

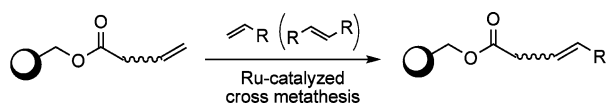
Solid-Supported Cross Metathesis and the Role of the Homodimerization of the Non-immobilized Olefin

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We have prepared immobilized olefins as models for the cross metathesis using different olefin partners in the presence of second generation Grubbs and Hoveyda–Grubbs precatalysts. We have demonstrated that solid-phase cross metathesis is strongly dependent on the degree of homodimerization of the non-immobilized olefin and the reactivity of such a homodimer. As in the homogeneous phase, the Hoveyda–Grubbs precatalyst was better for immobilized α,β -unsaturated carbonyl compounds.

The emergence of structurally well-defined catalysts has established the olefin metathesis as an outstanding tool for modern organic and polymer synthesis.¹ Particularly, cross metathesis (CM) represents an interesting alternative to more traditional carbon–carbon bond forming reactions. In addition to the mild reaction conditions, functional group tolerance, high activity, and stability of modern olefin metathesis precatalysts, CM requires little synthetic labor in the preparation of starting material. Alkenes are readily available materials compared to vinyl stannanes, vinyl halides, and boronates, which are usually required in more classical transition metal cross-coupling reactions (e.g. Stille, Heck, and Suzuki). Furthermore, CM is especially useful in stepwise syntheses since it allows the use of functionalized olefin substrates and since functional groups can take part in subsequent reactions avoiding the employment of protecting groups.

However, application of alkene cross metathesis in synthetic chemistry is far behind its ring-closing counterpart, mainly due to the difficulty of avoiding the formation of unwanted homodimeric products.² In contrast, immobilization of one of the olefin substrates has a series of potential advantages: (i)

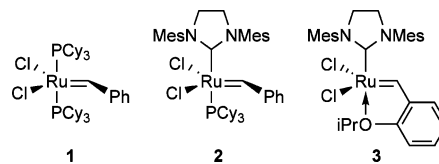


FIGURE 1. Grubbs and Hoveyda–Grubbs precatalysts.

(ii) The olefin that remains in solution can be added in excess in order to drive the reaction to completion (its homodimer can be eliminated easily by simple filtration, avoiding time-consuming separation techniques). (iii) Automation can be easily accomplished.

Despite its enormous potential, few examples of alkene cross metathesis on solid phase can be found in the literature.^{3,4} The increase in activity from the first generation Grubbs precatalyst (1) (Figure 1) to those of the second generation (2 and 3) further improves the importance of an efficient application of alkene cross metathesis to a solid support.⁵

Herein, we wish to report a study on the solid-supported olefin cross metathesis by different ruthenium carbene complexes in order to contribute to the understanding of the reaction under the particular environment of the solid-phase chemistry.

We prepared three Wang resin-immobilized olefins (**4a–c**) that were employed as models for the cross metathesis using different olefin partners (**5**) (Scheme 1). These non-immobilized olefin partners were chosen by taking into account the olefin classification recently reported by Grubbs et al. that established a rule for olefin cross metathesis selectivity.² Type-I olefins are those that undergo fast homodimerization; type-II go through a slow homodimerization; type-III do not undergo homodimerization, and type-IV are spectators to CM. Which olefin belongs to which category depends on the catalyst used. In the case of having one of the olefins immobilized, such as in solid-phase metathesis, this classification could be useful to understand the behavior of the olefin partner.

Under our optimized conditions, the resin (**4a–c**) was heated to reflux in DCM for 20 h with excess olefin (**5**) and the corresponding ruthenium carbene complex. The amount of the precatalyst was kept to a minimum (5 mol %) in order to reduce the formation of ruthenium metal byproducts to get both a less ruthenium-contaminated resin and a less contaminated product. The resin was resubjected to the same reaction conditions to ensure the formation of the coupled product (**7**, **10**, **12**) which was then released from the resin with 10% TFA/DCM.

