Chapter 5

Ruthenium-Catalyzed Ring-Closing Metathesis to Form Tetrasubstituted Olefins

As mentioned previously, ruthenium-based NHC complexes, such as **2**–**4**, possess activity similar to molybdenum-based complexes, such as **1**, yet possess high functional group tolerance and air and moisture stability.[1] Nevertheless, there remain transformations for which molybdenum-based catalysts are significantly more efficient, such as ring-closing metathesis to form tetrasubstituted olefins. In this chapter are presented new ruthenium complexes with increased efficiency for this transformation.[2]

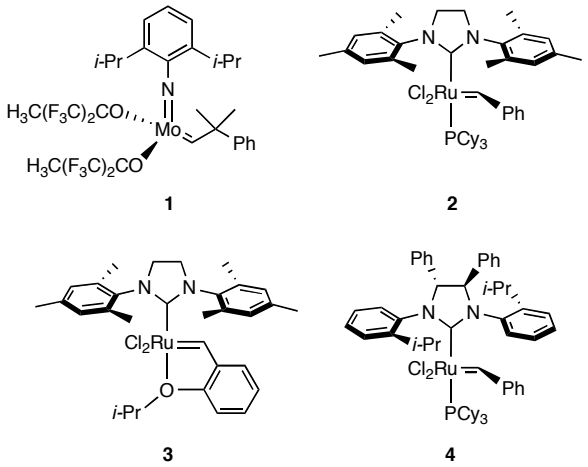
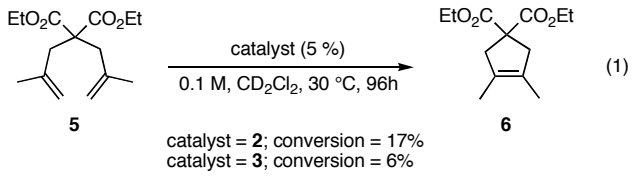


Figure 5.1. Olefin metathesis catalysts.

Recently our laboratory developed a standard set of activity comparisons for olefin metathesis catalysts.[3] During this work, it was observed that diethyl dimethallylmalonate (**5**) is a very challenging substrate for catalysts **2** and **3** (Equation 1).

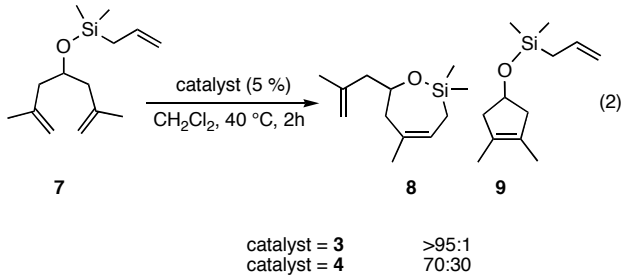


(1)

Using more forcing reaction conditions (60 °C, C_6D_6) for 24 hours with **3**, the reaction still only proceeded to 30% conversion. Under identical conditions, catalyst **1** formed carbocycle **6** in 93% yield. Seeking to continue to expand the applications of ruthenium-

catalyzed olefin metathesis, our laboratory sought catalysts that would be more active for the formation of tetrasubstituted olefins.

In the course of the ARCM studies discussed in Chapter 3,[4] a product containing a tetrasubstituted olefin was unexpectedly obtained in one asymmetric ring-closing reaction (Equation 2). When **7** was treated with catalyst **3,** only the trisubstituted olefin **8** was observed. However, when the asymmetric ring-closing was performed with catalyst **4**, a 70:30 ratio of **8** to the tetrasubstituted olefin **9** was obtained. It was hypothesized that the absence of one ortho substituent on each N-bound aryl ring of catalyst **4** resulted in the additional space necessary to form the tetrasubstituted olefin.



A catalyst was designed in which the substitution on the N-bound aryl rings was removed from the ortho positions and placed at the meta positions. This catalyst (**18**) was initially designed with the meta *tert*-butyl groups with the belief that the bulky *tert*-butyl groups would both prevent ring rotation with concomitant C-H activation[5] and protect the methylidene from nucleophilic attack by phosphine.[6] Indeed, the *tert*-butyl groups do impart stability, as efforts to prepare similar catalysts with meta methyl or trifluoromethyl groups were unsuccessful. Catalyst **18** was prepared from 3,5-di-*tert*-butylaniline as shown in Figure 5.2.[7] Unfortunately, the PCy_3 containing variant of this architecture (**14**) could not be prepared. It was hypothesized that the meta *tert*-butyl containing NHC was

too bulky to accommodate the PCy_3. Thus, an effort was made to prepare a PPh_3 containing variant because PPh_3 is considerably smaller than PCy_3. Surprisingly, when imidazolium salt **12** was converted to the carbene and reacted with $(PPh_3)_2(Cl)_2Ru{=}CHPh$ (**15**), it was found by X-ray crystallography that in the resulting ruthenium complex **16** the PPh_3 ligand was cis to the NHC. This pale blue complex was completely inactive over 24 hours for the RCM reaction of diethyl diallylmalonate at 60 °C.

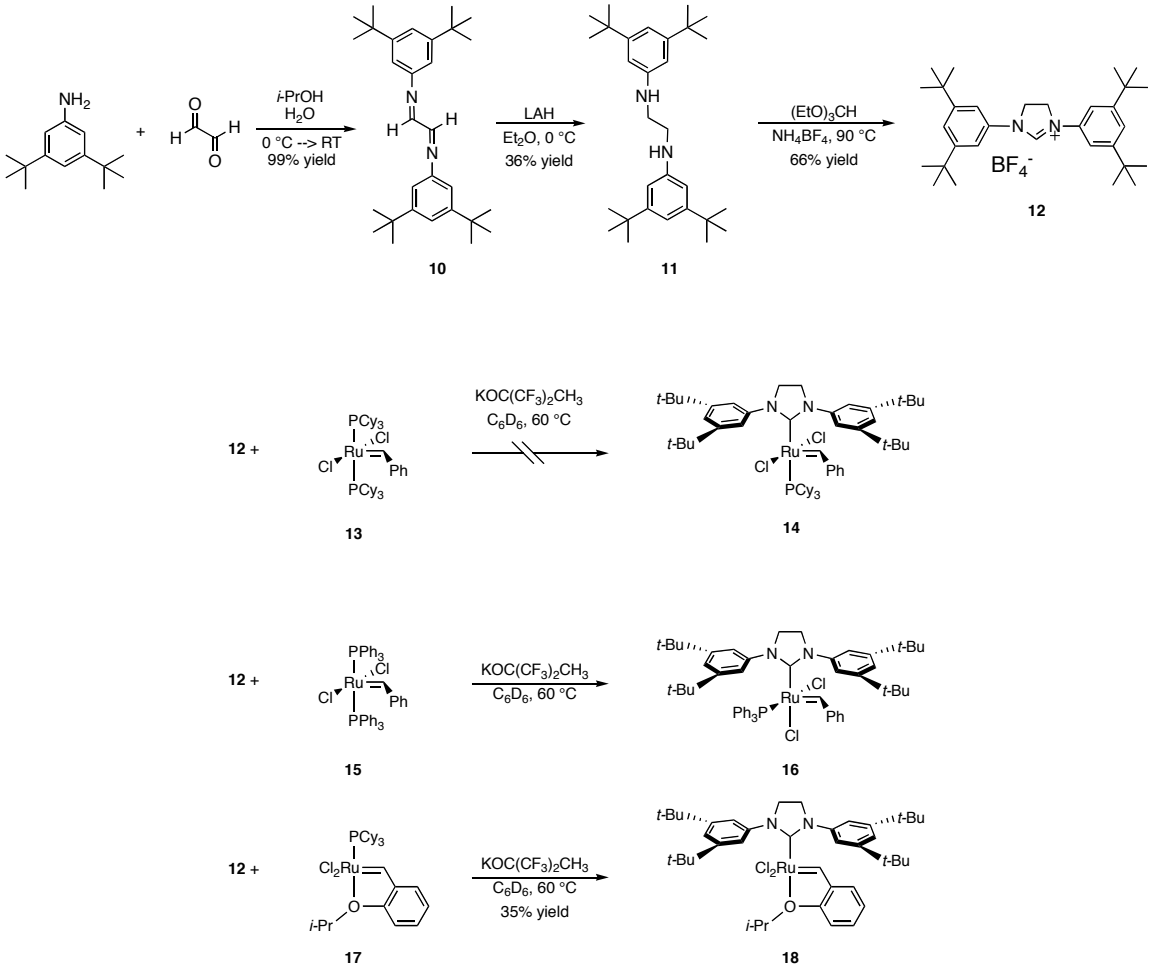
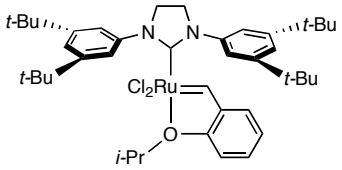
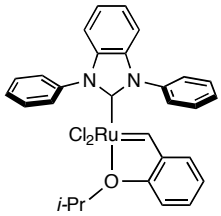


Figure 5.2. Synthesis of **14** and **18** and attempt to prepare **16**.

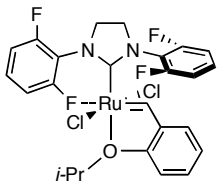
Two additional catalysts (**19**–**20**) were also prepared with reduced bulk at the ortho positions of the N-bound aryl rings.[8] These catalysts were prepared by Dr. Katie Campbell and Dr. Tobias Ritter, respectively.



18



19



20

Figure 5.3. Catalysts with increased activity in RCM to form tetrasubstituted olefins.

In order to compare catalysts **18**–**20** to catalysts **2** and **3** for the ability to form tetrasubstituted olefins by RCM, the reaction of **5** with these catalysts was monitored over time (Figure 5.4). These reactions were performed under the conditions developed for standard activity comparisons: 30 °C, 5 mol% catalyst, 0.1 M in CD_2Cl_2 (0.8 ml). All three of the new catalysts performed significantly better in this reaction than either **2** or **3**. Catalysts **18**–**20** all eventually reached similar conversions. Increasing the reaction temperature to 60 °C, along with the necessary changes in solvents, catalysts **18**–**20** reached their maximal conversions in just 24 hours.

