The non-metathetic role of Grubbs' carbene complexes: from hydrogen-free reduction of α,β-unsaturated alkenes to solid-supported sequential cross-metathesis/reduction†

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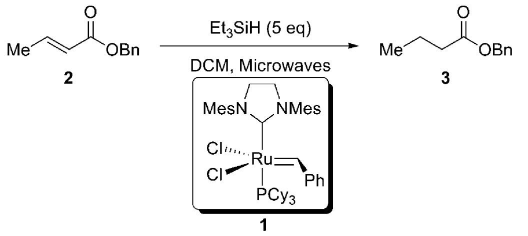
An efficient and high-yielding "hydrogen-free" reduction of α,β-unsaturated alkenes was carried out employing Grubbs' catalyst in a non-metathetic role and Et_3SiH. Conditions were optimized under microwave irradiation. Application to the solid-phase organic synthesis allows a facile construction of sp^3–sp^3 carbon bonds through a sequential cross metathesis/olefin reduction.

The development of stable, highly active ruthenium–carbene complex precatalysts has ensured mild reaction conditions for olefin metathesis, making this transformation one of the most successful C–C bond forming reactions in recent years.[1] Besides, new non-metathetic activities of these carbenes have started to be discovered, extending their synthetic usefulness beyond alkene generation.[2]

For many reasons, an ancient and traditional chemical transformation such as olefin reduction does not have yet a successful correlation in solid-phase organic synthesis (SPOS).[3] The major drawback is the impossibility to use heterogeneous catalysis with the commonly employed polystyrene resins due to the poor kinetic of solid–solid interaction and complications in the separation of catalyst and solid-supported compounds. On the other hand, polystyrene-immobilized olefin reduction employing homogeneous reagents has been scarcely reported[3–6] and none of those methods have reached yet a broad application. The most employed method has been the diimide reduction,[4,5] although some authors claim that results are hard to reproduce.[7,8]

In this communication we present our results that demonstrate that the olefin reduction by triethylsilane and Grubbs' second generation catalyst is especially useful for both solution-phase and solid-phase reduction of α,β-unsaturated carbonyl compounds.

Initially, we were not capable to obtain an efficient reduction of immobilized olefin employing Et_3SiH, adapting a procedure reported for homogeneous-phase chemistry.[9] We found two main problems: poor conversions and, above all, C=C double bond hydrosilylation which led to triethylsilane-derived by-products. Thus, attempts towards optimization were performed with several kinds of non-immobilized olefins and a variety of reaction conditions. Microwave irradiation turned out to be the best heating conditions and olefins from α,β-unsaturated esters were the best potential substrates. Reduction of benzyl crotonate (**2**) to obtain benzyl butyrate (**3**) was taken as a model reaction (Scheme 1). When **2** was treated with Et_3SiH (5 equiv.) in the presence of Grubbs' second generation catalyst (**1**) (5 mol%) in refluxing DCM, unreacted starting material was recovered after 20 h (Table 1, entry 1).[10] To our delight, when **2** was treated with the same reagents but for 1 h at 100 °C under microwave irradiation, the desired product **3** was obtained with a conversion of 66% (entry 2). Increasing temperature to 150 °C afforded **3** in 95% yield as the only detectable product (entry 3). Similar yield was obtained at the same temperature but in half time (entry 4). We have then demonstrated that this reduction is highly chemoselective since the benzyl ester moiety was not affected, something which is hard to get under classical hydrogenation methods.[11] Finally, the importance of the Grubbs' catalyst was pointed out by performing a negative control which gave no reaction (entry 5).



Scheme 1 Reduction of α,β-unsaturated esters employing benzyl crotonate (**2**) as the model substrate and Et_3SiH/Grubbs' catalyst as reagents.

