives of amylin(20–29), which is the highly amyloidogenic region of amylin, a peptide hormone involved in the pathogenesis of type II diabetes. This incorporation led to two peptides (one of them **74**, when **73** was used) for which delayed fibril formation and altered sec-



Scheme 16. Proximity effect on cross-metathesis of resin-bound alkenes.

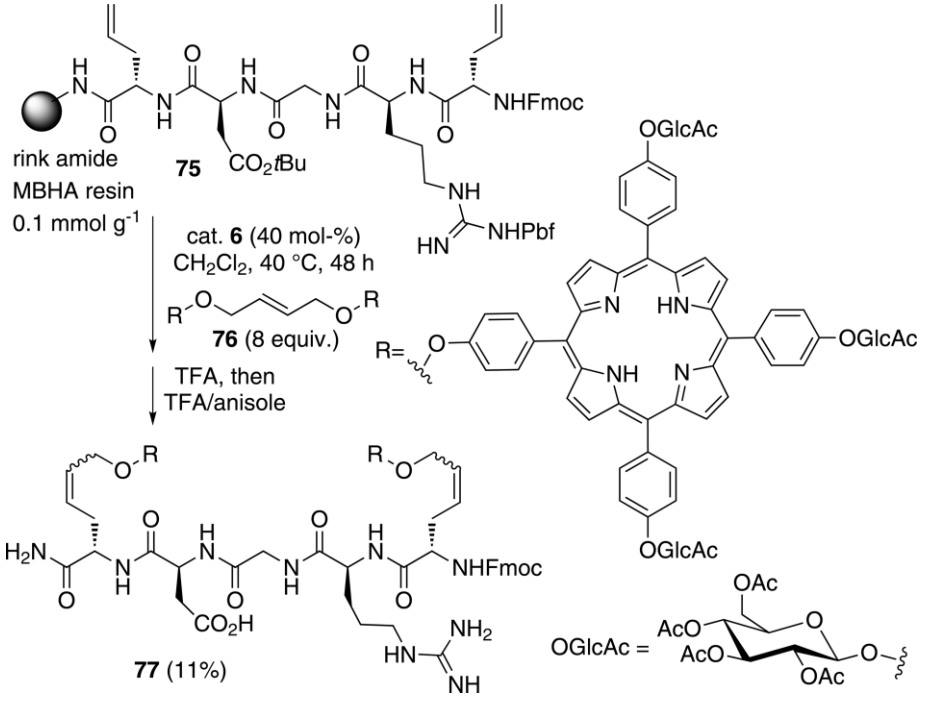


Scheme 17. Synthesis of amide-bond surrogates by SPCM.

ondary structures in comparison with native amylin(20–29) were observed.

Sol and co-workers employed an olefin CM reaction to synthesize the dimeric porphyrin-peptide conjugate **77** as a promising candidate for use in photodynamic therapy (Scheme 18).[37] The linear peptide **75**, prepared on a Rink MBHA resin, contains an arginyl-glycyl-aspartyl (RGD) sequence, required for cellular recognition, located between two allylglycine residues. CM with glycosylated porphyrin dimer **76**, in the presence of precatalyst **6**, delivered, after removal of protecting groups and detachment, the desired product **77** in only 11 % overall yield. Unfortunately, the behavior of the monomer of **76** as a CM partner was not explored for comparative purposes.

In 2009, pursuing our interest in β-lactam heterocycles as interesting biologically active scaffolds and valuable intermedi-

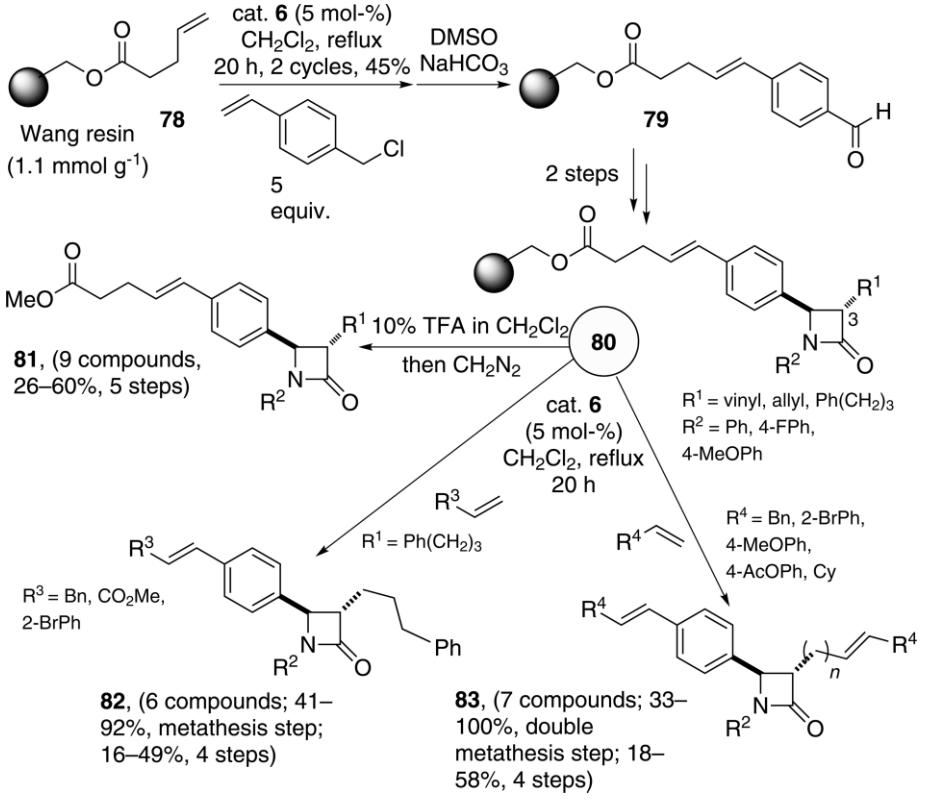


Scheme 18. Synthesis of a dimeric porphyrin-peptide conjugate by SPCM (Pbf = 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl).

