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Ring-closing metathesis in glycerol under microwave activation

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Glycerol, a biodegradable and virtually non-toxic bio-sourced chemical can be used as an alternative, reusable, sustainable solvent, with so far limited application in the field of green organic chemistry. Herein, the reaction conditions have been screened for the ring-closing metathesis (RCM) of *N*,*N*-diallyltosylamine and diethyl diallylmalonate in glycerol, under microwave irradiation and in the presence of the most common commercially available RCM catalysts. The products were isolated in high yield after extraction and the catalyst could be recycled up to two times. Results with simultaneous cooling of the reaction vessel under microwave irradiation are also reported.

Very recently glycerol (1,2,3-propanetriol or glycerin) appeared as an alternative feed-stock source[1–5] for green and sustainable organic chemistry. Glycerol is easily available as a byproduct in bio-diesel fuel production, obtained from the saponification of triglycerides of all natural fats and oils,[6] becoming a cheap (760 USD/ton in 2006),[4] large volume market product (1.5 Mt/year in 2008).[7] Being virtually non-toxic[8,9] (LD 50 oral rat = 12.600 mg/kg; except in very high concentrations where a dehydrating effect is noted) and biodegradable,[10] it is the intermediate of large valued fine chemicals, as well as the solvent of choice for many industrial and pharmaceutical preparations (foods, cosmetics, liquid detergents, and antifreeze).

Despite its high potential application as an environmentally friendly solvent in organic synthesis, very few examples are reported on its use, and data are not exhaustive in some cases.[11] Known examples relate to its use in the synthesis of alkenyl chalcogenides,[12] Heck and Suzuki couplings,[13] Michael[14] and aza-Michael[15] additions, enzymatic asymmetric hydrogenation of pro-chiral β-keto esters and ketones,[16] micellar systems[7] or the synthesis of glycerol-based dendrimers[17] or branched polymers[18–20] via metathesis reactions,[17,21–26] using conventional heating. Because of its hydroxyl groups, glycerol has solubility characteristics similar to those of water or simple aliphatic alcohols, and it can be considered as 'organic water', as recently suggested by Jérôme and co-workers.[15] It is completely miscible and compatible with most inorganic compounds (carbonates or sulfate, metal salts, acids, bases, and transition metal complexes), organic and low molecular weight alcohols (MeOH, EtOH, Pr-OH and *i*-Pr-OH, BuOH, *sec*-BuOH, short chain glycols and phenol), halogens (iodine or bromine), heterocyclic compounds containing a nitrogen atom in the ring (e.g., pyridine, quinoline, piperidine and α-picoline), acetone, ethyl acetate or boronic acids (more soluble in glycerol than in water). It is sparingly soluble in dioxane or diethyl ether and it is practically insoluble in higher alcohols, hydrocarbons (cyclohexane, petroleum ether) or chlorinated solvents. Its intrinsic characteristics such as high-boiling point (T = 290 °C), low vapor pressure (0.0025 mm at 50 °C), high dielectric constant (ε = 42.48 at 25 °C), and a polarity similar to other organic solvents such as DMSO or DMF allow its use as a suitable solvent for microwave irradiation,[27] where the heating characteristics of the solvent play a crucial role. Despite all these considerations, and to overcome problems related to its molecular structure (high viscosity due to the high hydrogen bonding density) provoking poor substrate diffusion in the medium, it was very surprising to notice that only very few examples in which microwave heating is used when glycerol is the reaction solvent are reported in the literature.[11,14,26,28]

For this reason, and with the aim of studying alternative solvents for green and sustainable chemistry,[29,30] we decided to study the ring-closing metathesis (RCM) reaction[17,21–26] of *N*,*N*-diallyltosylamine **4** investigating the efficacy of the most common commercial RCM catalysts (Fig. 1) in glycerol under microwave activation.