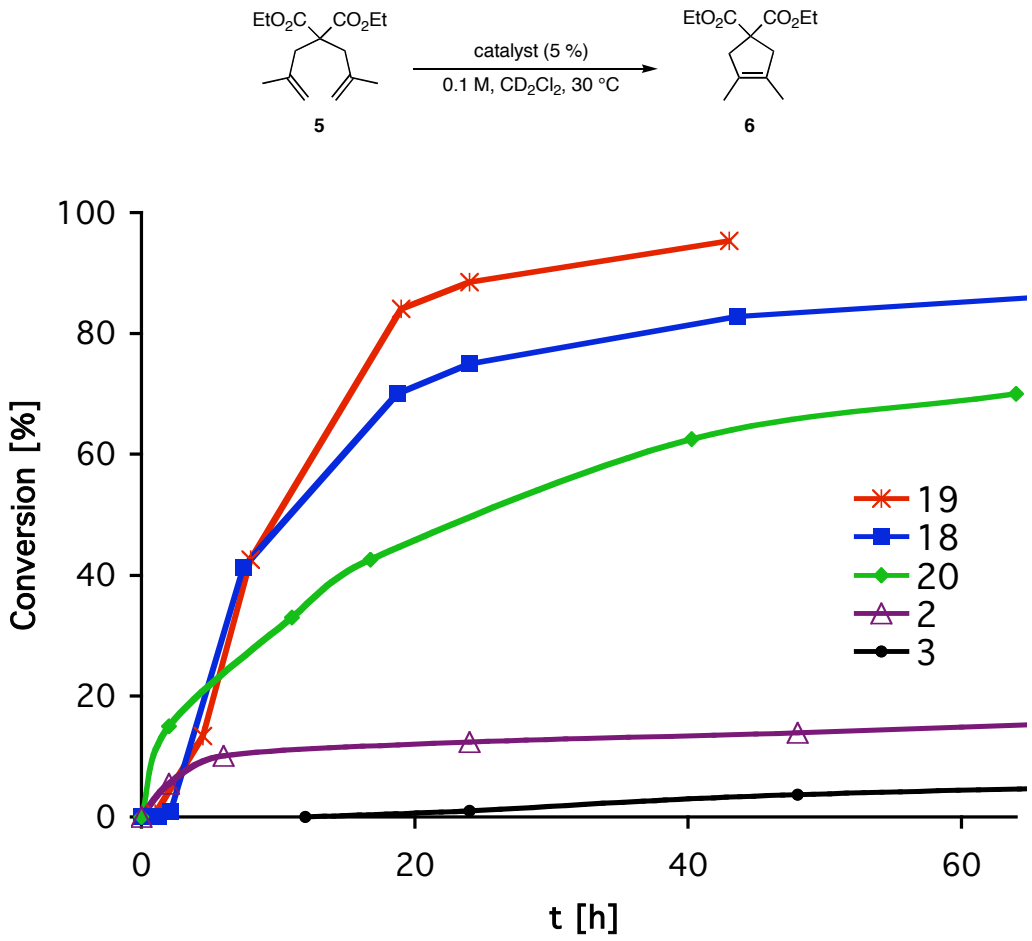
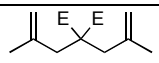
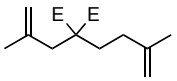
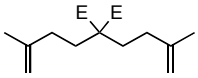
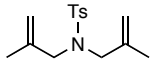
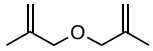
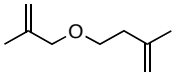
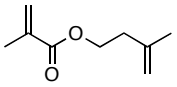
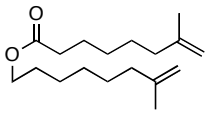


Figure 5.4. RCM of diethyl dimethallylmalonate (**5**).

Using these elevated temperature conditions, catalysts **18**–**20** were compared against catalyst **3** for a number of substrates (Table 5.1). Substrate **5** proved to be uniquely challenging for catalyst **3**; for all of the other substrates **3** performed in a similar fashion to **18**–**20**. None of the catalysts showed any conversion for **26** or **27**, precursors to an electron-deficient tetrasubstituted olefin and a tetrasubstituted olefin in a macrocycle, respectively.[9] Substrate **25** warrants further discussion. Use of catalyst **3** gave a mixture of three compounds, with 43% conversion to product, 32% conversion to an unidentified by-product and 25% remaining starting material (**25**). Use of catalyst **18** resulted in complete consumption of **25**, but with only 60% conversion to product and 40%

conversion to the by-product. Interestingly, catalyst **20** gave 43% conversion to the product and no by-product formation. It was hypothesized that the by-product could arise from the action of a ruthenium-hydride. Repeating the reactions using **3** and **18** with 10% 2,6-dichloroquinone added to consume any hydride formed,[10] catalyst **3** gave very poor conversion, but catalyst **18** gave 78% conversion to product with no by-product formation. Overall, catalyst **18** performed as well as or better than **3** for all of the substrates, so isolated yields for all substrates were obtained for the reactions with **18** to confirm that the conversions were accurate.

Table 5.1. RCM to form tetrasubstituted olefins

Substrate	Conversions (isolated yields) with catalysts 3, 18, 19, 20 [%]			
	3	**18**	**19**	**20**
 **5**	30	93 (86)	> 95	88[a]
 **21**	>95	>95 (99)	> 95	>95[a]
 **22**	50	51 (47)	36[b]	34[a]
 **23**	85	>95 (99)	> 95	>95[a]
 **24**	>95	>95[c]	55	>95[a]
 **25**	43[d]	78[c,e]	NR	43[a]
 **26**	NR	NR	NR	NR[a]
 **27**	NR	NR	NR	NR[a]

[a] $CDCl_3$ used as solvent due to the poor solubility of **20** in aromatic solvents.
[b] Reaction time: 96 hours.
[c] Isolated yield not determined due to product volatility.
[d] 75% consumption of **25**.
[e]10% 2,6-dichlorobenzoquinone added. Without 2,6-dichlorobenzoquinone: 60% conversion to product, 95% consumption of **25**.
NR = no reaction

While **18** gave good to excellent conversions for the formation of tetrasubstituted olefins by RCM over 24 hours, often there was little or no conversion apparent for the first few hours. This is likely due to poor initiation of the catalyst caused by slow dissociation of the ethereal ligand. For this reason, a phosphine containing catalyst was targeted. In particular, because the unsaturated NHC analogue of **2** performed better than catalyst **2**

for the RCM of **5** under standard conditions (31% conversion vs. 17% conversion), an unsaturated NHC analogue of catalyst **18** with a phosphine ligand was sought.

Unsaturated imidazolium salt **28** was prepared in one step and, pleasingly, both a catalyst containing an chelating ether ligand (**29**) and a phosphine ligand (**30**) were prepared (Figure 5.5).

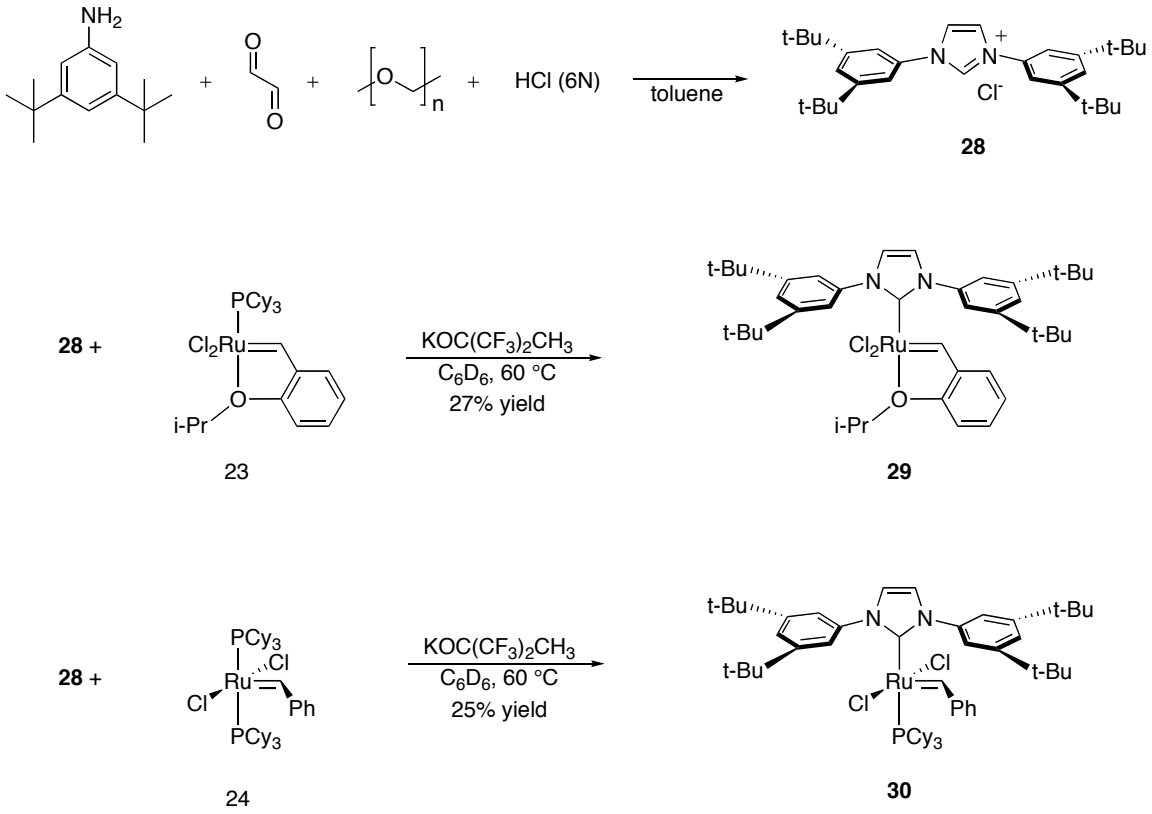
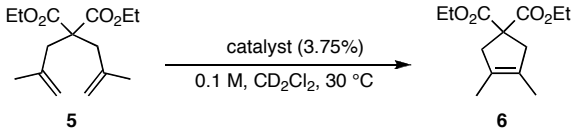
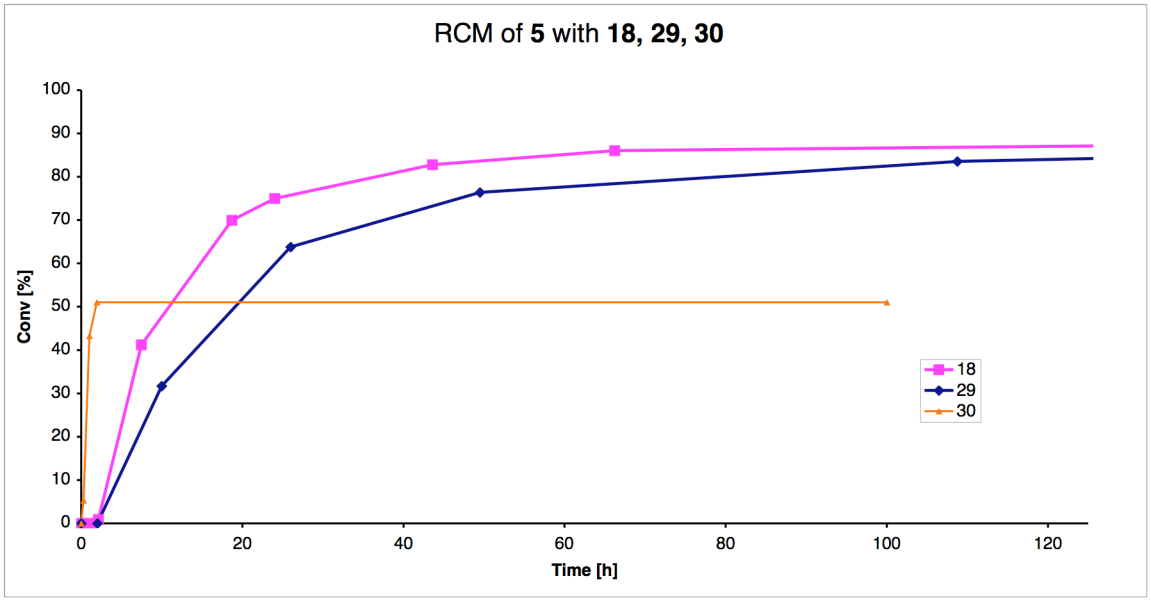


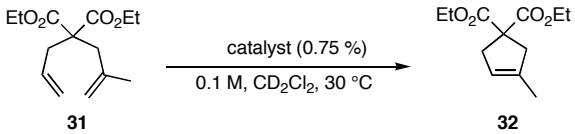
Figure 5.5. Preparation of catalysts with unsaturated NHCs.