ates in synthesis, we took advantage of multicleavable linker **79** to assemble new libraries of analogues of cholesterol absorption inhibitors such as ezetimibe.[38] Immobilized aldehyde **79** was prepared from Wang resin by loading of pent-4-enoic acid to provide **78**, SPCM with 4-vinylbenzyl chloride (with precat. **6**), and subsequent oxidation (Scheme 19). After imine formation with an array of anilines, use of Staudinger reaction conditions with either α,β-unsaturated or nonconjugated acids provided resin-bound β-lactams **80** in a stereoselective manner. The multicleavable linker clearly allowed the introduction of structural variation into the assembled library. Standard acid cleavage followed by methylation delivered an initial library of β-lactam methyl esters **81** in good overall yields. For resins **80** not bearing an olefin moiety in the C3 side chain, CM with a variety of alkenes allowed functionalization at the cleavage step to give the β-lactam library **82**. This CM step proceeded efficiently with use of precatalyst **6** and olefins such as methyl acrylate and allylbenzene (81–92 % yield); reduced yields were only found when sterically hindered 2-bromostyrene was used (41 % and 50 % yield). On the other hand, for β-lactams **80** bearing a vinyl or allyl substituent at C3, treatment with Ru complex **6** in the presence of a soluble olefin could proceed through a double-metathesis event. Indeed, this double CM released ezetimibe analogues **83**, in some cases quantitatively. It is worth mentioning that, with the exception of only one substrate, the CM reactions were completely *E*-selective.

In 2003, the Grubbs research group published a general empirical model for predicting selectivity in CM reactions.[15] Olefins are categorized into four classes, based on their relative ability to undergo homodimerization and the propensity of these dimers towards secondary metathesis. Type I consists of sterically unhindered non-electron-deficient olefins capable of undergoing fast homodimerization, with their homodimers also being able to engage in CM reactions. Type II olefins have slower homodimerization rates and these dimers are sparingly consumed by secondary metathesis events. Type III olefins do not undergo dimerization but are still able to participate in CM reactions with either Type I or Type II substrates. Type IV olefins, on the contrary, act as spectators to olefin metathesis; they cannot participate in CM reactions and do not poison the catalyst either.

According to this model, a selective CM reaction will be the result of combining olefins that differ in reactivity considerably: that is to say, belong to different types. Because the "olefin ranking" in this classification depends on the nature of the catalyst, the choice of catalyst is essential for achieving CM selectivity, as well as the manipulation of substituents that can exert steric and electronic effects on olefin reactivity. The model predicts nonselective CM as the outcome of matching olefins of the same type. If these are Type I substrates, which are highly active, this will be translated into a statistical product mixture resulting from equilibration between the desired cross-product and the corresponding homodimers formed through efficient secondary metathesis events. As shown, almost every olefin employed throughout these literature precedents is Type I, and hence the solid support comes to the rescue by lowering, to some extent, the reactivity of the immobilized olefin, for which homodimerization is hampered, and by circumventing the un-



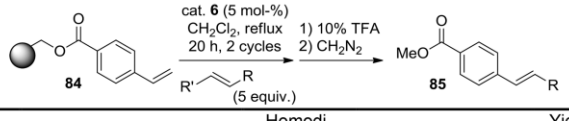
Scheme 19. β-Lactam libraries based on a multidetachable linker.

desired homodimerization of the soluble counterpart through filtration.

During the course of our studies, we conducted a thorough investigation to unravel the complex interplay between the different factors affecting the reaction outcome, such as the catalyst activity, the reactivity of the soluble olefin, and the ability of the immobilized one to undergo on-bead metathesis.[39–41] The role of homodimerization of the soluble olefin was revealed first on evaluation of the reactivity of 4-vinylbenzoic acid loaded on Wang resin (**84**, 1.1 mmol g^{-1}, Table 1). Notably, under the conditions assayed with use of the Grubbs precatalyst **6** and without the presence of a soluble olefin, no site–site interactions could be detected for the rigid system **84**. Instead, when different cross-partners were examined, the reactivity of the system was modulated by the differences in reactivity between monomers and their corresponding homodimers and by the rate of dimerization (Table 1). By employing soluble olefins that do not dimerize and those that undergo dimerization to produce equally reactive olefins, satisfactory CM selectivities could be attained (e.g., Entries 1–2, 5–6, 9, and 10). In contrast, an unreactive dimer that forms rapidly ensured low cross-product production (e.g., Entries 3–4 and 7–8). Noticeably, whereas the Hoveyda–Grubbs precatalyst **7** behaved similarly to **6**, replacement by less reactive precatalyst **3** had a gargantuan effect. With allylbenzene – a highly reactive Type I olefin – as soluble partner, only a 22 % yield of cross-product was obtained, unlike the 86 % achieved with precatalyst **6** (Entry 1). In addition, crotonic acid became a spectator to olefin metathesis in the presence of **3**.

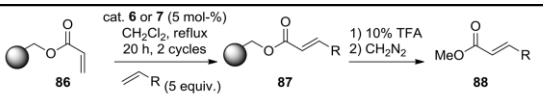
When the immobilized component was switched to an acryloyl moiety, an electron-deficient Type II olefin (resin **86**, Table 2), CM reactions with both Type I and II olefins catalyzed by **6** were unsuccessful, with yields ranging from 10 % to 35 %. Nevertheless, the catalyst choice was critical, with the more active Hoveyda precatalyst **7** providing on average a twofold increase in yields of cross-products. This is consistent with solution-phase studies addressing the efficiency of **7** with use of α,β-unsaturated carbonyl compounds.[42]

Table 1. Cross-metathesis of resin-bound 4-vinylbenzoic acid.



	Soluble olefin	Homodimerization	Product	Yield (%)
1	R'=H, R=	15 min	R=	86
2	R'=R=	-	R=	72
3	R'=H, R=	2 h	R=	31
4	R'=R=	-	R=	n.r.
5	R'=H, R= Cl	20 h	R= Cl	80
6	R'=R= Cl	-	R= Cl	58
7	R'=H, R=	5 h	R=	57
8	R'=R=	-	R=	39
9	R'= Me, R= O OH	no	R= O OMe	97
10	R'= Me, R= O OBn	no	R= O OBn	96
11	R'=H, R= Br	no	R= Br	43

Table 2. Cross-metathesis of acryloyl Wang resin.

