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Note

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DESIGN OF A SELECTIVE RCEYM-REDUCTION FOR THE GENERATION OF DIFFERENT SYNTHETIC SCAFFOLDS

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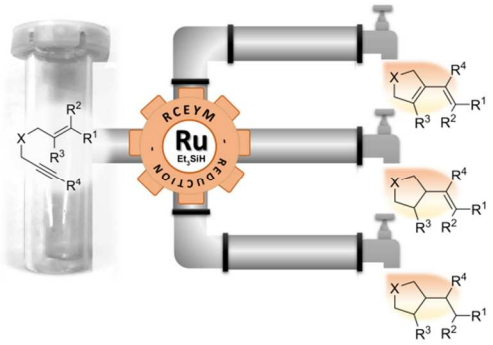
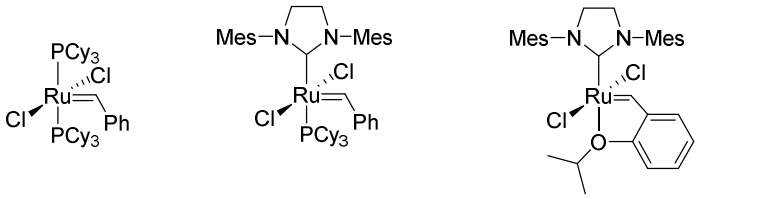
ABSTRACT: A tandem process of RCEYM-reduction using modern ruthenium catalysts and a hydrogen donor is described. This straightforward methodology is useful for C(sp^3) generation under mild reaction conditions. Variables such as solvent, catalyst, hydride source and temperature were adjusted towards the exclusive formation of different products.



Nowadays, the availability of selective and environmentally friendly synthetic methods is essential for fine chemicals and pharmaceutical processes.[1] Although, for methodological simplicity, the tendency to generate molecules with a high percentage of planarity is very elevated, it is clearly counterintuitive since biological world have a 3D-geometry. The incorporation of a greater degree of saturation in organic molecules has been recently proposed for improving clinical outcomes.[2] Double bond formation and reduction reactions are widely used in organic synthesis, being the latter very suitable for the generation of sp^3 carbon atoms.

In general, not very safe, high hydrogen pressure experiments are required in the conventional C-C double bond reductions.[3] In recent years, with the development of modern transition metal catalysts, new options have emerged, much more ecological, secure and selective. On this line, the transition metal-catalyzed hydrogen transfer strategy is a practical and safer alternative for this type of chemical transformations. Furthermore, various elegant reports about sequential catalytic reactions, using a single catalyst in one tandem process, have been reported.[4] Tandem processes are economic, environmentally friendly and efficient methodologies, mainly because several transformations occur in one-pot and in a single vessel, without isolating the intermediates, avoiding unnecessary work-ups and purifications between synthetic steps.[5] In addition, the whole process could involve the formation of synthetically useful multiple bonds and stereocenters.

Ruthenium carbenes (Figure 1) are interesting catalysts for a large number of metathetic or non-metathetic reactions, exhibing remarkable functional group tolerance and good catalytic power in mild and easy-to-use conditions.[6] Among the Ru-catalyzed reactions, ring-closing enyne metathesis (RCEYM) allows an efficient, easy and rapid access to high added-value carbo or heterocyclic derivatives from simple substrates.[7] Since Ru-catalyzed non-metathetic reductions have been also reported, the same catalyst could be used to promote both transformations.



Ru1: Grubbs 1st Gen. **Ru2:** Grubbs 2nd Gen. **Ru3:** Hoveyda - Grubbs 2nd Gen.

Figure 1. Commonly used ruthenium carbene catalysts.

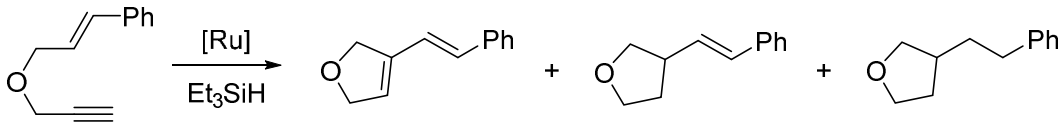
Ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP) and cross metathesis (CM), combined with reduction in a one-pot procedure, have been reported using Grubbs catalysts and different hydride donors (triethylsilane, H_2, formic acid).[8] In these systems, ruthenium hydride species are likely involved as hydrogen transfer source.[9] These complexes act as mild reducing agent, allowing a better control of the hydrogenation selectivity. Thus, a one-pot RCEYM-reduction strategy could be highly attractive for the synthesis of libraries of synthetic and biologically interesting compounds.

In this work, an efficient and practical tandem RCEYM-reduction process is described, being an excellent strategy for the synthesis of cyclic and heterocyclic compounds with different degrees of saturation.