Table 1 Optimization of microwave-assisted conditions for the reduction of α,β-unsaturated esters employing Et_3SiH/Grubbs' catalyst (**1**)[a]

Entry	Microwave	Time	**1** (mol%)	°C	Product	(%)[b]
1	No[c]	20 h	5	40	**2**	100
2	Yes	1 h	5	100	**2/3** (1 : 1.9)	66[d]
3	Yes	1 h	5	150	**3**	95
4	Yes	30 min	5	150	**3**[e]	96
5	Yes	1 h	0	150	**2**	100

[a] See Scheme 1. [b] Isolated yield after column chromatography. [c] DCM reflux under conventional heating. [d] 100% of mass was recovered, yield was calculated based on the compounds ratio determined by ^1H NMR. [e] Traces of starting material were recovered.

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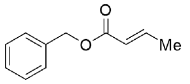
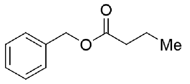
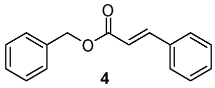
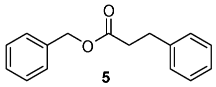
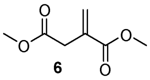
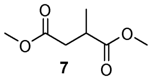
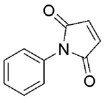
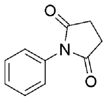
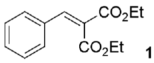
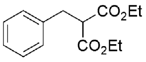
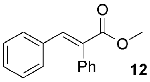
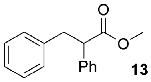
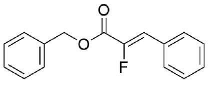
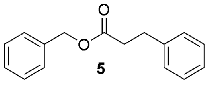
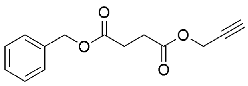
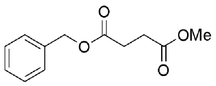
Once the optimal conditions were established, we applied them to a set of α,β-unsaturated esters (Table 2). The reaction outcome seemed to be affected by the substituent volume: while benzyl crotonate (**2**) was reduced in 96% yield (entry 1), benzyl cinnamate (**4**) was reduced to obtain **5** in 73% yield (entry 2). Geminally disubstituted olefin such as dimethyl itaconate (**6**) led to the corresponding product (**7**) in a very good yield (84%) (entry 3). *N*-Phenyl maleidimide (**8**) which is a *cis*-disubstituted olefin gave compound **9** in 75% yield (entry 4). Even trisubstituted olefins gave the corresponding reduction product in good yields (entries 5–7). Interestingly, fluorocinnamate (**14**) was also dehalogenated in the same reaction step to give benzyl 3-phenylpropanoate (**5**) (entry 7).[12] Finally, an unexpected result came out when we tried to reduce the triple bond of the benzyl 2-propynyl succinate **15** (entry 8): a clean and selective deprotection of the propargyl ester group. After re-esterification with diazomethane, benzyl methyl succinate (**16**) was obtained in 91% yield.

Table 2 Non-immobilized olefin reduction under optimized conditions employing Et_3SiH/Grubbs' catalyst[a]

Entry	Starting material	Product	(%)[b]
1	 **2**	 **3**	96
2	 **4**	 **5**	73
3	 **6**	 **7**	84
4	 **8**	 **9**	75
5	 **10**	 **11**	82
6	 **12**	 **13**	64
7	 **14**	 **5**	61
8	 **15**	 **16**	91[c]

[a] *Reagents and conditions*: catalyst **1** (5 mol%), Et_3SiH (5 equiv.), DCM, microwave irradiation, 150 °C (300 W), 30 min. [b] Isolated yield after column flash chromatography. [c] Reaction product was esterified by treatment with diazomethane.

Although several mechanisms have been suggested for non-metathetic reactions of ruthenium–carbene complexes,[2c] participation of ruthenium hydride species seems to be the key to understand not only the olefin reduction but also the collateral reactions: dehydrosilylation, defluorination and deprotection of the propargyl ester. Under the conditions used (MW, 150 °C, 30 min.) formation of the ruthenium hydride species can be expected during decomposition of Grubb's catalyst.[13]