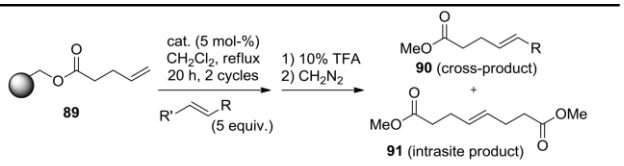


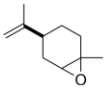
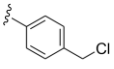
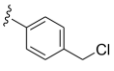
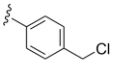
	Soluble olefin	Homodimerization	Product	Yield (%) cat. 6	Yield (%) cat. 7
1	R=	15 min	R=	35	59
2	R= Cl	20 h	R= Cl	11	23
3	R=	5 h	R=	26	68
4	R= Br	No	R= Br	10	16

The interaction between polymer-bound olefin residues became apparent on evaluation of supported pent-4-enoic acid (**89**, Table 3). With use of the same loading of Wang resin as had been employed for immobilization of 4-vinylbenzoic acid (resin **84**), an excess of allylbenzene in the presence of precatalyst **6** furnished desired cross-product **90** (R = benzyl) in low yield (Table 3, Entry 1, 18 %). The major product found was the diester **91** arising from prevalent site–site interference. A well-known aspect of SP organic synthesis is the pseudo-dilution effect on resins, which makes reaction between supported reactive groups an unlikely process.[43–46] This notwithstanding, the feasibility of interaction between polymer-bound species has been known since the dawn of SP organic synthesis.[47,48] Although site–site isolation is usually achieved, intra-resin reactions can occur, and their likelihood depends on several factors such as swelling, loading level, degree of cross-linking, and nature of the linker.[49]

The relatively free motion of the carbon chain and the unhindered nature of the terminal olefin present in resin **89** clearly allowed this side metathesis reaction, and homodimeric **91** could indeed be obtained in 85 % yield in the absence of any soluble olefin, after release from the resin and esterification (Table 3, Entry 2). Further experiments with supported pentenoic acid **89** were performed and shed light to aid understanding of the influence of different factors on such interference.

Table 3. Cross-metathesis of resin-bound pent-4-enoic acid.

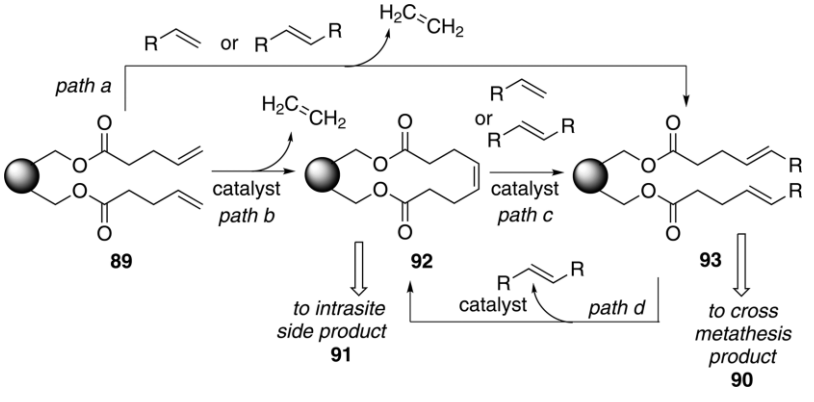


	Soluble olefin	Homodimerization	cat.	90 (%)	91 (%)
1	R'=H, R= 	15 min	**6**	18	70
2	none	-	**6**	-	85
3	R'=  Me, R= OH	no	**6**	100	0
4		no	**6**	0	85
5		no	**6**	0	85
6	R'=H, R= 	no	**3**	14	70
7	R'=H, R= 	20 h	**6**	45	35
8	R'=H, R= 	5 h	**7**	43	33
9	R'=H, R= 	no	**3**	6	83
10	R'=H, R= 	no	**6**	87	0
11	R'=H, R= 	partially	**7**	57	17

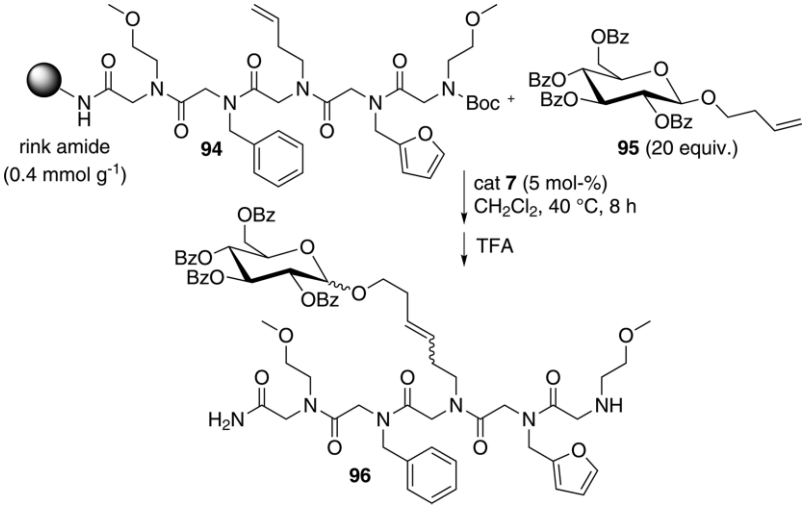
As shown in Scheme 20, several metathetic events occur if a highly reactive olefin such as allylbenzene (R = benzyl) reacts with a reactive immobilized alkene such as **89**. This scenario gets even more complicated if site–site interaction is then possible. If a sealed vessel is avoided then, as ethylene departs from the system, the fate of the reaction depends on **92** and **93**, one of which leads to the intra-site by-product and the other to the desired cross-product.

Interestingly, when less reactive Type II olefins such as crotonic acid and 2-bromostyrene were used, formation of desired CM products **90** was prominent (Table 3, Entries 3 and 10). These outstanding results could be explained in terms of the resilience of the resulting resin-bound cross-products **93** to further metathesis events. In other words, when these non-homodimerizable olefins undergo CM with the immobilized olefin, "*path d*" becomes blocked and equilibrium is no longer shifted toward intra-site resin-bound product **92** but to **93**, which becomes a spectator to further catalytic events. Attempts performed with even less reactive substrates such as limonene oxide and β-pinene, each containing a 1,1-disubstituted olefin moiety, led to the isolation only of intra-site product **91**, which means that they act as spectators to the metathesis events (Entries 4 and 5).