(2) A great improvement in olefin cross metathesis selectivity has been achieved through the recent advances in catalyst design and the development of empirical models for predicting the outcome of cross metathesis reactions. See: Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

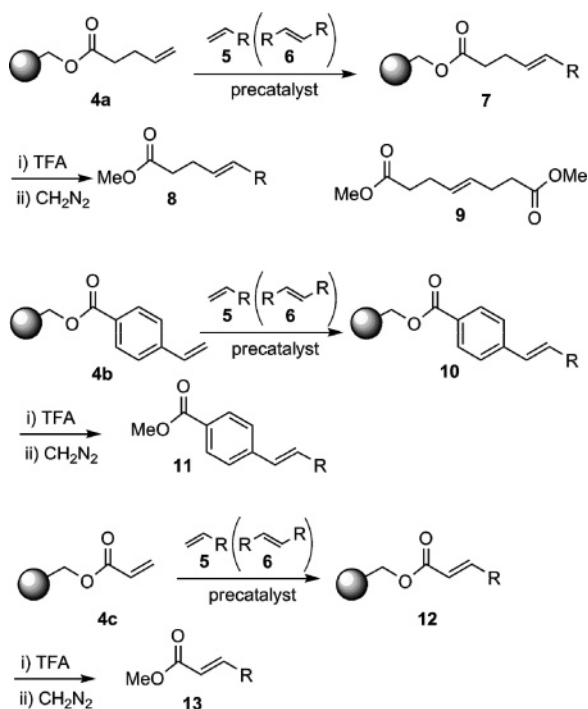
(3) For previous reports on cross metathesis of polymer-supported olefins under first generation Grubbs catalyst, see: (a) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979. (b) Breed, P. G.; Ramsden, J. A.; Brown, J. M. *Can. J. Chem.* **2001**, *79*, 1049.

(4) For previous reports on cross metathesis of polymer-supported olefins under second generation Grubbs catalyst, see: (a) Chang, S.; Na, Y.; Shin, H. J.; Choi, E.; Jeong, L. S. *Tetrahedron Lett.* **2002**, *43*, 7445. (b) Testero, S. A.; Mata, E. G. *Org. Lett.* **2006**, *8*, 4783. (c) Garner, A. L.; Koide, K. *Org. Lett.* **2007**, *9*, 5235.

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SCHEME 1. Solid-Phase Olefin Cross Metathesis



Esterification with diazomethane followed by flash chromatography afforded desired products (**8**, **11**, **13**) (Scheme 1). Initial attempts with immobilized pentenoic acid (**4a**) gave disappointing results. Reaction of type-I olefins, such as allyl benzene (**5a**) or 4-vinylbenzyl chloride (**5c**) in the presence of second generation Grubbs precatalyst (**2**),⁶ afforded after cleavage from the resin and subsequent esterification a mixture of desired product (**8a** or **8c**), with 4-octenedioic acid dimethyl ester (**9**).

We envisioned that a more rigid system such as resin **4b** could avoid those site–site interactions. Thus, when a similar synthetic sequence was applied to the coupling between resin **4b** and allyl benzene (**5a**), the expected product, methyl 4-(3-phenylprop-1-en-1-yl)benzoate (**11a**), was obtained in excellent isolated yield (86%) with no trace of the corresponding intra-site byproduct (Table 1, entry 1). On the other hand and considering that the non-immobilized olefin **5a** was added in excess, formation of the homodimer in the reaction media can influence the reaction output. Under the optimized conditions, CM of olefin **5a** in the absence of the solid-supported olefin **4b** gave the corresponding homodimer (*E*)-1,6-diphenylhex-3-ene (**6a**) in very high yield in just 15 min. As expected, when the homodimer **6a** was submitted to the CM with resin **4a**, product **11a** was isolated in a yield similar to that obtained when using olefin **5a** (compare entries 1 and 7). It was clear that the homodimer **6a** was the reactive olefin in both cases.

Surprisingly, 4-methyl styrene (**5b**), which can be considered as a type-I olefin according to Grubbs classification, gave only 31% yield of the CM product (**11b**) under similar reaction conditions (entry 2). Explanation can be found in the formation of the corresponding homodimer (**6b**). While **6b** was obtained in homogeneous phase in 2 h, it was unreactive to resin **4b** under our solid-phase conditions (entry 8). Even though 4-methyl styrene (**5b**) is very reactive, reaction was low yielding

due to the rapid formation of the essentially inactive dimer **6b**. Very efficient CM was achieved using 4-vinylbenzyl chloride (**5c**) (80%) (entry 3). In this case, it can be concluded that the active monomer contributes largely to the formation of the CM product (**11c**), given that homodimerization is slow (20 h) and the homodimer gave lower reaction yield (58%) (entry 9). In the middle range was 4-phenyl-1-butene (**5d**) in which both monomer **5d** and homodimer **6d** gave CM product in moderate yields (entries 4 and 10).

On the other hand, when a prototypical “type-II” olefin was used [e.g., crotonic acid (**5e**)], the coupling product (**11e**) was obtained in a quantitative manner (entry 5). Although crotonic acid is an electron-deficient olefin, reaction was favored by the forced conditions (reflux, large excess of olefin), while homodimerization was negligible. Resin-supported cross metathesis is then an alternative to Horner–Wadsworth–Emmons for the solid-phase synthesis of cinnamic acid derivatives.⁷ In the case of using 2-bromostyrene (**5f**), another type-II olefin, CM product **11f** was obtained in lower (although still acceptable) yield (43%) (entry 6). The extra steric hindrance of the bromine atom can be the reason for the lower yield by affecting the approach to the polymer matrix.