For the development of the proposed synthetic strategy, our first experiments were performed treating the acyclic oxygenated enyne **1** with different Grubbs catalysts, using Cl_3CH as a solvent.[10] As shown in Table 1, Entry 1, heating the enyne **1** at reflux for 15 h, in presence of Grubbs 1st Generation catalyst (**Ru1**, Figure 1), triethylsilane (TESH) and chloroform, yields only the metathesis product **2**. However, under the same conditions but using **Ru2** (Grubbs 2nd Generation catalyst) or **Ru3** (Hoveyda-Grubbs 2nd Generation catalyst), a mixture of the partial **3** and totally reduced **4** tetrahydrofuran derivatives were obtained (Entries 2 and 3). With these results in hand, the selective formation of **3** and **4** was studied in depth. Accordingly, we assumed that the **Ru2** catalyst would have the adequate reactivity to provide the semi-reduced structure **3** exclusively. In order to accelerate the reaction times, microwave conditions were evaluated, giving mostly the metathesis product **2**, using 2 equiv of silane (Entry 4), and a mixture of **3** and **4** in a 1: 1 ratio, when TESH equivalents were increased to 3 (Entry 5). When other donor proton

sources were employed in the reaction, such as pyrrolidine,[11] selectivity did not increase and reproducibility became a challenge (data not shown). The main problem of these reactions was the lack of reproducibility. Some encouraging results could not be reproduced, and small modifications in the variables led to unexpected and even illogical results. Reviewing the literature, low hydrogenation activity in Ru-catalyzed reductions have been reported using chlorinated solvents,[12] which was attributed to the presence of chlorinated ruthenium species. Based on that, different solvents were evaluated, including protic solvents such as methanol. Under the conditions of entry 6, only metathesis product was achieved employing toluene or acetonitrile (Entries 7 and 8).

Table 1. Initial study of the RCEYM-reduction conditions



1 **2** **3** **4**

Entry	Equiv of Et_3SiH	Catalyst	Conditions[a]	Solvent	Product[b] (yield)		
					2	**3**	**4**
1	2	**Ru1**	reflux, 15 h	Cl_3CH	1	-	-
2	2	**Ru2**	reflux, 15 h	Cl_3CH	-	3	1
3	2	**Ru3**	reflux, 15 h	Cl_3CH	-	1	2
4	2	**Ru2**	100 °C, 20 min, MW	Cl_3CH	5	1	-
5	3	**Ru2**	100 °C, 20 min, MW	Cl_3CH	-	1	1
6	3	**Ru2**	80 °C, 20 min, MW	Cl_3CH	1	-	-
7	3	**Ru2**	80 °C, 20 min, MW	Toluene	1	-	-
8	3	**Ru2**	80 °C, 20 min, MW	Acetonitrile	1	-	-
9	3	**Ru2**	80 °C, 20 min, MW	MeOH	1	1.3	-
10	3	**Ru2**	90 °C, 20 min, MW	MeOH	-	1 (62%)	-
11	3	**Ru2**	90 °C, 20 min, MW[c]	MeOH	-	1 (85%)	-
12	3	**Ru2**	CuI, 90 °C, 20 min, MW[c]	MeOH	2.4	1	-
13	3	**Ru2**	reflux, 15 h	MeOH	1[d]	-	-
14	20	**Ru3**	90 °C, 20 min, MW	MeOH	-	-	1 (88%)
15	20	**Ru3**	90 °C, 25 min, MW	MeOH	-	-	1 (100%)

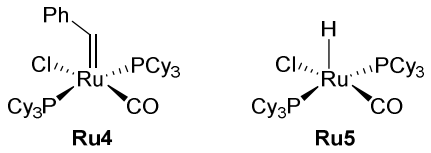
[a] A mixture of substrate **1**, 10 mol% Ru catalyst and Et_3SiH was stirred in the solvent and the described conditions in the corresponding entries, unless otherwise stated. [b] Rates and yields were determined by ^1H NMR. Yields in brackets were calculated by internal standard. [c] A mixture of **1**, 10 mol % of **Ru2** in MeOH was stirred in MW at 90 °C during 10 min, then 3 equiv of Et_3SiH were added and the reaction was stirred 10 more minutes under the same conditions. [d] Products of decomposition materials were detected.

A promising result was obtained using methanol as solvent since compound **3** was the major product (Entry 9). The semi-reduced structure **3** was obtained exclusively at 90 °C (Entry 10), while a greater increase in reaction performance was accomplished when the

process was carried out in two stages, adding Et_3SiH after 10 minutes of MW treatment (Entry 11), condition that we have called Method A. Under these conditions, compound **3** was obtained in 85% yield by internal standard and 72% yield after column chromatography. The selectivity observed is opposite to the RCM-reduction sequence published by Grubbs and coll. in 2001, in which the less-substituted alkene was hydrogenated.[8c] Considering that steric environment around both double-bounds in diene **2** is similar, probably stereoelectronic properties could govern the reduction process. No better results were obtained by adding copper iodide (Entry 12), although it has been reported that the use of this additive improves the performance of the metathesis reaction, due to catalyst stabilizing effects.[13] Analogous conditions of entry 11 but employing reflux of methanol were unsuccessful, giving the metathesis product **2** and some decomposition (Entry 13).