Results from evaluation of different catalysts were consistent with the scenario portrayed above. With, for instance, 2-bromostyrene (for which the CM product with **89** was found in 87 % yield when precatalyst **6** was employed, Entry 10), first-generation precatalyst **3** failed to achieve cross-selectivity (Entry 9). On the other hand, the higher reactivity of second-generation precatalyst **7** led to an unwieldy mixture of both **90** and **91** (Entry 11). As a consequence of such reactivity, secondary metathesis events on the cross-product ("*path d*") may become available, increasing the tendency to displace the reaction outcome toward product equilibration (Scheme 20). As previously stated, the choice of catalyst is crucial for appropriate CM selectivity and, in certain cases, this will mean the use of a less reactive one. For instance, during the synthesis of the alkaloid prosophylline, precatalyst **3** clearly discriminates between the internal and the terminal olefin moieties of the metathesis precursor **56** (Scheme 14).



Scheme 20. Metathetic pathways for a homodimerizable immobilized olefin.



Scheme 21. A glycopeptoid assembled on solid-phase through cross-metathesis.

As a fast and practical way to reach high temperatures, the use of microwave irradiation has been particularly welcomed in SP synthesis because reaction times are considerably shortened, preventing polymer degradation in some cases and accelerating production of compound libraries.[50] Although microwave irradiation has been successfully applied to CM reactions,[51–54] the lack of reports on the corresponding SP variant prompted us to evaluate this potentially profitable methodology.[39] After considerable experimentation using resin **84** (see Table 1) and different Type I and II soluble partners, we found that microwave heating provided excellent results in reaction times as short as 25 min (toluene, 75 °C, 120 W). This notwithstanding, in agreement with literature data,[55–57] no evidence of non-thermal effects was found, and under optimized conditions CM with conventional heating proved to be equally efficient.

As discussed in the following section, since the immobilization of glucosides by Blechert et al. (Scheme 5), carbohydrate derivatives have been valuable substrates in SPCM reactions. Because of the key role of glycosylation in processes such as cell growth regulation, protein folding, and immunological response, mastering the synthesis of glycoconjugates and glycopeptides as biological probes and lead compounds for glycobiology and drug discovery has become crucial. In this context, Grubbs, Kwon, et al. recently explored the SP synthesis of glycopeptoids.[58] Peptoids are readily accessible synthetic *N*-substituted polyglycines that exhibit diverse biological activities and have improved proteolytic stability and cell permeability over peptides.

These glycopeptide mimetics were prepared through CM between peracetylated or perbenzoylated *O*-alkenyl glycosides (e.g., **95**) and immobilized 4- or 5-*mer* peptoids bearing an *N*-allyl or *N*-butenyl moiety (e.g., **94**, Scheme 21). The three most commonly used metathesis precatalysts (**3**, **6**, and **7**) were evaluated, to find that the best results were obtained with the Hoveyda–Grubbs precatalyst **7** at a loading of 5 mol-%. Increasing this amount only caused an increase in the homodimerization of the soluble sugar derivatives. The stereochemistry at the anomeric carbon of the glycosides did not affect these reactions, but the chain lengths of the two olefin components turned out to be a crucial factor for the success of the CM. A combination of *N*-butenyl/*O*-butenyl or *O*-pentenyl fragments generally proceeded with highest levels of conversion.[59]

Although more specific precedents are presented in the following sections, all of the above efforts to unravel CM on solid supports have allowed the methodology to progress to become a fruitful field of study. Creativity has led to versatile and varied applications such as the immobilization and release of olefins, the synthesis of natural products in facilitated ways, the efficient production of libraries of potential therapeutic agents, and the preparation of complex molecular assemblies such as peptide mimetics. It is also noteworthy that no unconventional equipment, only standard laboratory glassware, is necessary to carry out these reactions. On this topic, strict exclusion of moisture and air are precautions that were taken seriously in early works involving the presence of the first-generation catalyst **3**. With regard to residual Ru impurities, although this has been a great concern in homogeneous catalysis,[60,61] only in the case of the SP synthesis of amylin(20–29) mimetics by CM (Scheme 17) did the authors comment on the removal of brown Ru by-products from the final assembled peptides.[36] With reference to the stereoselectivity of SPCM reactions, this point has not been meticulously addressed, yet in several cases complete *trans* selectivity is observed and in some others olefin geometry is not an issue, such as in those of intermediates **19**, **25**, **58**, and **61**, which are subsequently either hydrogenated or isomerized upon cleavage.

2.2. Application of CM to the Synthesis of Oligosaccharides

The synthesis of complex and structurally diverse carbohydrates is crucial to the understanding of important biological processes in which they are implicated, such as immune response, angiogenesis, and tumor cell metastasis. Oligosaccharide syn-

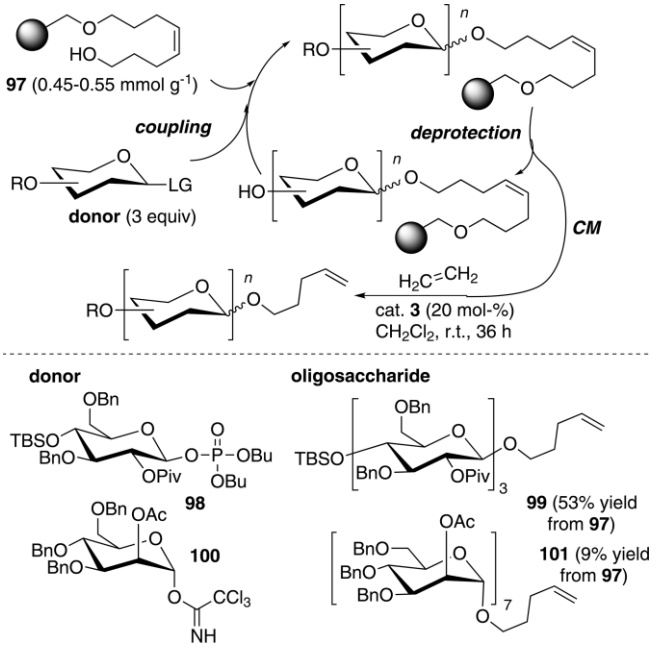
thesis is much more complex and challenging than the synthesis of oligopeptides and oligonucleotides, the other two major classes of biopolymers found in living systems. In the past two decades, lots of efforts have been made, in particular on their SP synthesis, leading to important advances in this field.[62–64]

In 1999, Seeberger's research group introduced a new metathesis-based linker that they envisioned should allow the efficient, fast, and eventually automated synthesis of complex oligosaccharides.[65] After some model studies in solution, Merrifield resin was functionalized with an octenediol-based linker to afford **97** (Scheme 22). The exposed primary hydroxy group was intended to act as an acceptor in the first glycosylation reaction (acceptor-bound strategy), whereas the olefin moiety should allow the final cleavage of the assembled oligomer by CM in the presence of ethylene.