Catalysts **29** and **30** were compared against catalyst **18** for the RCM reaction of **5** to form tetrasubstituted olefin containing carbocycle **6** and **31** to form trisubstituted olefin containing carbocycle **32** (Figure 5.6).



5 **6**





31 **32**

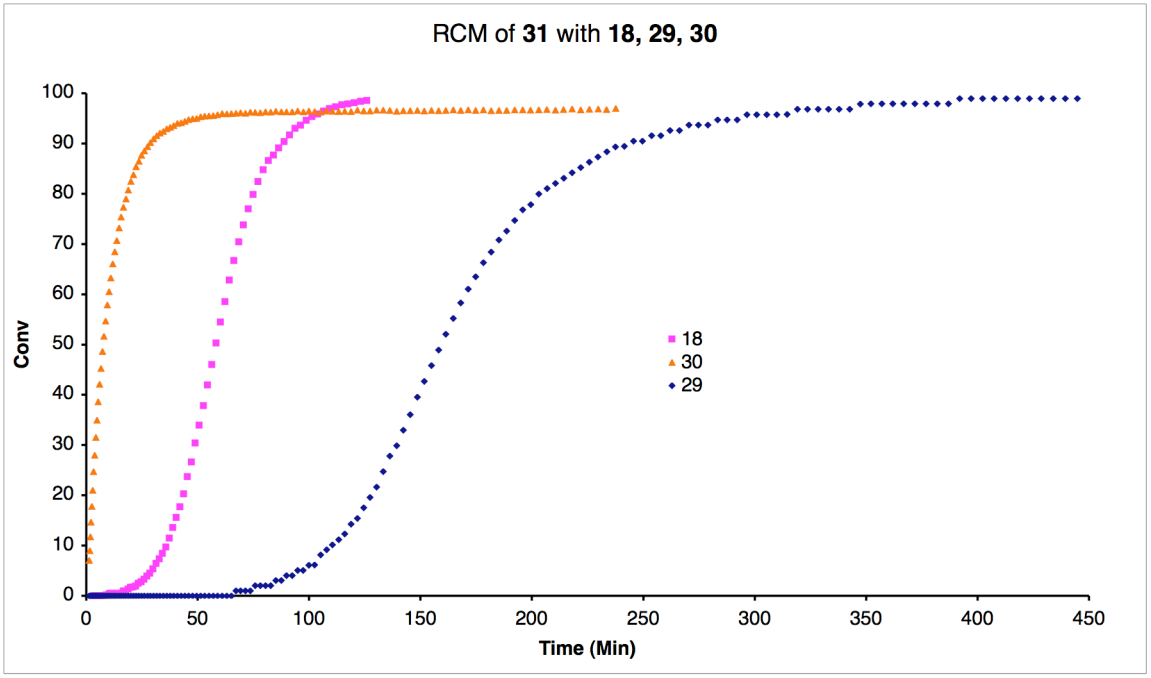


Figure 5.6. Comparison of catalysts **18**, **29**, and **30.**

In both RCM reactions, the same trends were observed. The unsaturated catalyst **29** was slower to initiate and propagate than the saturated catalyst **18** but reached similar final conversion, and the phosphine containing catalyst **30** initiated much faster than either **18** or **29** but decomposed before reaching as high a final conversion. A ligand was sought that would combine the rapid initiation of **30** with the stability of **18** and **29**. It seemed that the presence of phosphine was responsible for the sharp decrease in stability of **30**, likely due to nucleophilic attack on the methylidene. Thus, a catalyst containing a faster initiating chelating ether ligand (**33)** was prepared (Figure 5.7).[11]

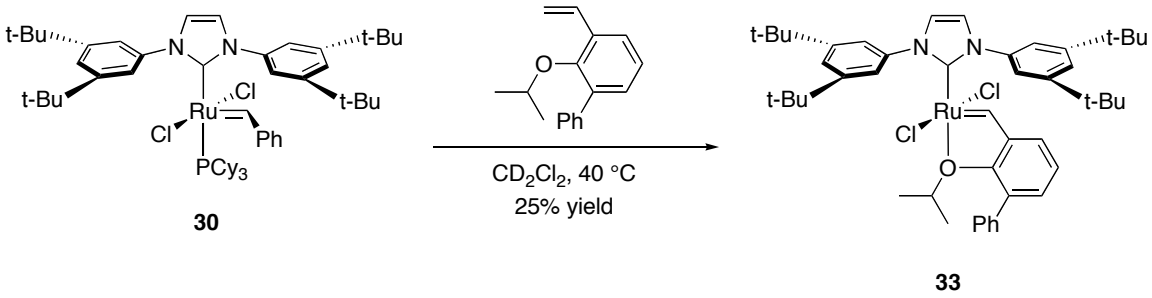
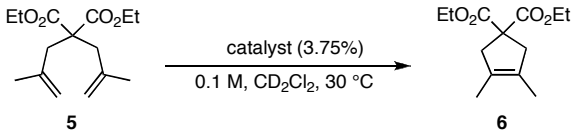
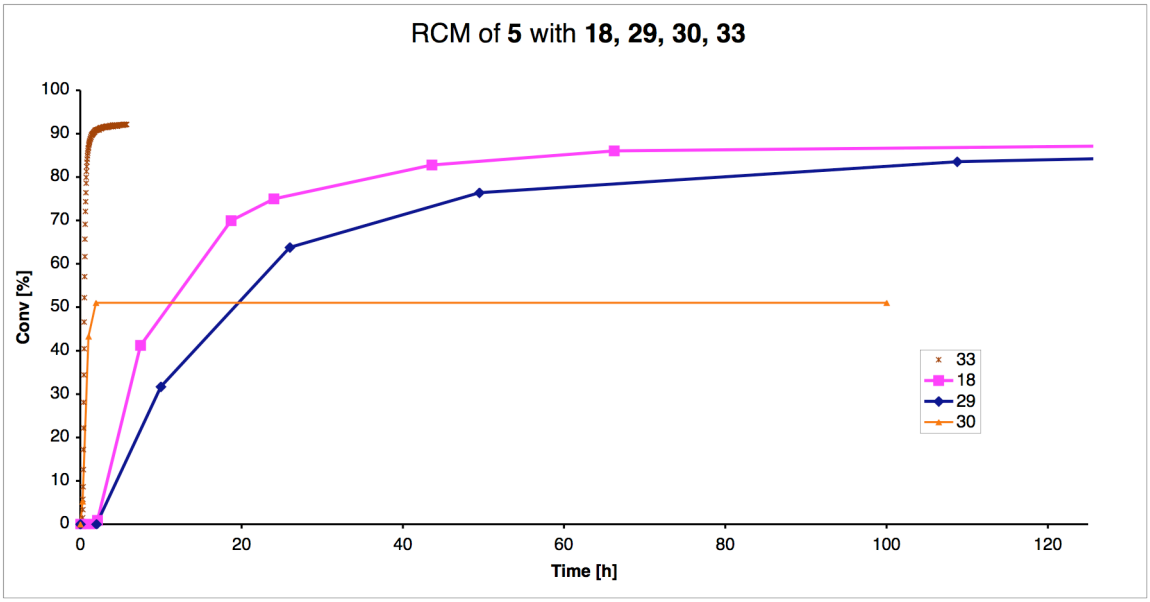


Figure 5.7. Preparation of a fast-initiating yet stable catalyst.

Catalyst **33** was compared against the other catalysts for the RCM reaction of **5** under the same conditions as before (Figure 5.8).



5 6



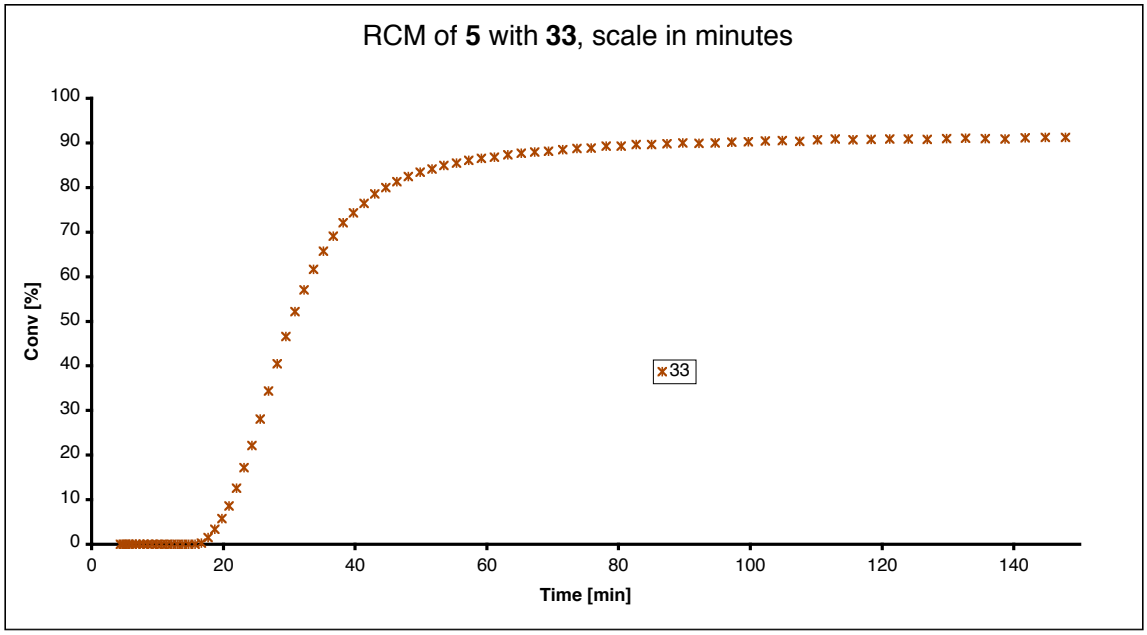


Figure 5.8. RCM of **5** reaches 87% in just one hour with **33**.