At this point, we were able to achieve an efficient microwave-assisted reduction of α,β-unsaturated esters using Et_3SiH/Grubbs' catalyst combination, so we turned our attention to the reduction of solid-supported olefins. Since immobilized α,β-unsaturated esters can be obtained by olefin cross metathesis,[14–16] we decided to perform these reactions back to back. Although it is possible to carry out a one-pot reaction, we preferred a sequential process in order to remove the olefin excess. Thus, an outstanding result was obtained when immobilized pentenoic acid **17** was subjected to cross metathesis with benzyl crotonate (**2**), followed by the reduction to the saturated ester **18** (Table 3, entry 1). Release from the solid support afforded the corresponding methyl ester **19** in very high yield for both, the reduction step and the whole synthetic sequence (93%). A similar result was obtained for the sequential process with immobilized acrylate **20**, which was reacted under cross metathesis conditions with 4-phenylbut-1-ene (**21**) and then reduced to obtain solid-supported phenylvalerate **22** in 91% yield for the reduction step (entry 2). Cross metathesis of immobilized vinyl benzoate **24** with benzyl crotonate (**2**) followed by reduction gave the saturated ester **25** in 53% yield (entry 3). Besides, we found that solid-supported α,β-unsaturated amide also underwent reduction under Et_3SiH/Grubbs' catalyst combination giving the corresponding butyryl amide **28** in 85% yield (entry 4).

In summary, we have developed microwave-assisted conditions for the "hydrogen-free" reduction of α,β-unsaturated esters and amides employing a non-metathetic behavior of Grubbs' catalyst. In the homogeneous phase, the saturated products were obtained in high to excellent yields. It is interesting to note that benzyl ester moiety is stable to the reaction conditions; whereas the propargylic ester group present in **15** was cleaved using the same procedure. This methodology allows a rapid reduction of the alkene moiety without contamination from hard-to-remove hydrosilylation by-products.[9] Extrapolation to the solid-phase organic synthesis was also very effective. A remarkable hint was the consummation of the sequential cross metathesis/olefin reduction, which allows a facile construction of sp^3–sp^3 carbon bonds. Further applications of this methodology are in progress in our laboratory and will be reported in due course.

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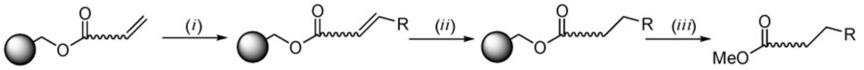
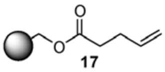
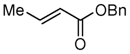
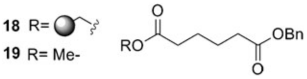
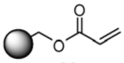
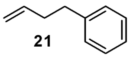
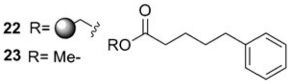
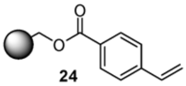
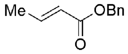
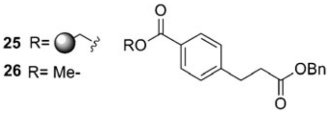
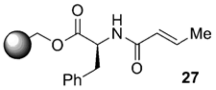
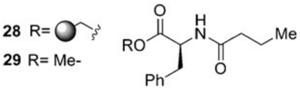
Table 3 Solid-supported sequential cross-metathesis/reduction[a]



Entry	Starting material	Non-immobilized olefin	Product	(%)[b,c]
1	 **17**		 **18** R= **19** R= Me-	93(93)
2	 **20**	 **21**	 **22** R= **23** R= Me-	62(91)[d]
3	 **24**		 **25** R= **26** R= Me-	51(53)
4	 **27**	—	 **28** R= **29** R= Me-	85[e]

[a] *Reagents and conditions*: (i) non-immobilized olefin (5 equiv.), catalyst **1** (5 mol%), DCM, 50 °C, 20 h. (ii) catalyst **1** (5 mol%), Et_3SiH (5 equiv.), DCM, microwave irradiation, 150 °C (300 W), 30 min. (iii) TFA 10%, DCM, 1 h, then 0 °C, diazomethane, DCM, 30 min. [b] Overall isolated yield after flash column chromatography. [c] Data in brackets are reduction step yields, based on the ratio between the final product yield and the yield of the intermediate alkyne after being released from the resin. [d] Hoveyda–Grubb's precatalyst[16] was used for the metathesis step. [e] Only reduction step was involved.

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