By this strategy, the synthesis of the β-(1–4)-linked trisaccharide **99** and the α-(1–2)-heptamannoside **101**, along with several other examples, provided initial validation for the potential of this stable and compatible system (Scheme 22). All CM reactions were performed with first-generation precatalyst **3** (20 mol-%, added in two portions) under ethylene.

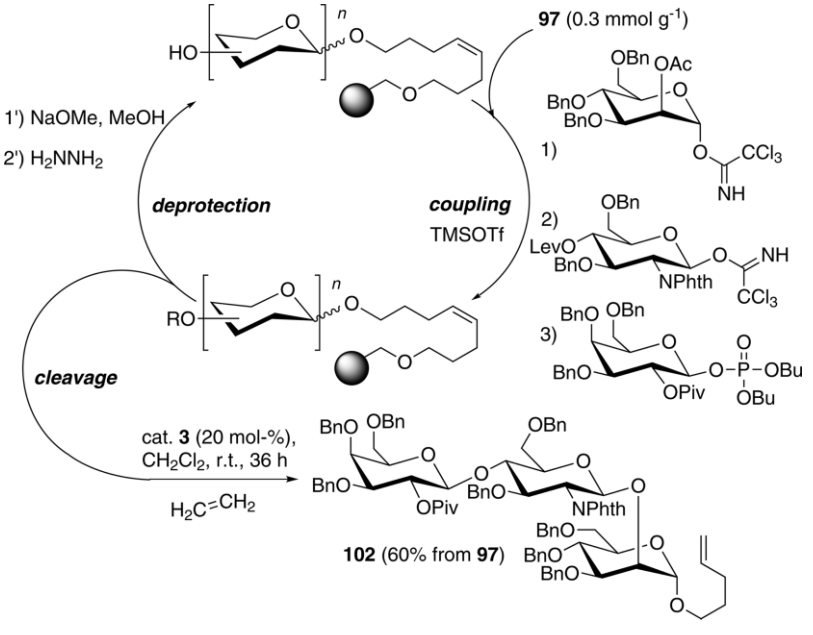
Because the olefin moiety present in **97** makes it incompatible with oligosaccharide synthesis using thioglycosides and *n*-pentenyl glycosides, which require strongly electrophilic activators, Seeberger et al. soon developed a masked variant based on dibromination.[66] The new 4,5-dibromooctane-1,8-diol linker supported on Merrifield resin was used to prepare a trisaccharide in 9 % overall yield from thioethyl glycosyl donors. The concealed alkene moiety was then regenerated by treatment with tetrabutylammonium iodide (TBAI), allowing the cleavage of the carbohydrate through CM. Although attractive, this approach was not further explored.

The initial success of the developed SP approach was eclipsed by a major breakthrough in oligosaccharide synthesis,



Scheme 22. Solid-phase oligosaccharide synthesis with use of a metathesis-cleavable linker (Piv = pivaloyl, TBS = *tert*-butyldimethylsilyl).

when Seeberger's research group reported their automated version in 2001.[67] A commercial peptide synthesizer was modified in order to conduct every coupling, washing, and deprotection function required, even at variable temperatures if needed. Alternation between different glycosyl donors was also possible, with one example being the synthesis of trisaccharide **102**, which bears a motif present in complex *N*-linked glycoprotein structures (Scheme 23). Strikingly, apart from the avoidance of tedious manipulations, the automated construction of oligosaccharides proved to be fast and high-yielding. For instance, the



Scheme 23. Automated solid-phase synthesis of oligosaccharides (Lev = levulinoyl, Phth = phthaloyl).

preparation of heptamannoside **101** (Scheme 22) was achieved in 42 % overall yield and only 20 hours, whereas the standard SP approach required 14 days to afford only a 9 % yield of the oligomer.

Several outstanding syntheses by this approach then followed, including those of **103**, a protected form of a cap tetrasaccharide found on the cell surface of protozoan parasite *Leishmania*,[68] of glycosylphosphatidylinositol malarial toxin **104** as a vaccine candidate,[69] and of **105** and **106**, protected forms (i) of a core N-linked pentasaccharide common to N-linked glycoproteins,[70] and (ii) of the tumor-associated carbohydrate antigens Gb-3 and Globo-H, respectively,[71] as well as other targets to adapt new synthetic strategies to automation (Figure 1).[72,73] In some cases the time required for their construction was reduced 20-fold in relation to solution-phase attempts. Release of the target structures was achieved with precatalyst **3** (20 or 30 mol-%) in all cases, and special attention was paid to the purities of the compounds with regard to Ru contamination, which led to the incorporation of a final versatile aqueous workup using a water-soluble phosphine prior to chromatographic purification.[60c] In addition, in view of the unique behavior of highly fluorinated molecules,[74] "cap-and-tag" approaches to SP oligosaccharide synthesis were explored; these resulted in simplified purifications of target molecules from deletion sequences and avoidance of any need for large excesses of building blocks or repeated couplings.[75,76]

During these studies, the incorporation of azide-containing glycosides as building blocks was also evaluated, in view of the fact that the protection of amines as azides is a strategy commonly applied to the assembly of amino-glycoside antibiotics and glycosaminoglycans such as heparin.[77] In some model solution systems, mimicking the SP scenario, it was found that precatalysts **3** and **6** were inefficient for CM of azide-containing sugars. This failure was attributed to the incompatibility of the azide functional group with the phosphine ligands of the catalysts.[78] After considerable experimentation, it was found that a commercially available bispyridine complex, belonging to a family of third-generation Ru catalysts,[79] was suitable for this task provided that liquid pent-1-ene was used instead of ethylene as the other CM component.