In a typical experiment, a mixture of substrate **4** (0.171 mmol, 0.342 mM) and the catalyst (5 mol %) in glycerol (0.5 mL) was heated under microwave irradiation (initial power 400 W) at 40 °C for 1 h, in a sealed reactor. After cooling, water (0.1 mL) was directly added to the crude mixture together with diethyl

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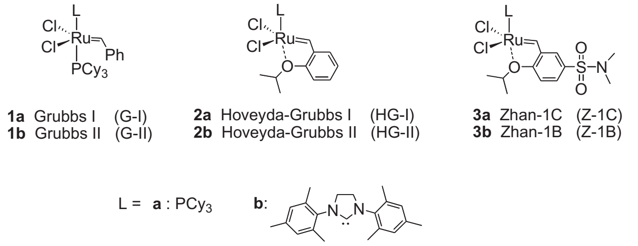


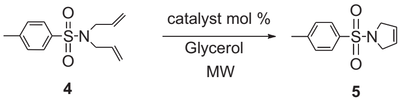
Figure 1. Most common commercially available RCM catalysts.

ether (1.0 mL). The RCM product **5** was not soluble in glycerol and it could be directly extracted through an easy and complete decantation with diethyl ether. Several reaction conditions were studied: reaction time, temperature, substrate concentration and catalyst amount. The most significant results are reported in Table 1.

MW results can be analyzed on the basis of different factors: (i) relative solubility of substrate and catalyst in glycerol phase; (ii) viscosity of the medium and diffusion properties of the compounds; (iii) microwave absorption of the medium, which is also a function of the hydration layer thickness surrounding the glycerol and/or molecules,[31] glycerol being able to absorb moisture from the atmosphere.

We could demonstrate that independent of its nature, 5 mol % of catalyst was necessary to obtain good yields of product **5**. Any attempt to increase the yield by raising the temperature, modulating catalyst loading, or extending the reaction time was unsuccessful. They resulted in a low conversion of substrate **4** or in the formation of unidentified byproducts. We also tried to maintain higher the level of microwave energy during the irradiation of the reaction mixture by simultaneous cooling of the vial with a stream of compressed air[32] (Table 1, entries 4, 6, 8, 11, 13 and 15) without observing any satisfactory improvement, except in the case of Hoveyda–Grubbs I catalyst **2a** (entry 8). Zhan-1B **3b** catalyst[33] (Table 1, entries 16 and 21), rarely used[34,35] in RCM reactions, and never used under microwave activation, afforded a quantitative yield of product **5**, in shorter reaction times, which maybe due to its better solubility in the reaction medium. Comparative experiments for catalyst Zhan-1B **3b** were also run in dichloromethane (Table 1, entries 20 and 22), commonly used for RCM reactions, obtaining a quantitative yield of the cyclized product **5**. One of the advantages of glycerol as the solvent is related to the possibility to extend RCM reactions to substrates like the *N*,*N*-diallylamine hydrochloride, displaying a good solubility in glycerol but not in dichloromethane.

Table 1
Screening the conditions for RCM of *N*,*N*-diallyltosylamine **4**[a]



Entry	Catalyst	Amount (%)	*T* (°C)	*t* (h)	Yield[b] (%)
1	**1a**	10	40	0.5	83
2	**1a**	5	40	1	80
3	**1a**	2.5	40	1	53
4	**1a**	5	40 cooling[c]	1	68
5	**1b**	5	40	1	98
6	**1b**	5	40 cooling[c]	1	78
7	**2a**	5	40	1	60
8	**2a**	5	40 cooling[c]	1	85
9	**2b**	5	40	1	68
10	**2b**	2.5	40	1	46
11	**2b**	5	40 cooling[c]	1	73
12	**2b**	1	40	2	75
13	**2b**	1	40 cooling[c]	1	80
14	**3a**	5	40	0.5	69
15	**3a**	5	40 cooling[c]	0.5	72
16	**3b**	5	40	0.5	100
17	Cycle 2	—	40	0.5	99
18	Cycle 3	—	40	0.5	97
19	Cycle 4	—	40	0.5	19
20	**3b**	5	40	0.5	100[d]
21	**3b**	5	40	0.25	100
22	**3b**	5	40	0.25	99[d]

[a] Substrate concentration was 0.342 mM.
[b] Yields were calculated by ^1H NMR using CH_2Br_2 as the internal standard.
[c] Experiments were run with simultaneous cooling.
[d] Experiment was run in CH_2Cl_2 (0.241 mL).