Catalyst **33** performs the ring-closing reaction of **5** dramatically faster than any of the other catalysts developed. The initiation is still not optimal, as there is nearly no

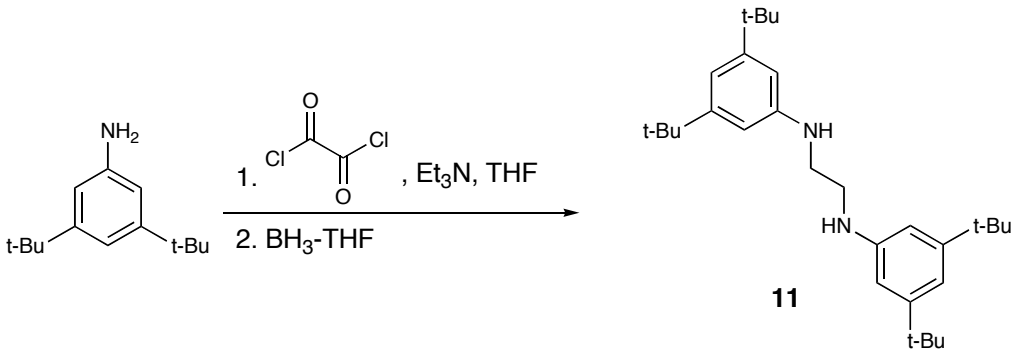
conversion for almost 20 minutes. Nevertheless, a reaction which previously took 24 hours at 60 °C to reach 90% conversion takes only 1 hour to reach 87% conversion at 30 °C with catalyst **33**. This result is extremely exciting and work is ongoing in the Grubbs laboratory and at Materia, Inc. to further explore olefin metathesis of highly hindered olefins.

Experimental

General Information. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from H_3PO_4 for ^{31}P NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stains or UV light. Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh), and flash column chromatography of ruthenium compounds was performed using silica gel 60 (230-400 mesh) from TSI Scientific (Cambridge, MA). All glassware was either oven dried or flame dried, and reactions were done under an atmosphere of argon unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated

alumina. All commercial chemicals were used as obtained. Catalyst precursor **S3** was a gift from Materia, Inc.

Catalyst Synthesis

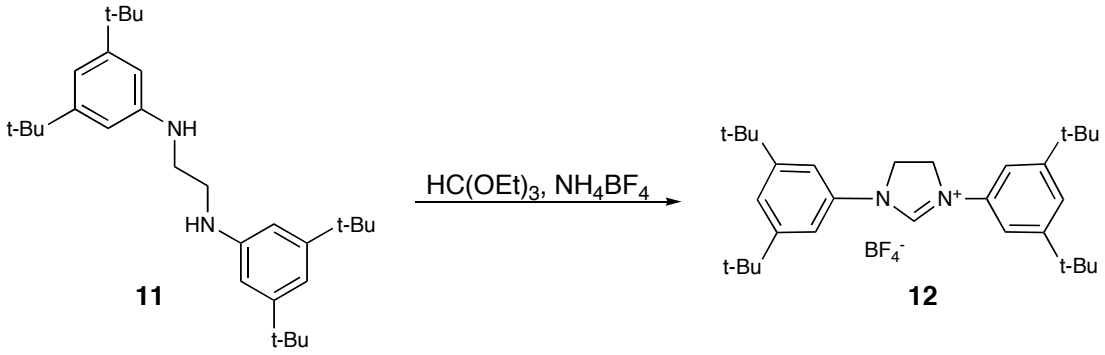


Preparation of diamine S1. This is a two-step procedure.

***N,N'*-Bis(3,5-di-t-butylphenyl) oxamide.** Oxalyl chloride (2.16 mL, 25 mmol) was added dropwise to a stirred solution of 3,5-di-t-butylaniline (10.28 g, 50 mmol) and triethylamine (7.0 mL, 50 mmol) in THF (200 mL) at 0 ºC. Upon addition, the reaction was allowed to warm up to rt and stirred for 1 h. The reaction mixture was then concentrated *in vacuo* and diluted with water (100 mL). The white precipitate was collected by filtration, washed with dilute HCl (100 mL), water (2x100 mL), and dried *in vacuo*. Obtained 9.07 g (78%) of *N,N'*-Bis(3,5-di-t-butylphenyl) oxamide as a white solid.

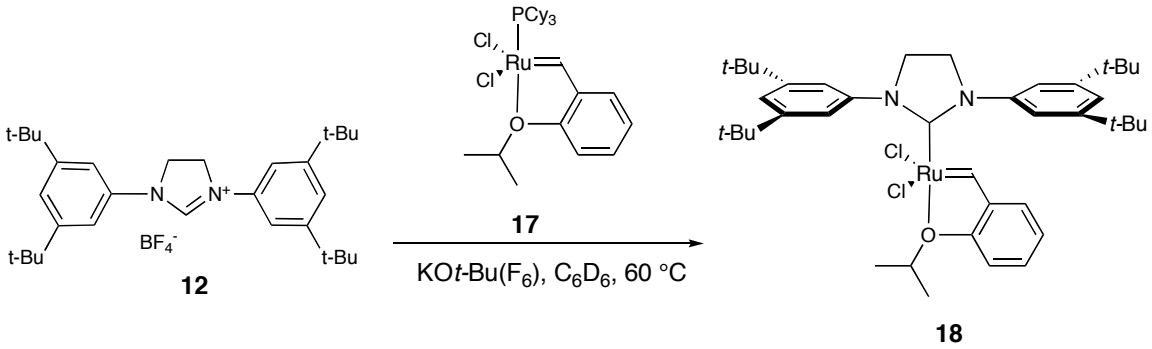
***N,N'*-Bis(3,5-di-t-butylphenyl)ethylenediamine (11).** A 1M solution of BH_3-THF in THF (125 mL, 125 mmol) was added dropwise with stirring to the solid oxamide (9.06 g, 19.52 mmol) at r.t. The resulting homogeneous mixture was then refluxed for 15

h, allowed to cool down to r.t. and carefully quenched by adding water. The mixture was then concentrated and extracted with ether. Column chromatography (2:1 hexanes – dichloromethane, silica gel) afforded 6.51 g (76%) of pure **11** as a colorless oil and 1.27 g of impure **11** (contaminated with 3,5-di-t-butylaniline) which was subjected to a second chromatographic purification. The combined yield of **11** was 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (2H, t, J = 1.5 Hz), 6.55 (4H, d, J = 1.8 Hz), 5.31 (2H, s), 3.45 (4H, s), 1.31 (36H, s); ^{13}C (75 MHz, $CDCl_3$) δ 152.1, 147.8, 112.8, 107.9, 44.1, 35.1, 31.7; HRMS (EI+) calc for $C_{30}H_{49}N_2$, 437.3896. Found 437.3902.



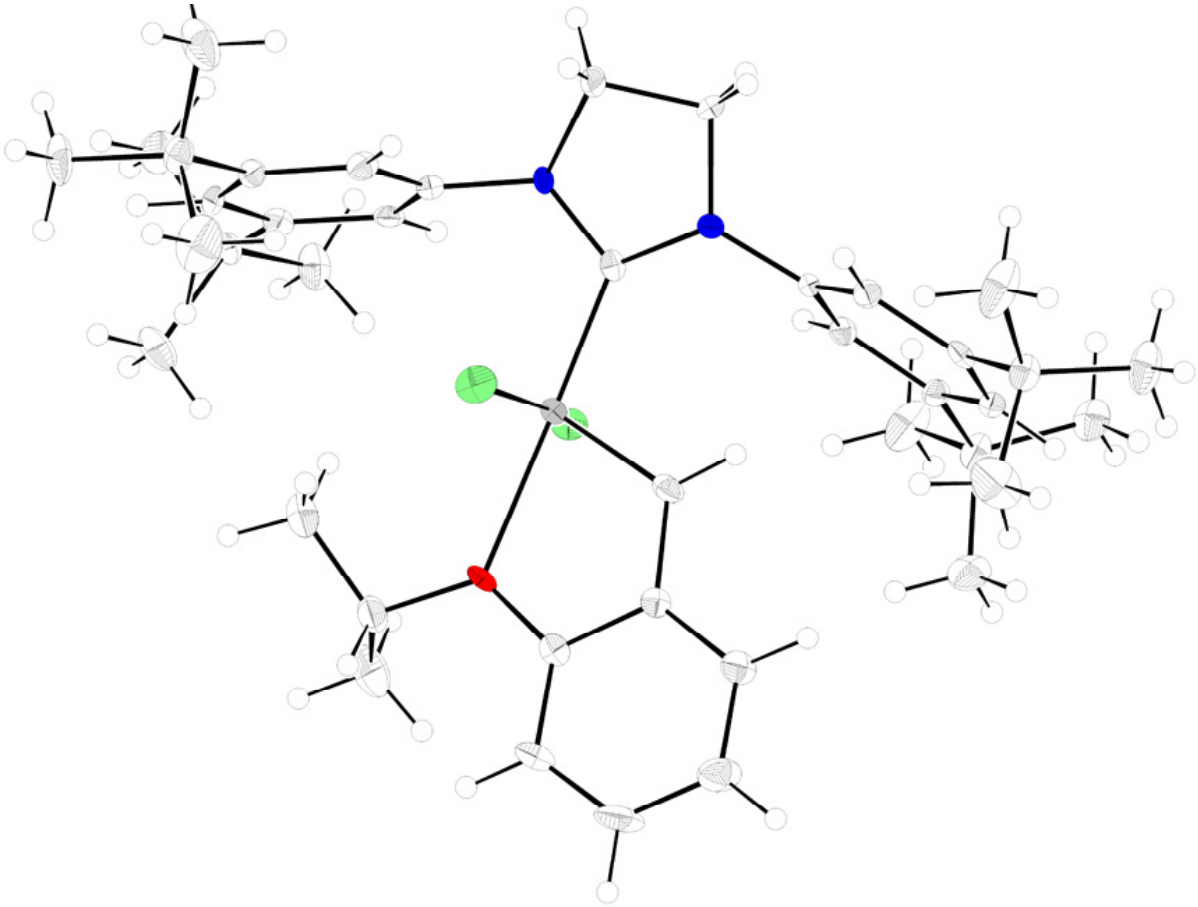
Preparation of diamine salt 12. Triethyl orthoformate (150 mL) was added to a mixture of **11** (6.51 g, 14.93 mmol) and ammonium tetrafluoroborate (1.57 g, 14.93 mmol) in a 250-mL flask. The flask was equipped with a distillation head and heated for about 1 h, during which ethanol distilled over at 78-80 ºC, followed by about 70 mL of triethyl orthoformate at 135-140 ºC. Upon cooling, **12** precipitated as white needles. The precipitate was collected by filtration, washed with hexanes and dried *in vacuo* to afford 7.9 g of **12** (>90%) containing a small amount of triethyl orthoformate in the crystal

lattice. Dissolving this crude product in a minimal amount of dichloromethane and adding diethyl ether afforded pure **12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (1H, s), 7.42 (2H, t, J = 1.5 Hz), 7.23 (4H, d, J = 1.8 Hz), 4.69 (4H, s), 1.32 (36H, s); ^{13}C (75 MHz, $CDCl_3$) δ 153.6, 151.4, 135.4, 123.1, 114.9, 50.5, 35.4, 31.5. HRMS (EI+) calc for $C_{31}H_{47}N_2$, 447.3739, found 447.3729.