More recently, β-mannuronic acid alginates with up to twelve challenging 1,2-*cis*-linkages and a set of hyaluronic acid oligomers up to the pentadecamer level were also produced with the aid of the automated platform.[80,81]

The automated synthesis of oligosaccharides, as opposed to peptides and oligonucleotides, by means of SP techniques had long been neglected. All the efforts described above have already changed this scenario. SPCM has played a vital role in this achievement, with an extremely stable linker combined with a robust and functional-group-tolerant precatalyst having made the birth of automated SP oligosaccharide synthesis possible.

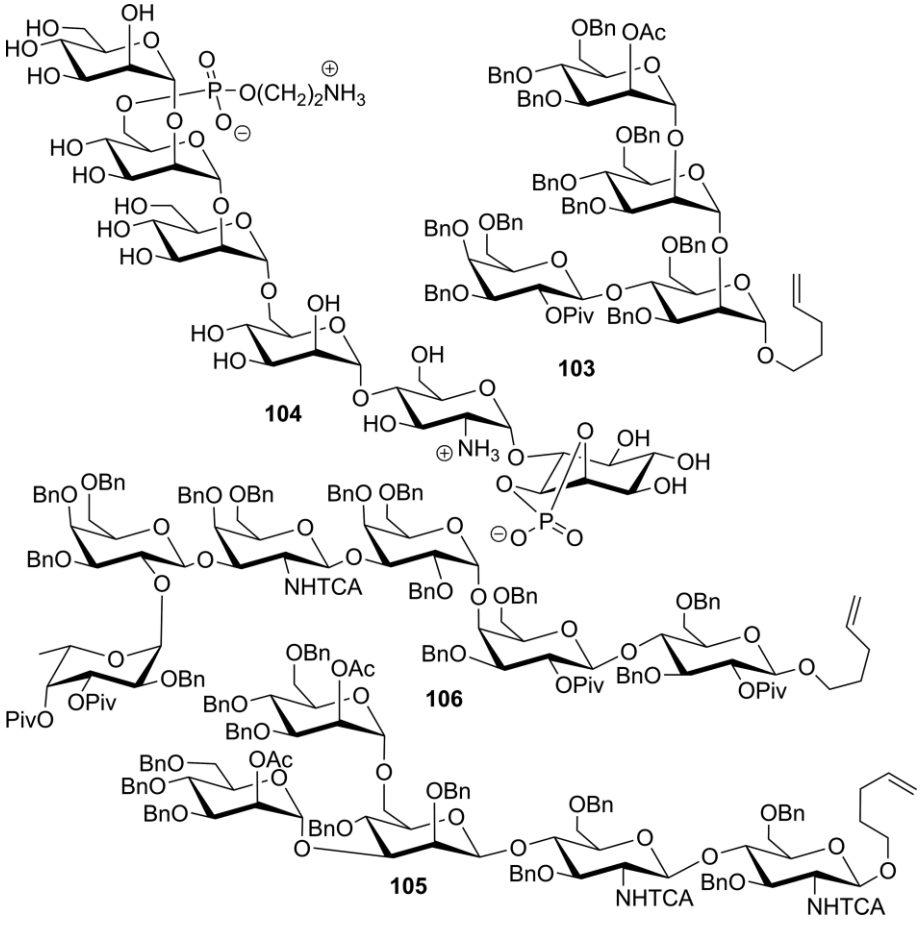
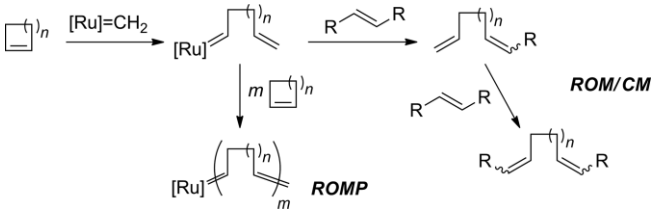


Figure 1. Some target oligosaccharides prepared by automated SP synthesis (TCA = trichloroacetyl).

2.3. Solid-Phase Ring-Opening/Cross-Metathesis

Tandem ring-opening metathesis/cross-metathesis (ROM/CM), as shown in Scheme 1, consists of a reaction between a cyclic olefin and an acyclic counterpart to deliver an end-differentiated diene as product. For this to hold true, the active alkylidene metal species needs to react with the two substrates in the correct sequence: that is, after initial opening of the cycloolefin, triggered by ring-strain release, the metal–carbene intermediate interacts with a suitable cross-partner to deliver the desired diene product, either as an end-differentiated one or as a symmetrically capped diene if a possible second CM event takes place (Scheme 24). Otherwise, if the cyclic component proves to be more reactive, successive self-metathesis events may lead to polymeric products. This process, known as ring-opening metathesis polymerization (ROMP), has been widely explored in polymer science, both in industry and in academia.[82] In combinatorial synthesis, this methodology has found particular use for the preparation of both soluble and insoluble high-loading polymer supports.[83]

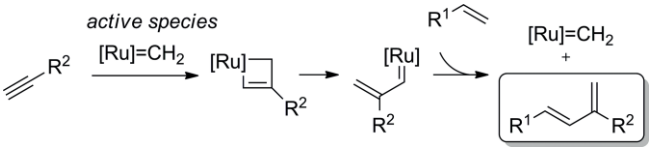


Scheme 24. Potential metathetic pathways after ring-opening of a cyclic olefin.

Cuny and co-workers established that ROM/CM can be conveniently adapted to SP chemistry and combinatorial library strategies. They envisioned that by immobilization of a strained norbornene derivative, competing ROMP would be prevented and that, therefore, through the use of different CM partners and linkers, highly functionalized cyclopentanes could be generated. To this end, monomethyl *cis*-4-norbornene-*endo*-2,3-dicarboxylate was first attached to Wang resin (0.85–1.01 mmol g^{-1}) through different diamine linkers to provide derivatives **107** (Scheme 25).[84] CM with an array of styrenes in the presence of precatalyst **3** then led to substituted cyclopentanes **108**, obtained in good overall yields as mixtures of pairs of possible regioisomers (1:1 to 2.7:1). Interestingly, no double CM event took place and complete *trans* selectivity was observed for the newly formed disubstituted olefins. The influence of electronic and steric factors on regioselectivity was remarkable, with enhanced regioselectivity being observed when electron-rich styrenes were used. Indeed, only single isomers were obtained when substrates attached through primary diamine linkers were used in combination with these electron-rich cross-metathesis partners. However, in these cases further cyclization involving the diamine linkers occurred during acidic cleavage, leading to bicyclic products **109**. With all of these results to hand, a combinatorial approach based on the same synthetic sequence was then undertaken.[85]