The implementation of MeOH as solvent, in addition to provide high reproducibility, allowed the selective formation of the mono-reduced cyclic product **3**. Then, the role of MeOH as hydride donor was considered. There are several published articles describing the use of primary or secondary alcohols as "hydrogen donors".[14] Therefore, when the reaction was carried out in absence of Et_3SiH, diene **2** was the only product, proving that the silane is essential for the reaction outcome. Regarding the effectiveness of methanol in this kind of processes, formation of complexes like **Ru4** or **Ru5** in methanolic solvents were described in previous papers (Figure 2).[15] Species like **Ru5** have been described by Mol as an efficient hydrogenation catalyst at high temperatures, being very effective in tandem metathesis-hydrogenation pathways.

On the other hand, employing the more reactive Hoveyda-Grubbs catalyst (**Ru3**) and more equivalents of Et_3SiH, only saturated product **4** was obtained (Entries 14 and 15). By applying 20 equiv of Et_3SiH in presence of 10 mol% of **Ru3** in MeOH at 90 ºC during 25 minutes, under MW heating, the saturated tetrahydrofuran derivative **4** was achieved in quantitative yield (Entry 15), condition that we have called Method B.



Ru4 **Ru5**

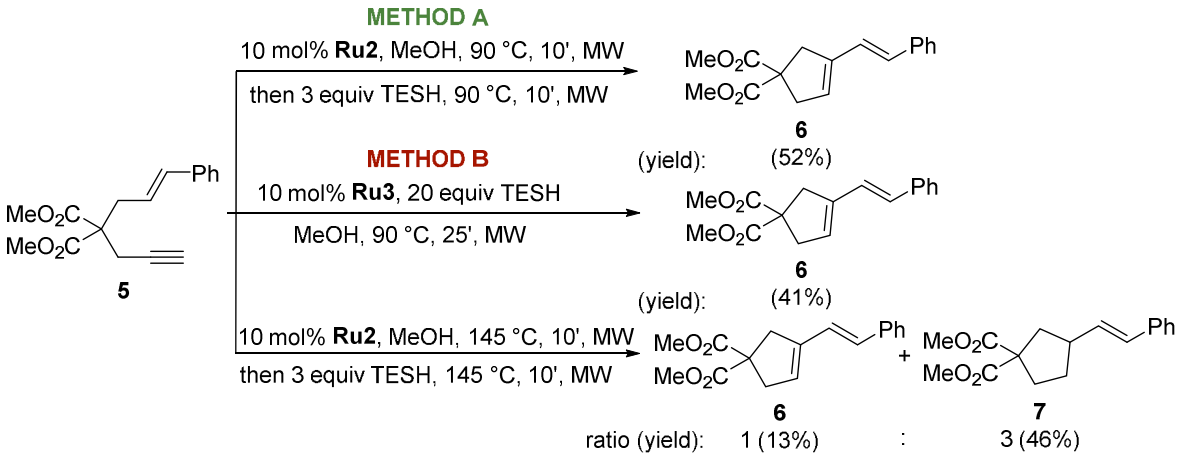
Figure 2. Complexes proposed by Mol for Ru1 in MeOH[15]

Scope and reactivity

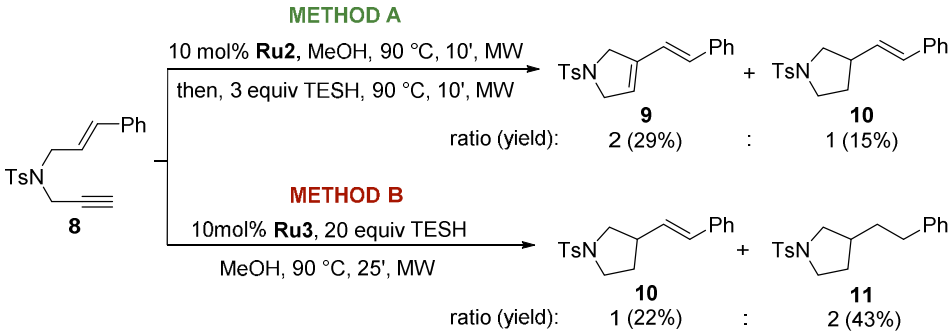
In order to further determine the influence of the starting material substitution in the reactivity, we have applied the optimized conditions for the formation of **1**, entry 11 (Method A) and entry 15 (Method B), on a set of substrates. The relative quantities of different products obtained were dependent on the enyne substitution.

To analyze the influence of the main chain nature on the reactivity, the malonic ester derivative **5** (Scheme 1) and the nitrogen derivative **8** (Scheme 2), were evaluated. The decrease in reduction reactivity could be explained by the presence of electron-attracting groups within the chain.[16] Nevertheless, the selectivity of the most-substituted double bond reduction was maintained, giving the mono-reduced cyclic derivatives **7** and **10**.