Preparation of Catalyst 18

Diamine salt **12** (156 mg, .3 mmol), KO*t*-Bu(F_6) (66 mg, .3 mmol), and ruthenium complex **17** (132 mg, .22 mmol) were all combined in toluene in a glove box. The flask was removed and stirred at 60 °C for 18 hours in a fume hood. The reaction mixture was then directly purified by flash column chromatography (5% Et_2O/Hexanes, run 2 times) to yield catalyst **18** (34 mg, 20%) as a green oil. The catalyst was then lyophilized from benzene to give a pale green solid. It should be noted that by ^{1}H NMR the conversion to **18** is 50%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.91 (1H, s), 8.14-8.13 (2H, m), 7.73 (2H, m), 7.64 (1H, m), 7.52 (1H, m), 7.06-6.92 (2H, m), 6.62 (1H, t, J = 7.5 Hz), 6.31 (1H, d, J = 8.4 Hz), 4.47 (1H, quint, J = 6 Hz), 3.51 (4H, s), 1.51 (18H, s), 1.35 (6H, d, J = 6 Hz), 1.24 (18H, s); HRMS (EI+) calc for $C_{41}H_{58}N_2OCl_2Ru$ 766.2970. Found 766.3007. An X-ray crystal structure has also been obtained for this structure.

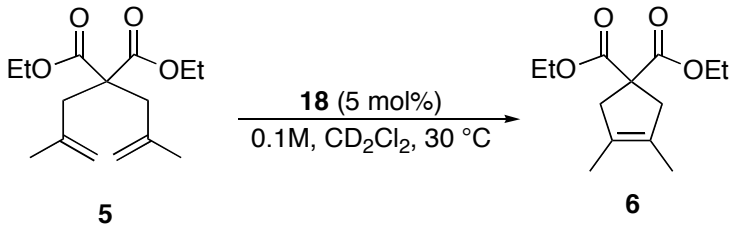


CCDC 622049

Standard activity plots for 18.

Preparation of stock solutions. Catalyst **18** (14 mg) was placed in a 2ml volumetric flask and taken into a glove box. In the glove box, 2ml of CD_2Cl_2 was added to make stock solution **A**. 0.44 ml of **A** was then transferred to another 2ml volumetric flask and diluted to 2ml with CD_2Cl_2 to make stock solution **B**.

Activity studies.



5 **6**

In a glove box, 0.44 ml of stock solution **A** (3.1 mg of **18**, 0.004 mmol) was transferred to a screw cap NMR tube. CD_2Cl_2 (.36 ml) was added and then **5** (21.5 µl, 0.08 mmol). The NMR tube was sealed, removed from the glove box and heated to 30 °C. A graph of conversion over time follows.

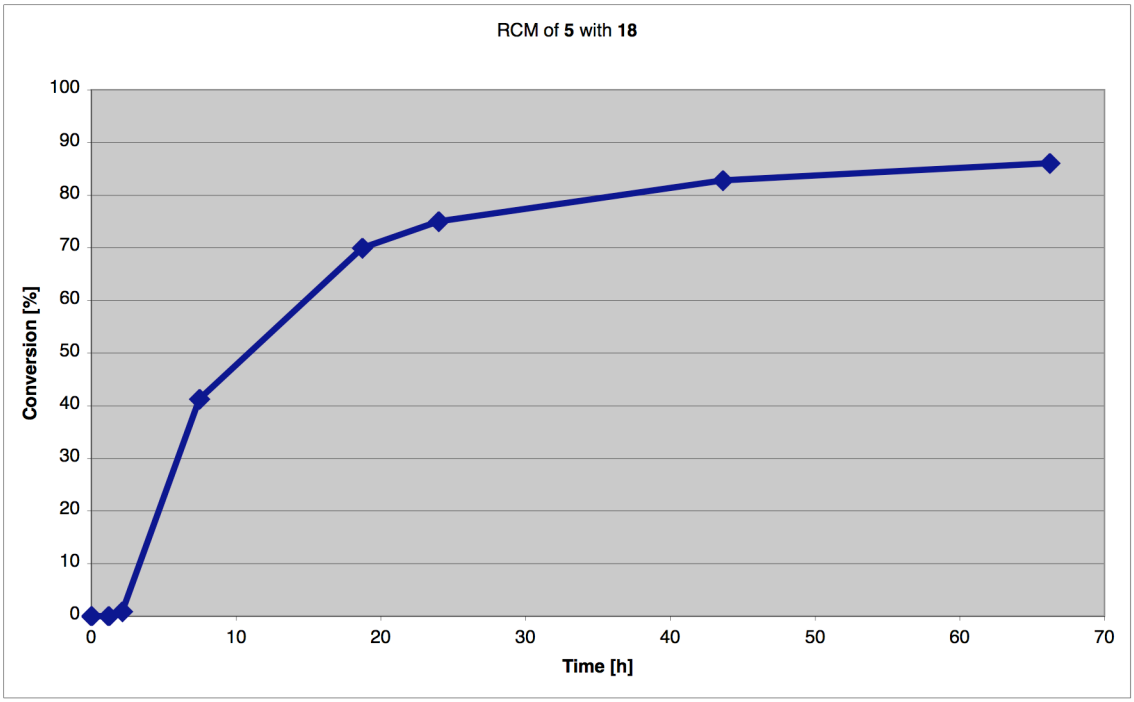
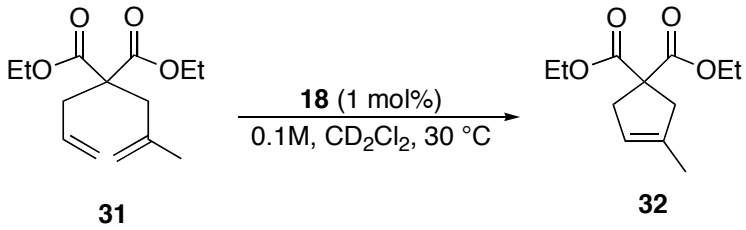


Figure S5.1. RCM to form a tetrasubstituted olefin using **18**.



31 **32**

In a glove box, 0.4 ml of stock solution **B** (0.6 mg of **18**, 0.0008 mmol) was transferred to a screw cap NMR tube. CD_2Cl_2 (.4 ml) was added and the NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **31** (20.5 μl, 0.08 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

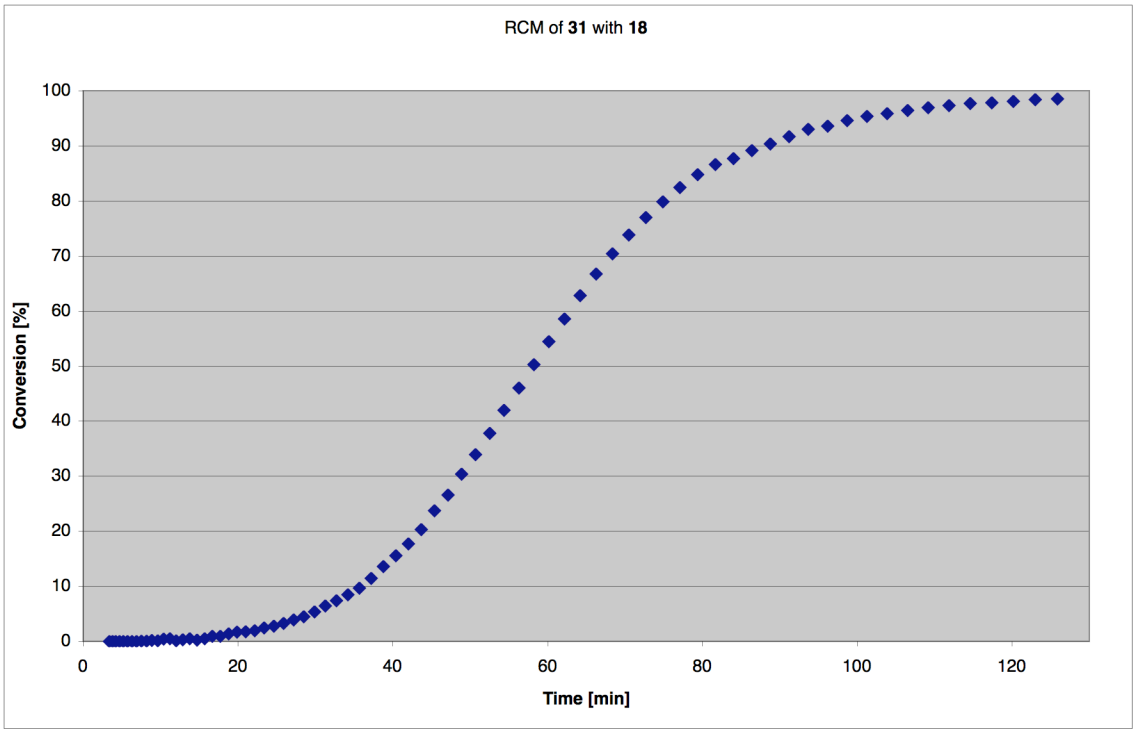
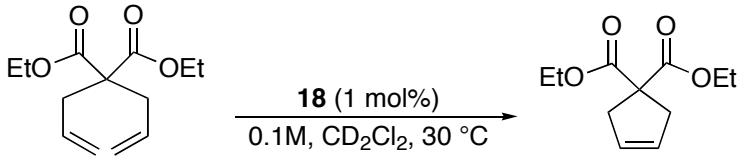


Figure S5.2. RCM to form a trisubstituted olefin using **18**.



S1 **S2**

In a glove box, 0.4 ml of stock solution **B** (0.6 mg of **18**, 0.0008 mmol) was transferred to a screw cap NMR tube. CD_2Cl_2 (.4 ml) was added and the NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **S1** (19.5 µl, 0.08 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