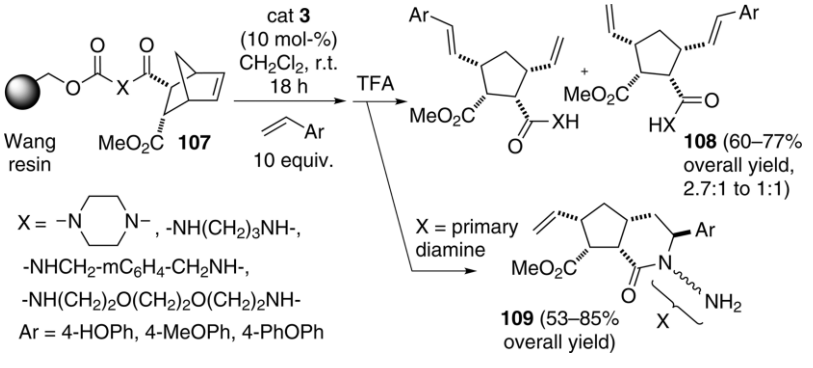
2.4. Enyne Cross-Metathesis on Solid Supports

Alkynes are viable substrates in intermolecular metathesis events with olefins.[86,87] These reactions, enyne metathesis, are also catalyzed by carbene complexes and involve metallacyclobutenes as intermediates to deliver 1,3-dienes as final products (Scheme 26).

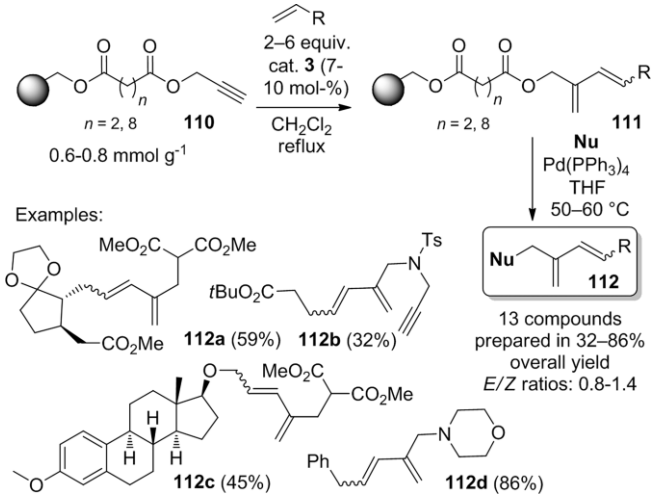


Scheme 26. Simplified mechanism for intermolecular enyne metathesis.

The adaptation of this atom-economical reaction to SP synthesis began shortly after the first report on the immobilization of olefins on polymer resins through CM.[88] Blechert et al. employed resin-supported propargyl esters **110**, which, on treatment with different soluble olefins under Ru catalysis conditions, afforded immobilized dienes **111** in acceptable yields (Scheme 27). These allyl ester resins could then be selectively cleaved under Pd^0 catalysis conditions and subsequently trapped with various nucleophiles, giving rise to a wide array of functionalized diene products **112**, showing no traces of the linkers used.

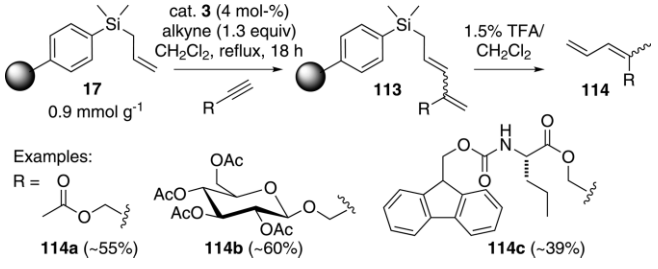


Scheme 25. Ring-opening cross-metathesis on solid support.



Scheme 27. First examples of enyne metathesis on solid supports.

By using allyldimethylsilyl-functionalized polystyrene resin **17** and soluble terminal alkynes, the same research group then provided another efficient route to different substituted 1,3-dienes **114** through enyne metathesis followed by protodesilylation under mild acidic cleavage conditions (Scheme 28).[89]



Scheme 28. Examples of enyne cross-metathesis with soluble alkynes and an allyldimethylsilyl-functionalized polystyrene resin.

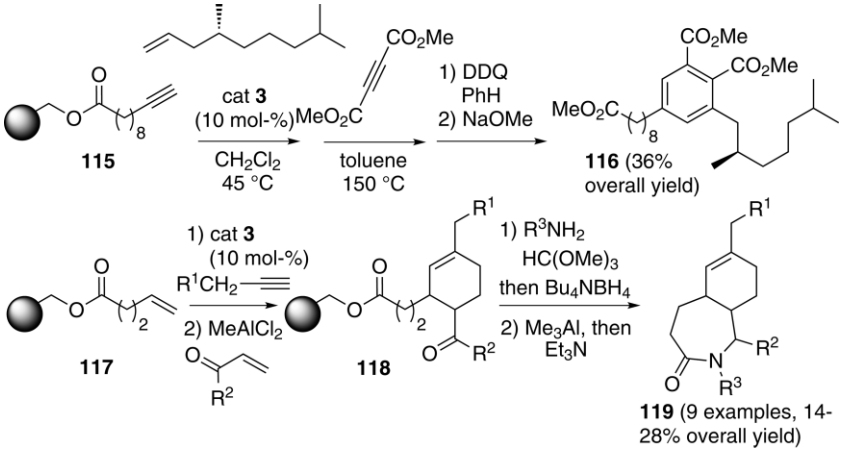
The fact that these diene products are versatile starting materials for subsequent cycloaddition processes stimulated the group to engage in diversity oriented synthesis (DOS) and combinatorial chemistry approaches.[90] Accordingly, different solid-supported alkynes and olefins underwent enyne CM with their soluble counterparts, and the resulting immobilized dienes were treated with activated olefins or alkynes to yield valuable cyclohexene or cyclohexadiene scaffolds. These products were shown to participate in further chemical manipulations such as oxidations and further cyclizations to furnish different types of molecular frameworks such as substituted benzene derivatives and even bicyclic scaffolds such as isochromanone and benzazepinone derivatives (Scheme 29).