Scheme 1. Reactivity of enyne 5 under the RCEYM-reduction conditions

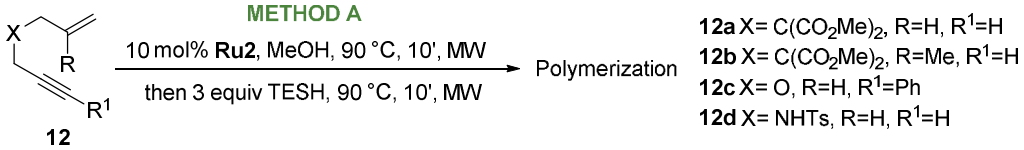


Scheme 2. Reactivity of enyne 8 under the RCEYM-reduction conditions

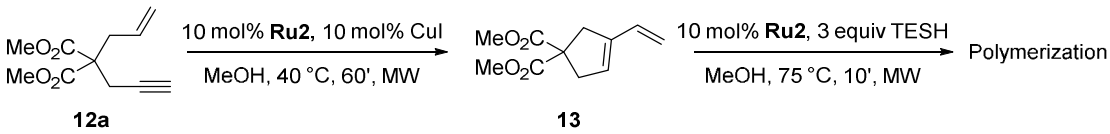


When the conditions of the Method A were employed on enynes with terminal alkenes (substrates **12a-d**), only polymerization and decomposition products were recovered (Scheme 3), showing a prevalence of intermolecular metathetic events. No better results were observed applying copper iodide under the conditions previously tested. Additionally, we carried out the RCEYM and reduction in a stepwise manner using CuI for the metathesis step. RCEYM of **12a** was performed at temperatures below 60 °C, yielding the expected product **13** (Scheme 4). No reaction was observed after further treatment of this crude with the catalytic system and TESH at 60 °C, giving polymerization at 75 °C or higher temperatures. According to these results, polymerization could be mainly due to the temperature, which is necessary to achieve an effective reduction.

Scheme 3. Reactivity of enynes with terminal alkenes

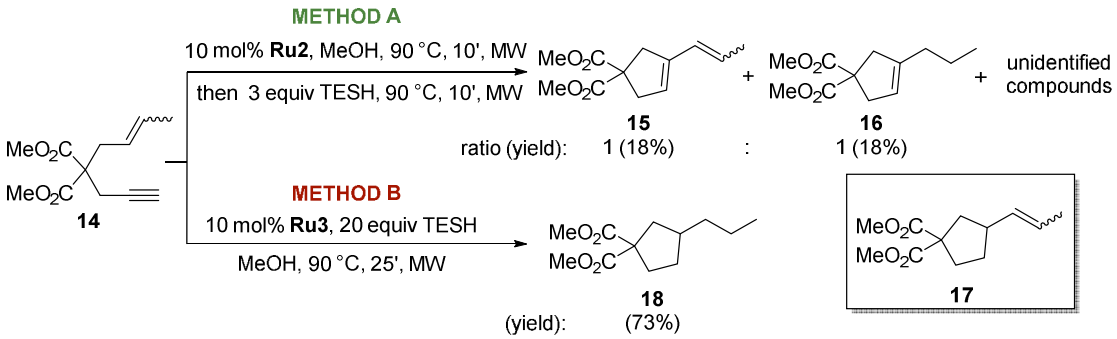


Scheme 4. RCEYM and reduction of 12a using CuI

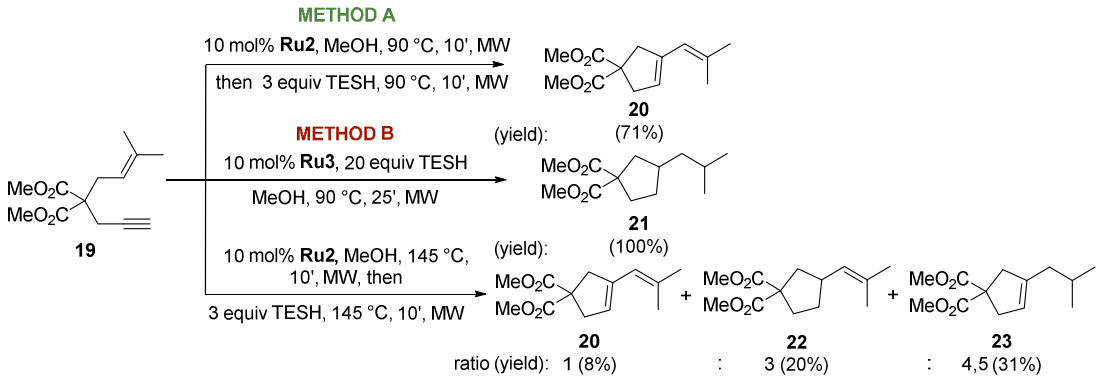


Finally, enynes with vicinal-disubstituted and trisubstituted alkenes were evaluated. Under the metathesis-reduction conditions of Method A, the crotyl derivative **14** was transformed into the diene **15** and the cycloalkene **16** in equal amounts (Scheme 5). Several unidentified products were also detected in the crude material (spectroscopy and spectrometry data are in agreement with the presence of the compound **17** in the mixture). Furthermore, using Method A conditions on the enyne **19,** yielded only metathesis product **20**, which has two equivalent trisubstituted double bonds (Scheme 6). This structural similarity leads to a loss of selectivity, obtaining a mixture of mono-reduced products **22** and **23**, when the reaction was carried at 145 °C. The saturated cyclic compounds **18** and **21** (Scheme 5 and 6) were obtained by applying the conditions of the Method B on substrates **14** and **19**. Using this methodology, **18** and **21** were synthesized in 40% and 62% yield respectively, after purification by column chromatography.