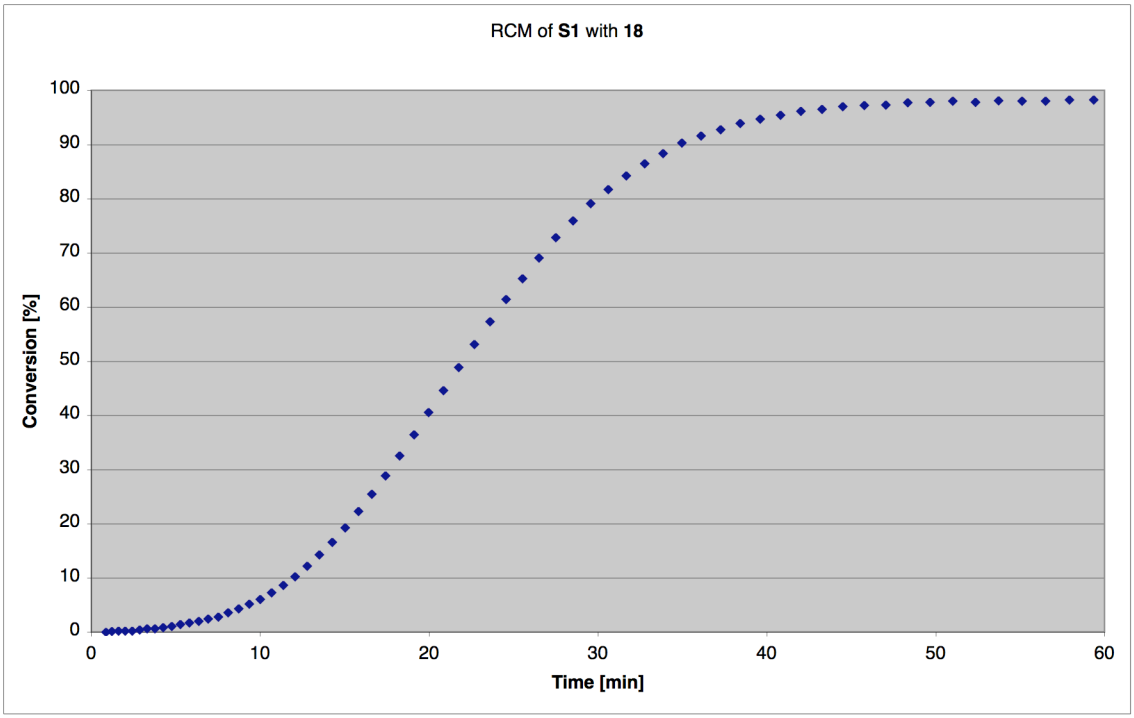
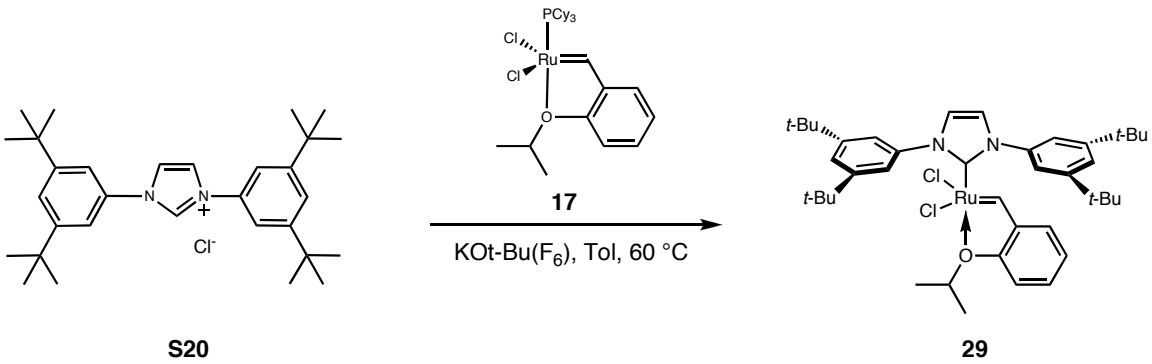


Figure S5.3. RCM to form a disubstituted olefin using **18**.

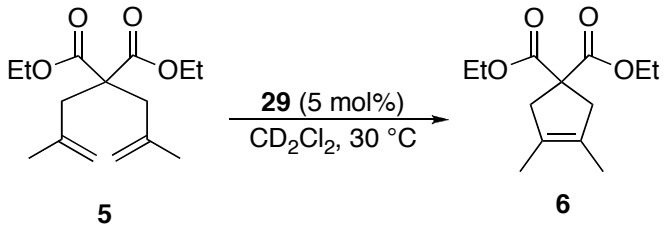


S20 **29**

Ruthenium Catalyst 29. In a glove box, diamine salt **S20** (63 mg, .13 mmol), ruthenium precursor **17** (78 mg, .13 mmol) and KO*t*-Bu(F_6) (29 mg, .13 mmol) were combined in toluene. The flask was sealed, removed from the glove box and stirred at 60 °C for 18 hours. The reaction was concentrated and purified by flash column chromatography (5% --> 20% Et_2O/Pent). There were 3 bands that could be isolated from this column, first 2 brown bands and then one green band. The second brown band was the desired product; however, it was not completely pure after one column. Recolumning in 10% Et_2O/pentane gave a brown oil product completely pure by ^1H NMR (9 mg, 9%) and another fraction still slightly impure (18 mg, 18%). The products were lyophilized from benzene to give solids. ^1H NMR (300 MHz, $CDCl_3$) δ 16.78 (s, 1H), 8.13 (br, 2H), 7.74-7.62 (m, 4H), 7.07-7.04 (m, 1H), 6.97 (dd, J = 3, 1.5 Hz, 1H), 6.66 (t, J = 7.5 Hz, 3H), 6.34 (d, J = 8.4 Hz, 1H), 4.49 (sept, J = 6 Hz, 1H), 1..44 (d, J = 6 Hz, 6H), 1.44 (br, 18H), 1.18 (br, 18H); HRMS (EI+) calc for $C_{41}H_{56}Cl_2N_2ORu$, 764.2814. Found 764.2842.

Activity plots for **29**.

Preparation of stock solutions. Catalyst **29** (9 mg) was placed in a 2ml volumetric flask and taken into a glove box. In the glove box, 2ml of CD_2Cl_2 was added to make stock solution **A**. 0.33 ml of **A** was then transferred to another 2ml volumetric flask and diluted to 2ml with CD_2Cl_2 to make stock solution **B**.



5 **6**

In a glove box, 0.67 ml of stock solution **A** (3 mg of **29**, 0.004 mmol) was transferred to a screw cap NMR tube. CD_2Cl_2 (.13 ml) was added and then **5** (21.5 µl, 0.08 mmol). The NMR tube was sealed, removed from the glove box and heated to 30 °C. A graph of conversion over time follows.

RCM of **5** with **29** at 30 °C

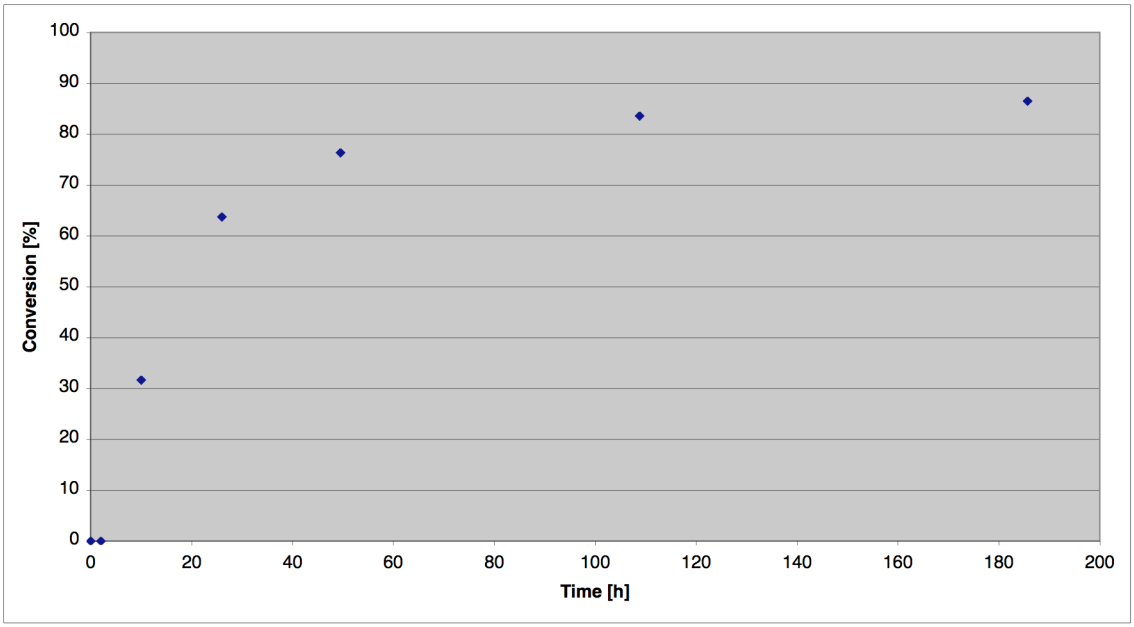


Figure S5.4. RCM to form a tetrasubstituted olefin using **29**.

This experiment was repeated in C_6D_6 at 60 °C to examine the impact of temperature. Catalyst **29** (3 mg, 0.004 mmol) and C_6D_6 (.8 ml) were combined in a screw cap NMR tube and **5** (21.5 µl, 0.08 mmol) was added. The NMR tube was sealed, removed from the glove box and heated to 60 °C. A graph of conversion over time follows.

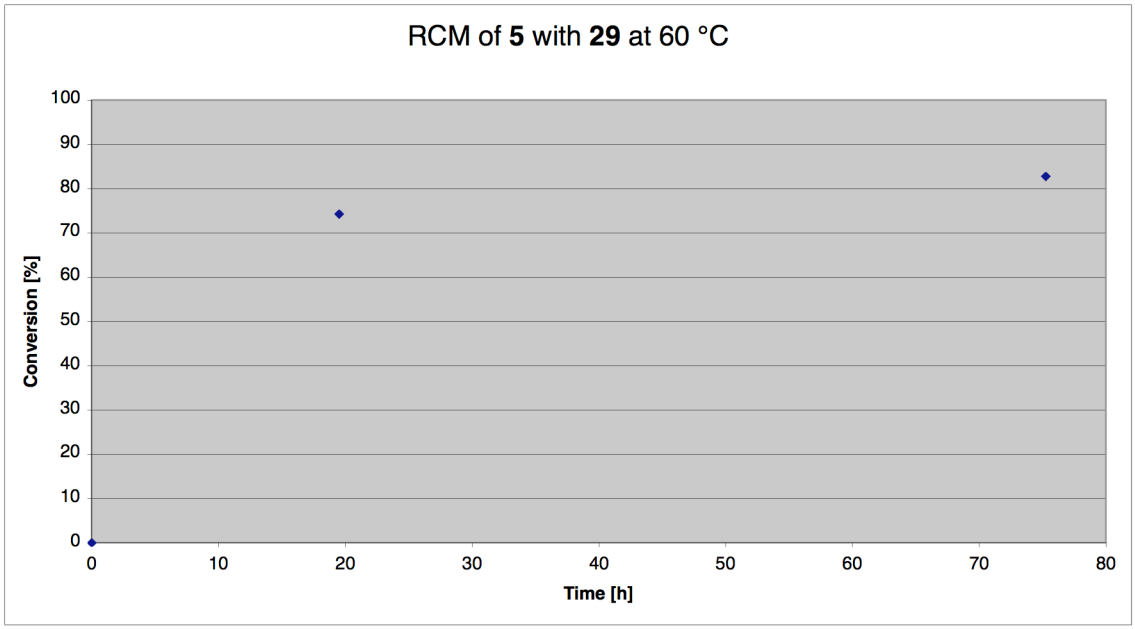
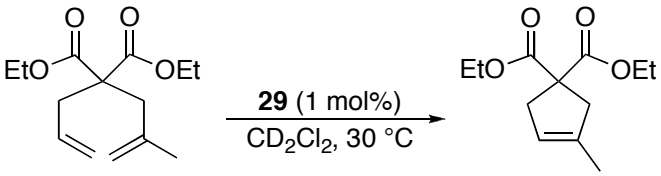


Figure S5.5. RCM to form a tetrasubstituted olefin using **29** at 60 °C.