Recyclability of the glycerol-catalyst system was also investigated. As shown in Table 1 (entries 17–19), catalyst Zhan-1B **3b** could be recycled up to two times without any significant loss of activity. In a typical recycling experiment, the glycerol phase issued from the first run was lyophilized to remove excess water and traces of diethyl ether, charged again with substrate **4**, without any additional catalyst, and the mixture was irradiated under the reaction conditions used for the first run. After each run, the yields were comparable, very high and similar to that of a fresh glycerol-catalyst mixture. After the third cycle the yield dropped drastically (Table 1, entry 19) and RCM product **5** was obtained in only 19% yield. Unfortunately, ^1H NMR analysis did not allow to determine the residual catalyst amount still present in the glycerol phase after each run and no data are reported on the Zhan-1B stability and solubility in glycerol. For these reasons we decided to quantify the catalyst amount transferred into the ether phase after decantation. The results are reported in Table 2.

The diethyl ether organic layer was analyzed by ^1H NMR, in the presence of CH_2Br_2 as the internal standard. After the work up on the crude issued from the first run (Table 2, entry 1), 18% (1.579 μmol) of catalyst **3b** with respect to the initial quantity used (8.566 μmol) was transferred into the ether phase, and a very high yield of RCM product **5** was obtained. In the fourth run (Table 2, entry 4), the ether phase contained only 0.7% of the initial quantity of the catalyst **3b**, most of the starting material remained unreacted, and product **5** was obtained in a very poor yield. After three runs, the quantity of catalyst **3b** transferred into the ether phase was quantified to be about 25% (Table 2, entries 1–3) with respect to the initial quantity. The estimated 75% of **3b** remaining in the glycerol phase should have been enough to obtain a high yield of product **5** also in the fourth run. On the contrary, the very low yield obtained in the third cycle (Table 1, entry 19) could be explained only if degradation of the catalyst was envisaged.

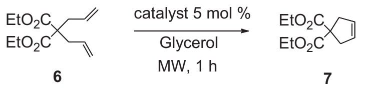
The catalytic activity of RCM ruthenium catalysts (Fig. 1) was also studied in the case of diethyl diallylmalonate **6** to afford product **7**, and selected results are reported in Table 3.

Table 2
^1H NMR[a,b] study of Zhan-1B catalyst (**3b**) amount transferred in the ether phase after work-up

Entry	Run	Catalyst residual amount[c] (μmol)	Extracted catalyst[c,d] (%)	Yield[e] (%)
1	1	1.579[e]	18.0	100
2	2	0.437	5.0	99
3	3	0.304	3.5	97
4	4	0.062	0.7	19

[a] $CDCl_3$ was used as a solvent.
[b] CH_2Br_2 (2 μL) was used as the internal standard for measuring the quantity of catalyst present in the diethyl ether phase after each extraction.
[c] Catalyst residual quantity in the ether phase after each extraction.
[d] Catalyst quantity at the beginning of the reaction (8.566 μmol, 5 mol %).
[e] Yields were calculated by ^1H NMR using CH_2Br_2 as the internal standard.

Table 3
Screening conditions for RCM of diethyl diallylmalonate **6**



Entry	Catalyst		*T* (°C)	Yield[a,b] (%)
1	**1a**	G-I	40	49[c]
2	**1a**	G-I	40 cooling	63[c]
3	**1b**	G-II	40	31
4	**2a**	HG-I	40	57
5	**2b**	HG-II	40	43
6	**3a**	Z-1C	40	54
7	**3b**	Z-1B	40	51

[a] Yields were calculated by ^{1}H NMR using CH_2Br_2 as the internal standard.
[b] Substrate concentration was 0.290 mM.
[c] Substrate concentration was 0.342 mM.

In all cases the conversion of the starting material was quantitative, but the yields were always compromised by the formation of unidentified byproducts probably by the transesterification reaction of glycerol with substrate **6**. With the Grubbs I catalyst **1a**, the simultaneous cooling during the microwave irradiation (entry 2) allowed to slightly improve the yield, without avoiding byproducts formation.

In conclusion, due to its physical and chemical properties, glycerol can be employed as an alternative, reusable, environmentally friendly solvent for RCM under microwave irradiation, in the presence of RCM catalysts. The products could be isolated in high yield after extraction and the catalyst could be used in three consecutive cycles. We are currently extending this reaction to other RCM substrates. We are also studying other organic transformations in this alternative solvent. The results will be presented in due course.

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