Scheme 5. Reactivity of enynes with vicinal-disubstituted alkenes



Scheme 6. Reactivity of enynes with vicinal- trisubstituted alkenes



CONCLUSIONS

In summary, a new microwave-based tandem RCEYM-reduction is reported. Depending on the substitution of the substrate, this methodology selectivity affords different cyclic and heterocyclic compounds with a variable degree of saturation. It could be applied to different enynes except to those with terminal alkenes, in which the cross metathesis and polymerization are the prevalent processes. Although formation of an exclusive product was not always achieved, the reduction selectivity was maintained, regardless the substitution of the double bonds present in the metathesis intermediate, being the most substituted double bond preferentially reduced. The use of methanol as a solvent was also studied, providing a reproducible and efficient procedure, due to its ability to form very effective complexes for metathesis-hydrogenation reactions, like **Ru5**. On the other hand, this methodology allows a selective preparation of synthetically useful compounds with a decrease in waste production and energy consumption. An asymmetric version of this methodology is currently in progress.

EXPERIMENTAL SECTION

General Procedures

Chemical reagents were purchased from commercial sources and were used without further purification unless otherwise noted. Solvents were analytical grade or were purified by standard procedures prior to use. Nuclear magnetic resonance spectra were obtained on a Bruker Avance 300 apparatus using $CDCl_3$ as solvent and with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) for NMR spectra were reported in units of parts per million (ppm) downfield from TMS (0.0) and relative to the signal of chloroform-*d* (7.26, singlet). NMR yields were determined using the internal NMR standard 1,3,5-trimethylbenzene (3H, 6.80 ppm, 9H, 2.27 ppm). Gas Chromatography-Mass Spectra (GC-MS) were recorded on a Shimadzu QP2010 Plus apparatus at an ionization voltage of 70 eV equipped with a SPBTM-1 capillary column (internal diameter 0.25 mm, length 30 m).

High Resolution Mass Spectra (HRMS) were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of ions was performed in electrospray ionization, positive ion mode. Analytical thin layer chromatography (TLC) was performed using F254 precoated silica gel plates. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh). Elution was carried out with hexane-ethyl acetate gradient, under positive pressure. Microwave-assisted reactions were performed using a CEM Discover microwave reactor. In all experiments, the temperature and the reaction time was setted, then the reactor automatically adjust the power (maximum of 200 W) in order to maintain a constant temperature. Reactions were performed in 5 mL sealed vessels. The specified reaction time corresponds to the total irradiation time. Compounds **1**,[17, 18, 19] **5**,[20] **8**,[21, 22, 23] **12a**,[20] **12b**,[20] **12c**,[24] **12d**,[25,22] **14**[20, 26] and **19**[20] were analogously prepared according to reported literature.

General Procedures for Ring Closing Enyne Metathesis and Reduction. *Method A.* In a microwave flask equipped with a magnetic stirrer, the enyne (1 equiv) and **Ru2** (0.1 equiv), were dissolved in anhydrous methanol and then, the vessel was placed in the microwave reactor. The reaction mixture was irradiated under constant microwave for 10 minutes temperature controlled at 90 °C. After this time, triethylsilane (3 equiv) was added to the flask and the vessel was place again in the microwave reactor. Then the sample was irradiated at 90 °C for 10 minutes. The solvent was evaporated under reduced pressure on a rotary evaporator. The yield was determined by NMR using an internal standard. *Method B.* In a microwave flask equipped with a magnetic stirrer, the enyne (1 equiv) and **Ru3** (0.1 equiv) were dissolved in anhydrous methanol and triethylsilane (20 equiv) was added. The reaction mixture was irradiated under constant microwave for 25 minutes at 90 °C. The solvent was evaporated under reduced pressure on a rotary evaporator. The yield was determined by NMR using an internal standard.

RCEM – Reduction of (*E*)-3-(prop-3-ynyloxy)-1-phenylpropene (1). Following Method A, **1** (0.025 g, 0.145 mmol, 1 equiv) and **Ru2** (0.012 g, 0.014 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.070 mL, 0.436 mmol, 3 equiv) was added. (*E*)-3-Styryltetrahydrofuran (**3**) was the only product obtained in 85% yield (NMR). Purification by silica gel column chromatography using EtOAc/Hexane (1:9) as the eluent, affords **3** (0.018 g, 72%) as a colorless oil. Following Method B, **1** (0.025 g, 0.145 mmol, 1 equiv) and **Ru3** (0.009 g, 0.014 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.463 mL, 2.907 mmol, 20 equiv) was added. 3-Phenethyl tetrahydrofuran (**4**) was the only product obtained in 88% yield (NMR). Purification by silica gel column chromatography using EtOAc/Hexane (1:9) as the eluent, affords **4** (0.008 g, 32%) as a colorless oil.