Different acrylate derivatives were obtained by cross metathesis when commercially available acryloyl Wang resin (**4c**) was used as immobilized starting material (Scheme 1 and Table 1). While the role of the non-immobilized homodimers was essentially the same as that of the resin **4b**, reaction of resin **4c** with type-I and type-II olefins was not very successful in the presence of second-generation Grubbs precatalyst **2**. Yields of the CM products **13** ranged from 11 to 35% (entries 11–14). However, the use of the newly developed Hoveyda–Grubbs precatalyst **3** (Figure 1)⁸ substantially increases the yields of the CM products. In the case of type-I non-immobilized olefins, such as allyl benzene (**5a**), 4-vinylbenzyl chloride (**5c**), and 4-phenyl-1-butene (**5d**) yields were increased 2-fold or more (entries 11–13). Precatalyst **3** has been reported as the best catalyst for α,β -unsaturated carbonyl compounds,⁹ and when that olefin is also an immobilized one, the advantage of this precatalyst seems to be even more clear.

In summary, we report a study in order to establish guidelines for the solid-supported olefin cross metathesis by ruthenium carbene complexes. Thus, it can be concluded that homodimerization of the non-immobilized olefin plays a key role in solid-phase CM. Very high yields were obtained when a type-I, easily homodimerizable olefin, was used, as long as that homodimer was also very reactive. Type-II olefins usually gave high yields since homodimerization was slow. Type-I olefins, which undergo fast homodimerization to generate an unreactive dimer, generally afforded low CM yields. As in the homogeneous phase, the Hoveyda–Grubbs precatalyst (**3**) has distinctive properties for CM involving α,β -unsaturated carbonyl compounds. We hope that this study could lead to a more general

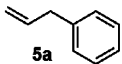
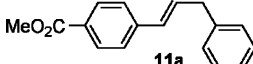
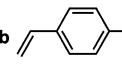
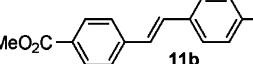
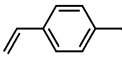
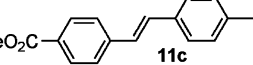
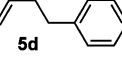
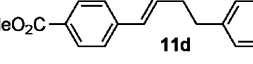
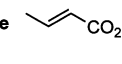
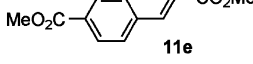
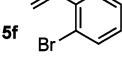
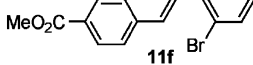
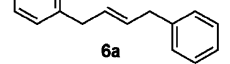
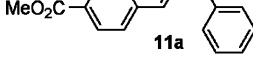
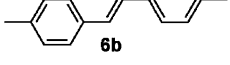
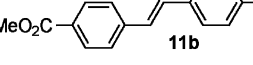
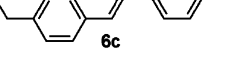
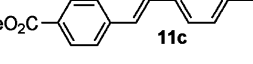
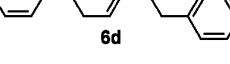
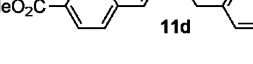
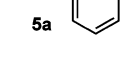
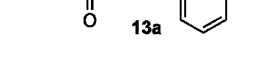
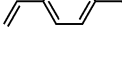
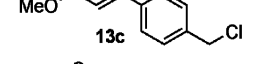
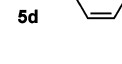
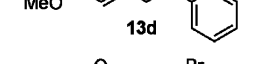
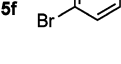
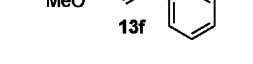
(7) Reaction of Wang resin-bound 4-formyl benzoate with triethylphosphonoacetate gave, after releasing from the resin and esterification, the cinnamic acid derivative **11e** in almost quantitative yield.

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TABLE 1. Solid-Phase Olefin Cross Metathesis by Ruthenium Carbene Complexes

Entry	Resin	Non-immobilized olefin	Homo-dimerization	Product	Precatalyst 2 (%) ^a	Precatalyst 3 (%) ^a
1	4b		Yes, in 15 min		86	
2	4b		Yes, in 2 h		31	32
3	4b		Yes, in 20 h		80	
4	4b		Yes, in 5 h		57	
5	4b		No		97	
6	4b		No		43	43
7	4b		—		72	
8	4b		—		NR ^b	
9	4b		—		58	
10	4b		—		39	
11	4c		Yes, in 15 min		35	59
12	4c		Yes, in 20 h		11	23
13	4c		Yes, in 5 h		26	68
14	4c		No		10	16

^a Overall isolated yield after flash column chromatography. ^b No reaction, starting material recovered.

application of solid-supported olefin cross metathesis to the generation of libraries of complex organic structures.