2.5. Solid-Phase Cross-Metathesis in Tandem Reactions

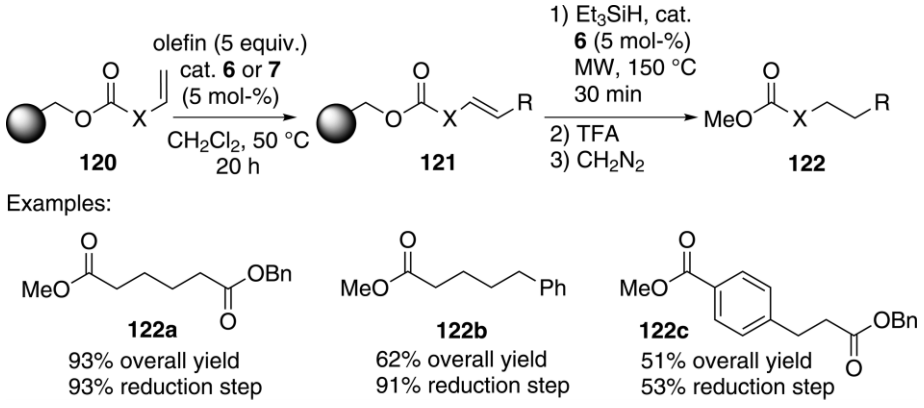
The stability of Ru catalysts toward a variety of functional groups, reagents, and reaction conditions makes them suitable for the development of tandem and domino alkene metathesis processes. Several investigations have led to a wide variety of examples in solution, whereas in the case of SP synthesis some pioneering work involves the tandem enyne metathesis reactions discussed above. In addition, the Grubbs carbene catalysts have been found to catalyze other non-metathetic reactions, and hence tandem catalysis processes can be imagined.[91–93]

It is well-known that olefin reduction – a classic chemical transformation – does not have a successful and reliable correlation in SP synthesis. In this context, we became particularly interested in devising an olefin CM/hydrogen-free olefin reduction sequence as a formal alkane metathesis process for the formation of sp^3–sp^3 carbon bonds. Ru carbene complex **6**, in the presence of triethylsilane, allowed such transformations to proceed and so unsaturated esters obtained by SPCM were efficiently reduced under microwave irradiation conditions in short reaction times (Scheme 30).[94]

We came back to this transformation during our studies on the first solid-supported synthesis of chalcones through CM.[95] On this occasion, a one-pot CM/reduction sequence was desirable in order to gain rapid access to biologically appealing β-phenylpropiophenones and derivatives. After some unsuccessful attempts using catalyst **6**, employment of complex **7** allowed the different supported olefins **120** and substituted

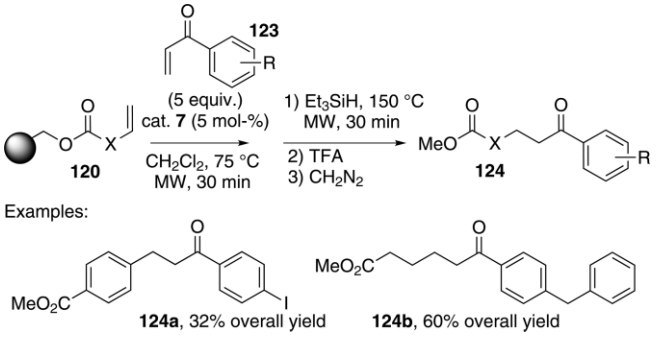


Scheme 29. SP enyne metathesis followed by chemical manipulations to give different types of molecular frameworks.



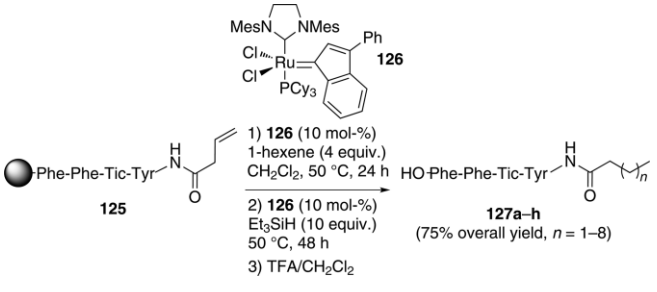
Scheme 30. Solid-supported sequential cross-metathesis/reduction.

1-phenylpropenones **123** to be coupled and reduced under microwave-assisted Ru catalysis conditions (Scheme 31). The ease with which unwanted homodimers and their reduced analogues can be disposed of makes this one-pot SP protocol attractive, particularly in the field of C_{sp3}–C_{sp3} bond-forming strategies.



Scheme 31. One-pot solid-phase formal alkane metathesis.

Driven by their interest in the development of improved opioid peptides, Jida and collaborators recently explored the same CM/reduction sequence to prepare more lipophilic alkyl-substituted analogues of prototype peptide H-Tyr-Tic-Phe-Phe-OH [TIPP; Tic = (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid].[96] Different immobilized tetrapeptide analogues carrying an allyl moiety (i.e., **125**) were subjected to CM with hex-1-ene followed by addition of a silane reducing agent (Scheme 32). Ru turned out also to catalyze olefin isomerization,[97] and, for example, peptide **125** underwent CM with hex-1-ene to give, after reduction, eight different lipopeptides (**127a**–**h**, n = 1 to 8), which were separated and purified by preparative HPLC. Although better conversions were achieved with third-generation complex **126** (Umicore M2),[98] precatalysts such as **7** also worked efficiently.



Scheme 32. One-pot tandem isomerizing self- or cross-metathesis/reduction for the synthesis of lipopeptides.

3. Conclusions and Future Perspectives

Even though SPCM has been much less widely explored than the ring-closing version of the process, the preceding pages demonstrate that its translation from solution phase has succeeded. There are many examples, from the SP synthesis of complex oligosaccharides and peptides to the preparation of biologically relevant small-molecule compounds, natural products included. Undoubtedly, there is still room for progress in the area and, in this regard, we expect that the evaluation of more efficient and powerful modern catalysts will lead to the development of faster protocols that will demand only minimal loadings. In this context, advances in the field of molybdenum catalyst development have allowed the birth of ring-closing alkyne metathesis (RCAM) on solid supports.[99,100] We believe that we shall see the SP cross-variant of the reaction in the near future.

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Keywords: Solid-phase synthesis · Cross-metathesis · Metathesis · Alkenes · Ruthenium · Catalysis

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