*(E)-3-Styryltetrahydrofuran (***3***)* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.12 (m, 6H), 6.46 (d, J = 15.8 Hz, 1H), 6.14 (dd, J = 15.8, 8.4 Hz, 1H), 4.05 – 3.91 (m, 2H), 3.84 (dt, J = 7.8, 7.3 Hz, 1H), 3.54 (dd, J = 8.3, 7.6 Hz, 1H), 3.02 (h, J = 7.8 Hz, 1H), 2.17 (dtd, J = 12.2, 7.5,

4.7 Hz, 1H), 1.81 (dq, *J* = 12.3, 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 137.2, 130.7, 130.5, 128.6, 127.3, 126.1, 73.0, 68.3, 43.2, 33.3. HRMS (ESI) *m/z*: $[(M+K)]^+$ calcd for $C_{12}H_{14}KO^+$ 213.0676, found 213.0892.

*3-Phenethyl tetrahydrofuran (**4**)* ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.35 – 7.24 (m, 1H), 7.24 – 7.13 (m, 4H), 3.91 (dd, *J* = 8.1, 7.4 Hz, 1H), 3.85 (dt, *J* = 8.1, 4.7 Hz, 1H), 3.74 (dt, *J* = 7.8, 7.2 Hz, 1H), 3.37 (dd, *J* = 8.2, 7.2 Hz, 1H), 2.63 (dt, *J* = 7.9, 3.5 Hz, 2H), 2.20 (p, *J* = 7.5 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.72 (q, *J* = 7.8, 7.4 Hz, 2H), 1.57 – 1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 142.1, 128.4, 128.3, 125.9, 73.3, 68.0, 38.9, 35.2, 34.9, 32.5. HRMS (ESI) *m/z*: $[(2M+Na)]^+$ calcd for: $C_{24}H_{32}NaO_2^+$ 375.2287, found 375.2294.

RCEM – Reduction of Dimethyl (*E*)-cinnamylpropargylmalonate (5). Following Method A, **5** (0.025 g, 0.087 mmol, 1 equiv) and **Ru2** (0.007 g, 0.009 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.042 mL, 0.262 mmol, 3 equiv) was added. Dimethyl (*E*)-3-styrylcyclopent-3-ene-1,1-dicarboxylate (**6**) was the only product obtained in 52% yield (NMR). Following Method B, **5** (0.025 g, 0.087 mmol, 1 equiv) and **Ru3** (0.005 g, 0.009 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.278 mL, 1.748 mmol, 20 equiv) was added. **6** was the only product obtained in 41% yield (NMR). Following Method A, but setting the reactor at 145 °C, **5** (0.025 g, 0.087 mmol, 1 equiv) and **Ru2** (0.005 g, 0.009 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.278 mL, 1.748 mmol, 20 equiv) was added. A mixture of **6** and Dimethyl (*E*)-3-styrylcyclopentane-1,1-dicarboxylate (**7**) was obtained in a 1:3 ratio in 13% and 46% yield (NMR), respectively.

NMR spectral data of **6**[27] and **7**[28] was identical to those reported in the literature**.**

RCEM – Reduction of *N*-Cinnamyl-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (8). Following Method A, **8** (0.025 g, 0.077 mmol, 1 equiv) and **Ru2** (0.007 g, 0.008 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.037 mL, 0.231 mmol, 3 equiv) was added. A mixture of (*E*)-3-Styryl-1-tosyl-2,5-dihydro-1*H*-pyrrole (**9**) and (*E*)-3-Styryl-1-tosylpyrrolidine (**10**) was obtained in a 2:1 ratio in 29% and 15% yield (NMR), respectively. Following Method B, **8** (0.025 g, 0.077 mmol, 1 equiv) and **Ru3** (0.005 g, 0.008 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.245 mL, 1.538 mmol, 20 equiv) was added. A mixture of **10** and 3-Phenethyl-1-tosylpyrrolidine (**11**) was obtained in a 1:2 ratio in 22% and 43% yield (NMR), respectively.

NMR spectral data of **9**[29] was identical to those reported in the literature**.**

*(E)-3-Styryl-1-tosylpyrrolidine (**10**)* ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.73 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.29 – 7.15 (m, 5H), 6.33 (d, *J* = 15.8 Hz, 1H), 5.88 (dd, *J* = 15.9, 7.8 Hz, 1H), 3.53 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.45 – 3.38 (m, 1H), 3.36 – 3.25 (m, 1H), 3.03 (dd, *J* = 9.9, 7.8 Hz, 1H), 2.84 (q, *J* = 9.3, 8.4 Hz, 1H), 2.42 (d, *J* = 3.2 Hz, 3H), 2.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 143.4, 136.7, 133.9, 131.0, 129.7, 128.5, 128.2, 127.6, 126.1, 52.9, 47.5, 42.0, 32.0, 21.5. HRMS (ESI) *m/z*: $[(M+H)]^+$ calcd for: $C_{19}H_{22}NO_2S^+$ 328.1366, found 328.1345.