31 **32**

In a glove box, 0.8 ml of stock solution **B** (0.6 mg of **29**, 0.0008 mmol) was transferred to a screw cap NMR tube. The NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **31** (20.5 μl, 0.08 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

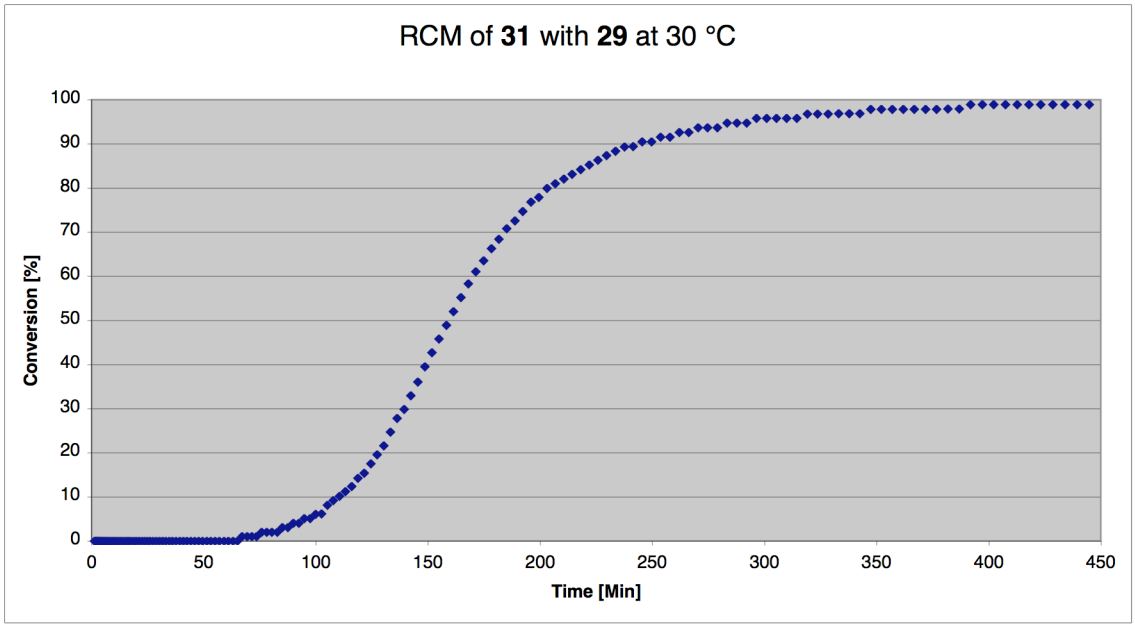
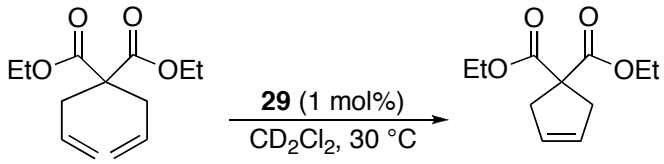


Figure S5.6. RCM to form a trisubstituted olefin using **29**.



S1 **S2**

In a glove box, 0.8 ml of stock solution **B** (0.6 mg of **29**, 0.0008 mmol) was transferred to a screw cap NMR tube. The NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **S1** (19.5 µl, 0.08 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

RCM of **S1** with **29** at 30 °C

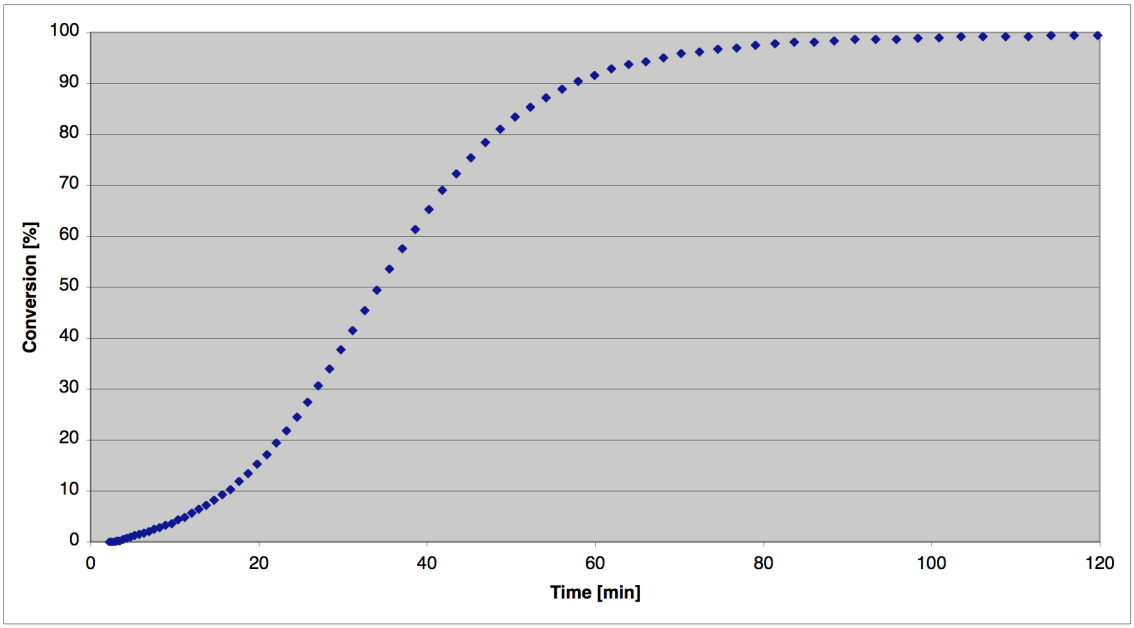
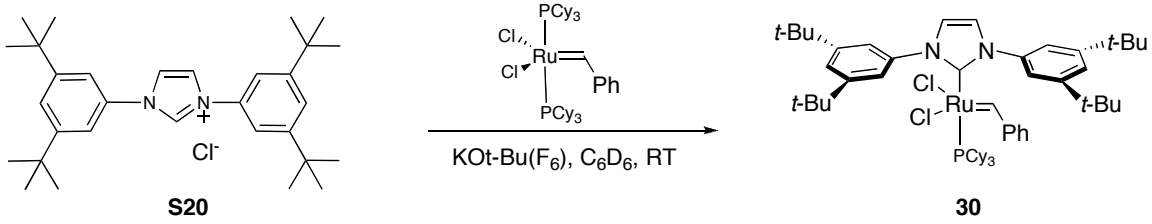


Figure S5.7. RCM to form a disubstituted olefin using **29**.



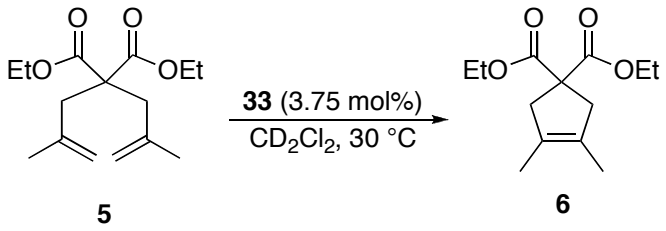
S20 **30**

Ruthenium Catalyst 30. In a glove box, diamine salt **S20** (162 mg, .34 mmol), ruthenium precursor $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (150 mg, .27 mmol) and KO*t*-Bu(F_6) (74 mg, .34 mmol) were combined in C_6D_6 and stirred at RT for 2.5 hours. The flask was sealed, removed from the glove box and the reaction was concentrated and purified by flash column chromatography (2.5% --> 5% Et_2O/Pent) to yield a brown oil. The brown oil was lyophilized from benzene to give a brown solid (66 mg, 25%). ^{1}H NMR (300

MHz, $CDCl_3$) δ 20.07 (d, J = 10.5 Hz, 1H), 8.03 (br, 2H), 7.60 (t, 1.8 Hz, 1H), 6.86-6.81 (m, 2H), 6.51 - 6.47 (m, 1H), 1.81 - 1.07 (m).

Standard activity plots for **30**.

Preparation of stock solutions. Catalyst **30** (11 mg) was placed in a 2ml volumetric flask and taken into a glove box. In the glove box, 2ml of CD_2Cl_2 was added to make stock solution **A**. 0.4 ml of **A** was then transferred to another 2ml volumetric flask and diluted to 2ml with CD_2Cl_2 to make stock solution **B**.



5 **6**

In a glove box, 0.55 ml of stock solution **A** (3 mg of **30**, 0.003 mmol) was transferred to a screw cap NMR tube. CD_2Cl_2 (.25 ml) was added and then **5** (21.5 μl, 0.08 mmol). The NMR tube was sealed, removed from the glove box and heated to 30 °C. A graph of conversion over time follows. No further conversion is observed after 2 hours.

RCM of **5** with **33** at 30 °C

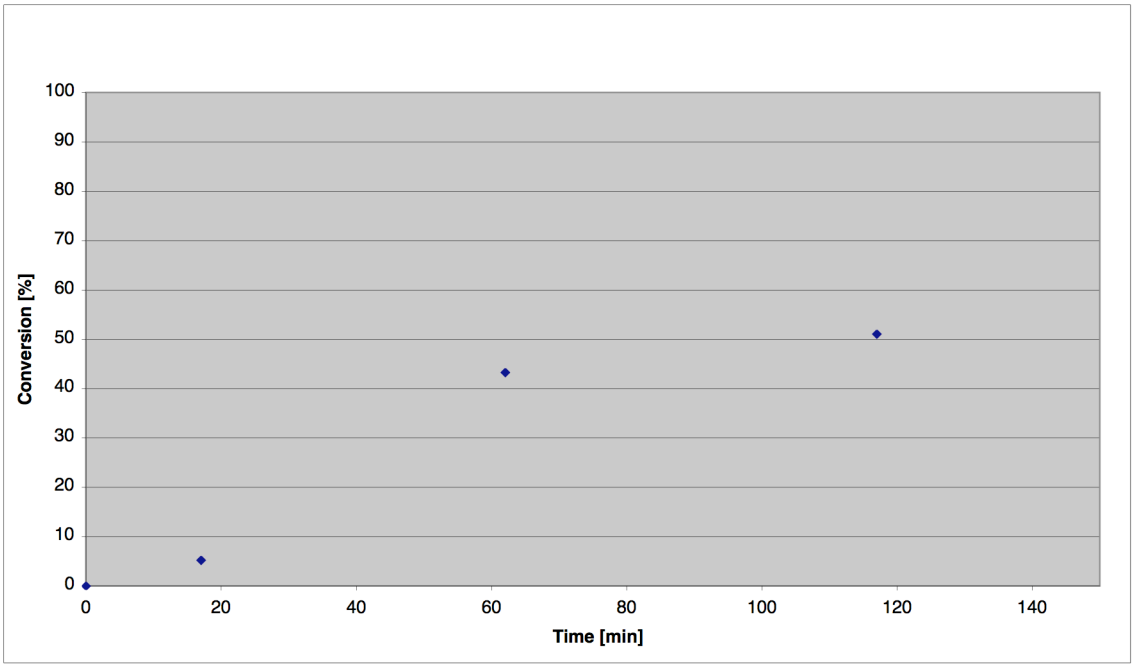


Figure S5.8. RCM to form a tetrasubstituted olefin using **30**.

This experiment was repeated in C_6D_6 at 60 °C to examine the impact of temperature. Catalyst **30** (3 mg, 0.003 mmol) and C_6D_6 (.8 ml) were combined in a screw cap NMR tube. The NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 60 °C. The NMR tube was then ejected, **5** (21.5 µl, 0.08 mmol) was added and the

tube was injected for data collection. A graph of conversion over time follows.