Experimental Section

General Procedure for the Solid-Phase Immobilization of Olefins. As a representative procedure, vinylbenzoic acid (551.0 mg, 3.7 mmol, 5.0 equiv) was dissolved in anhydrous DMF (10

mL) and diisopropylcarbodiimide (575 μ L, 3.7 mmol, 5.0 equiv) was added. The mixture was stirred for 30 min at room temperature and transferred via cannula to Wang resin (677.2 mg, 1.1 mmol/g, 0.74 mmol), which was previously washed with anhydrous DMF (5.0 mL). Dimethylaminopyridine (91.0 mg, 0.7 mmol, 1.0 equiv) was added, and the reaction was magnetically stirred for 16 h. The resin was washed with DMF (3 \times 10 mL), MeOH (3 \times 10 mL), and DCM (3 \times 10 mL) and dried under high vacuum. To determine

the vinylbenzoic acid loading, resin **4b** (151.3 mg, 0.96 mmol/g, 0.14 mmol) was treated with 10% TFA in DCM and the acid was in turn esterified with diazomethane to obtain methyl vinylbenzoate (20.1 mg, 0.12 mmol, 0.78 mmol/g) in 85% yield.

General Procedure for the Solid-Phase Cross Metathesis by Ruthenium Carbene Complexes. As a representative procedure, resin-bound olefin **4b** (192.3 mg, 0.15 mmol) was suspended in anhydrous DCM (10 mL) and the non-immobilized olefin **5a** (100 μ L, 0.75 mmol, 5.0 equiv) was added via syringe under a nitrogen atmosphere. Grubbs second generation catalyst **2** (6.4 mg, 7.5 μ mol, 5 mol %) was added, and the flask was fitted with a condenser and refluxed for 20 h, after which the resin was filtered, washed with DCM (3 \times 4 mL), MeOH (3 \times 4 mL), and DCM (1 \times 4 mL), and dried under high vacuum. The resin was resubjected to the same reaction conditions. Resin-bound olefin **10a** (205.4 mg, 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. The solvent was evaporated under reduced pressure, and the crude material was purified by flash column chromatography (hexane–AcOEt) to provide **11a** (32.5 mg, 0.13 mmol) in 86% yield: IR ν_{\max} (cm⁻¹) 3027, 2950, 1720 (CO), 1605, 1279; ¹H NMR (CDCl₃, 300 MHz) δ 7.95 (d, *J* = 6.1 Hz, 2H, ArH), 7.40–7.22 (m, 7H, ArH), 6.6–6.4 (m, 2H, H5–6), 3.90 (s, 3H, CH₃O), 3.57 (d, *J* = 4.9 Hz, 2H, H7); ¹³C NMR (CDCl₃, 75 MHz) δ 166.8, 141.9, 139.5, 132.1, 130.1, 129.8, 128.6, 128.5, 126.2, 126.0, 125.9, 51.9, 39.3; HRMS *m/z* 253.1232 [(M + H)⁺; calcd for C₁₇H₁₇O₂ 253.1229].

General Procedure for the Obtention of the Homodimeric Olefins (6a–d). As a representative procedure, the monomeric olefin **5b** (700.3 mg, 5.9 mmol) was dissolved in anhydrous DCM (10.0 mL) and precatalyst **2** (25.0 mg, 0.5 mol %) was added. The reaction was refluxed to starting material consumption monitored by TLC (see the reaction times in Table 1). Solvent was evaporated under reduced pressure to give a crude product, which was purified flash column chromatography (hexane–DCM) to provide **6b** (615.6 mg, 2.96 mmol) in 100% yield: IR ν_{\max} (cm⁻¹) 3019, 2912, 972, 822; ¹H NMR (CDCl₃, 300 MHz) δ 7.40 (d, *J* = 8.1 Hz, 4H), 7.15 (d, *J* = 8.1 Hz, 4H), 7.03 (s, 2H, vinylic), 2.35 (s, 6H, CH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 137.1, 134.6, 129.2, 127.5, 126.2, 21.1; HRMS *m/z* 209.1333 [(M + H)⁺; calcd for C₁₆H₁₇ 209.1330].

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Supporting Information Available: Spectroscopic data, ¹H NMR and ¹³C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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