*3-Phenethyl-1-tosylpyrrolidine (**11**)* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.29 – 7.16 (m, 3H), 7.09 (d, J = 7.2 Hz, 2H), 3.45 (dd, J = 9.6, 7.1 Hz, 1H), 3.34 (ddd, J = 9.7, 8.2, 3.6 Hz, 1H), 3.18 (ddd, J = 9.6, 8.5, 6.9 Hz, 1H), 2.83 (dd, J = 9.8, 7.7 Hz, 1H), 2.54 (t, J = 8.0 Hz, 2H), 2.43 (s, 3H), 2.10 – 1.86 (m, 2H), 1.56 (dt, J = 9.4, 6.7 Hz, 2H), 1.42 (dq, J = 12.1, 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 141.5, 133.9, 129.6, 128.4, 128.2, 127.5, 126.0, 53.1, 47.5, 38.2, 34.8, 34.4, 31.4, 21.5. HRMS (ESI) *m/z*: $[(M+H)]^+$ calcd for: $C_{19}H_{24}NO_2S^+$ 330.1522, found 330.1496.

RCEM – Reduction of Dimethyl (*E*)-2-(but-2-enyl)-2-(prop-2-ynyl)malonate and Dimethyl (*Z*)-2-(but-2-enyl)-2-(prop-2-ynyl)malonate (14). Following Method A, **14** (0.025 g, 0.111 mmol, 1 equiv) and **Ru2** (0.009 g, 0.011 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.053 mL, 0.335 mmol, 3 equiv) was added. A mixture of (*E*)-Dimethyl 3-(prop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate (**15**) and Dimethyl 3-propylcyclopent-3-ene-1,1-dicarboxylate (**16**) was obtained in a 1:1 ratio in 18% and 18% yield (NMR), respectively. Following Method B, **14** (0.025 g, 0.111 mmol, 1 equiv) and **Ru3** (0.007 g, 0.011 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.355 mL, 2.232 mmol, 20 equiv) was added. Dimethyl 3-propylcyclopentane-1,1-dicarboxylate (**18**) was the only product obtained in 73% yield (NMR). Purification by silica gel column chromatography using EtOAc/Hexane (1:99) as the eluent, affords the product **18** (0.010 g, 39%) as a colorless oil.

NMR spectral data of **15**[30] was identical to those reported in the literature**.**

*Dimethyl 3-propylcyclopent-3-ene-1,1-dicarboxylate (**16**)* ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.19 (s, 1H), 3.72 (s, 6H), 2.97 (d, J = 2.7 Hz, 2H), 2.90 (s, 2H), 2.00 (d, J = 7.0 Hz, 2H), 1.45 (h, J = 7.3 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H). HRMS (ESI) *m/z*: $[(M+Na)]^+$ calcd for: $C_{12}H_{18}NaO_4^+$ 249.1097, found 249.1093.

*Dimethyl 3-propylcyclopentane-1,1-dicarboxylate (**18**)* ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (d, J = 1.2 Hz, 6H), 2.45 (dd, J = 12.8, 7.1 Hz, 1H), 2.30 (tt, J = 8.9, 4.4 Hz, 1H), 2.20 – 2.07 (m, 1H), 2.03 – 1.77 (m, 2H), 1.69 (dd, J = 13.2, 9.9 Hz, 1H), 1.37 – 1.16 (m, 4H), 1.00 – 0.78 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 60.0, 52.6, 40.9, 39.5, 37.5, 33.9, 32.1, 21.6, 14.2. HRMS (ESI) *m/z*: $[(M+Na)]^+$ calcd for: $C_{12}H_{20}NaO_4^+$ 251.1254, found 251.1245.

RCEM – Reduction of Dimethyl 2-propargyl-2-prenylmalonate (19). Following Method A, **19** (0.025 g, 0.105 mmol, 1 equiv) and **Ru2** (0.009 g, 0.010 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.050 mL, 0.315 mmol, 3 equiv) was added. Dimethyl 3-(2-methylprop-1-enyl)cyclopent-3-ene-1,1-dicarboxylate (**20**) was the only product obtained in 71% yield (NMR). Following method B, **19** (0.025 g, 0.105 mmol, 1 equiv) and **Ru3** (0.007 g, 0.010 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.335 mL, 2.100 mmol, 20 equiv) was added. Dimethyl 3-isobutylcyclopentane-1,1-dicarboxylate (**21**) was the only product obtained in 100% yield (NMR). Purification by silica gel column chromatography using EtOAc/Hexane (1:99) as the eluent, affords the product **21** (0.016 g, 62%) as a colorless oil. Following method A, but setting the reactor at 145 ℃, **19** (0.025 g, 0.105 mmol, 1

equiv) and **Ru2** (0.009 g, 0.010 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.050 mL, 0.315 mmol, 3 equiv) was added. A mixture of **20**, Dimethyl 3-isobutylcyclopent-3-ene-1,1-dicarboxylate (**22**) and Dimethyl 3-(2-methylprop-1-enyl)cyclopentane-1,1-dicarboxylate (**23**) was obtained in a 1:3:4.5 ratio in 8%, 20% and 31% yield (NMR), respectively. Purification by silica gel column chromatography using EtOAc/Hexane (1:99) as the eluent, affords a mixture of **22** and **23** (0.011 g, 45%) as a colorless oil.

NMR spectral data of **20**[31] was identical to those reported in the literature**.**

*Dimethyl 3-isobutylcyclopentane-1,1-dicarboxylate (***21***)* ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (d, J = 2.2 Hz, 6H), 2.45 (dd, J = 13.1, 6.9 Hz, 1H), 2.30 (ddd, J = 13.6, 8.5, 3.6 Hz, 1H), 2.12 (ddd, J = 13.6, 9.5, 7.5 Hz, 1H), 2.01 (tt, J = 9.9, 7.1 Hz, 1H), 1.91 – 1.79 (m, 1H), 1.65 (dd, J = 13.3, 10.3 Hz, 1H), 1.55 (q, J = 6.9 Hz, 1H), 1.30 – 1.14 (m, 3H), 0.86 (dd, J = 6.6, 1.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 59.9, 52.6, 44.6, 41.1, 37.6, 33.9, 32.3, 26.9, 22.8. HRMS (ESI) *m/z*: $[(M+Na)]^+$ calcd for: $C_{13}H_{22}NaO_4^+$ 265.1410, found 265.1401.

Dimethyl 3-(2-methylprop-1-enyl)cyclopentane-1,1-dicarboxylate (**22***)* ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (dt, J = 8.8, 1.5 Hz, 1H), 3.70 (s, 6H), 2.77 (ddd, J = 26.2, 10.0, 7.2 Hz, 1H), 2.44 (dd, J = 13.2, 7.2 Hz, 1H), 2.32 (ddt, J = 13.6, 8.7, 8.5 Hz, 1H), 2.23 – 2.08 (m, 1H), 1.88 – 1.80 (m, 1H), 1.80 – 1.68 (m, 1H), 1.66 (d, J = 1.4 Hz, 3H), 1.60 (d, J = 1.4 Hz, 3H), 1.36 (dd, J = 12.5, 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (2), 132.1, 127.7, 59.9, 52.6 (2), 41.4, 38.7, 34.0, 33.1, 25.6, 18.0. HRMS (ESI) *m/z*: $[(M+Na)]^+$ calcd for: $C_{13}H_{20}NaO_4^+$ 263.1254, found 263.1254.

*Dimethyl 3-isobutylcyclopent-3-ene-1,1-dicarboxylate (***23***)* ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (s, 1H), 3.72 (s, 6H), 2.97 (q, J = 2.0 Hz, 2H), 2.88 (s, 2H), 1.91 (d, J = 7.6 Hz, 2H), 1.78 – 1.71 (m, 1H), 0.85 (d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (2), 141.1, 121.5, 59.2, 52.7 (2), 43.0, 40.6, 40.1, 26.4, 22.5 (2). HRMS (ESI) *m/z*: $[(M+Na)]^+$ calcd for: $C_{13}H_{20}NaO_4^+$ 263.1254, found 263.1254.

RCEM – Reduction of Dimethyl allylpropargylmalonate (12a). Following Method A, **12a** (0.025 g, 0.119 mmol, 1 equiv) and **Ru2** (0.010 g, 0.012 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.057 mL, 0.357 mmol, 3 equiv) was added. GC and NMR evidenced the presence of different polymerization products.

RCEM – Reduction of Dimethyl methallylpropargylmalonate (12b). Following Method A, **12b** (0.025 g, 0.111 mmol, 1 equiv) and **Ru2** (0.009 g, 0.011 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.053 mL, 0.335 mmol, 3 equiv) was added. GC and NMR evidenced the presence of different polymerization products.

RCEM – Reduction of (3-Allyloxy-prop-1-ynyl)-benzene (12c). Following Method A, **12c** (0.025 g, 0.145 mmol, 1 equiv) and **Ru2** (0.012 g, 0.014 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.070 mL, 0.436 mmol, 3 equiv) was added. GC and NMR evidenced the presence of different polymerization products.

RCEM – Reduction of N-(2-Propenyl)-N-(2-propynyl)-4-methylbenzenesulfonamide (12d). Following Method A, **12d** (0.025 g, 0.100 mmol, 1 equiv) and **Ru2** (0.009 g, 0.010 mmol, 0.1 equiv) were dissolved in anhydrous methanol (2.0 mL) and triethylsilane (0.048 mL, 0.301 mmol, 3 equiv) was added. GC and NMR evidenced the presence of different polymerization products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI xxxxxxx

Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **2**, **3**, **4**, **5**, **6**, **7**, **9**, **10**, **11**, **15**, **16**, **18**, **20**, **21** and **23**.

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