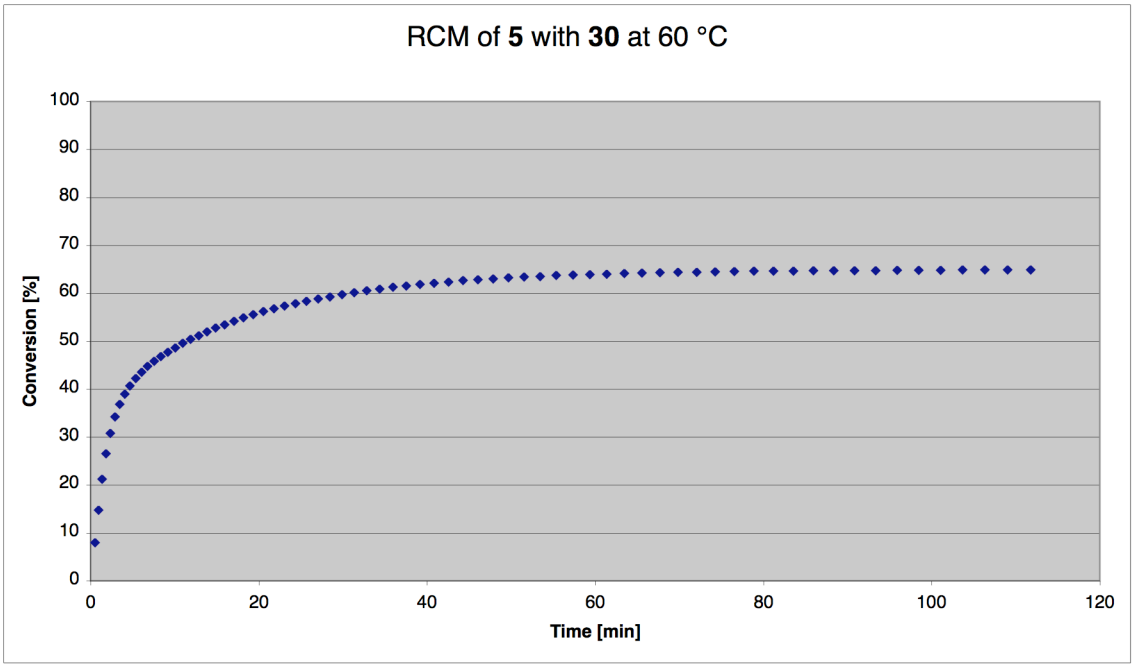
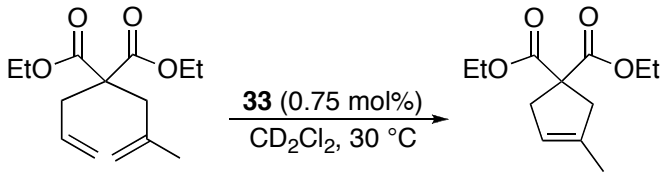


Figure S5.9. RCM to form a tetrasubstituted olefin using **30** at 60 °C.



31 **32**

In a glove box, 0.55 ml of stock solution **B** (0.6 mg of **30**, 0.0008 mmol) was transferred to a screw cap NMR tube and 0.25 ml of CD_2Cl_2 was added. The NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **31** (20.5 µl, 0.08 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

RCM of **31** with **30** at 30 °C

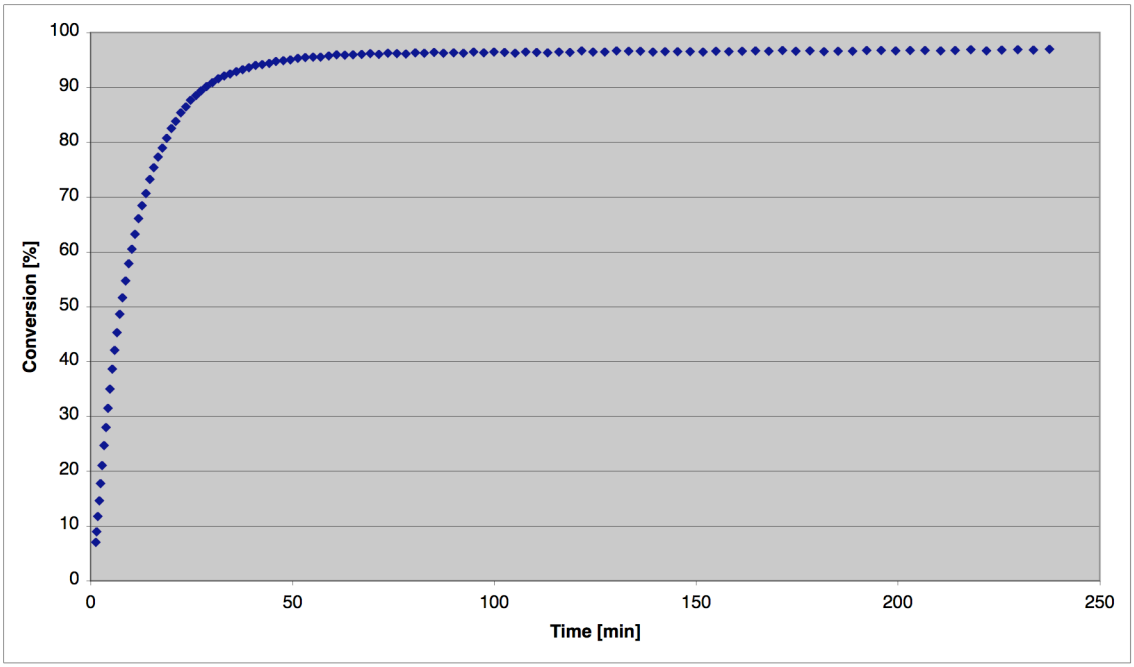
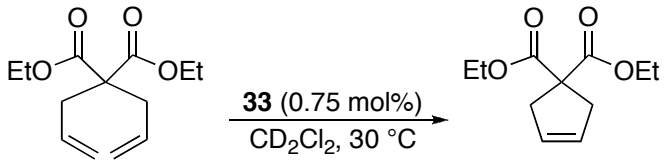


Figure S5.10. RCM to form a trisubstituted olefin using **30**.



S1 **S2**

In a glove box, 0.55 ml of stock solution **B** (0.6 mg of **21**, 0.0008 mmol) was transferred to a screw cap NMR tube and 0.25 ml of CD_2Cl_2 was added. The NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **S3** (19.5 μl, 0.08 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

RCM of **S1** with **30** at 30 °C

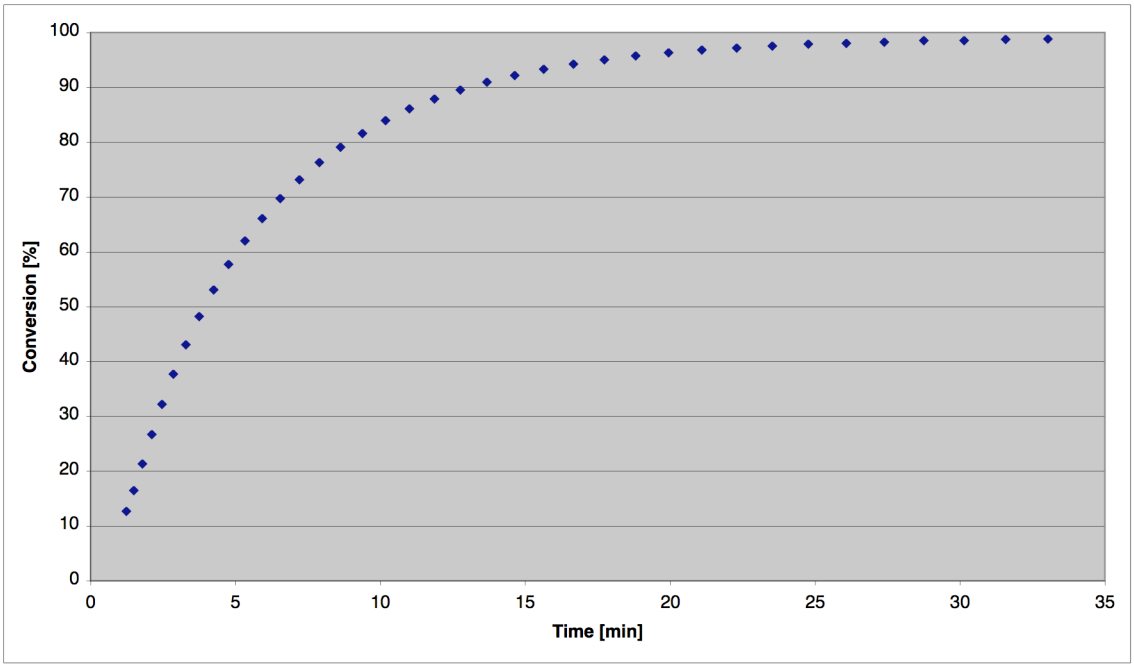
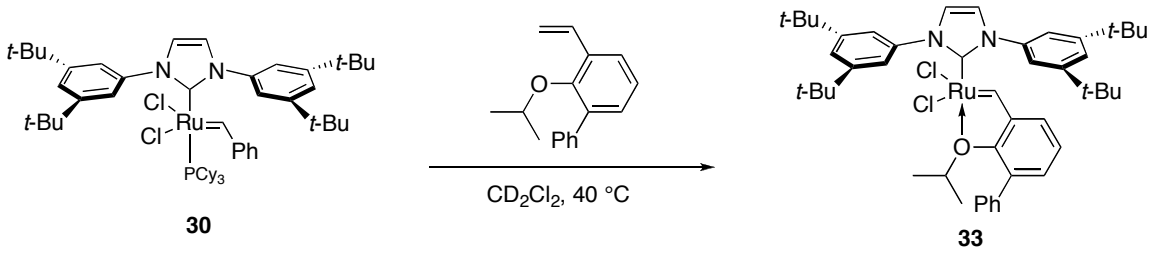


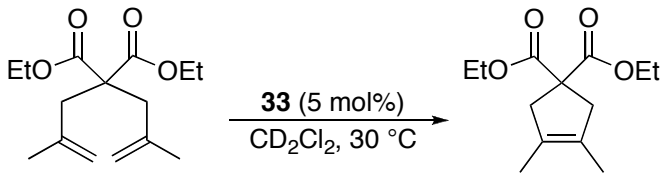
Figure S5.11. RCM to form a disubstituted olefin using **30**.



Ruthenium Catalyst 33. In a screw cap NMR tube, ruthenium compound **33** (10 mg, .01 mmol), 2-isopropoxy-3-vinylbiphenyl (5 mg, .02 mmol) and CuCl (1 mg, .01 mmol) were combined in CD_2Cl_2 (1 ml) in the glove box. The reaction was heated at 40 °C for 29 hours, concentrated and purified by column chromatography (10% --> 25% Et_2O/Pentange) to yield a grayish green oil. This oil was lyophilized from benzene to yield a solid (2 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.77 (s, 1H), 7.89 (s, 1H), 7.66 - 7.59 (m, 6H), 7.50 - 7.38 (m, 7H), 7.02 (t, J = 4.5 Hz, 1H), 6.72 (dd, J = 3.6, 1.2

Hz, 1H), 4.45 (sept, J = 3.6 Hz, 1H), 1.47 (s, 18H), 1.30 (s, 18H), 0.95 (d, J = 3.6 Hz, 6H).

Activity plot for **33**.



5 **6**

In a glove box, catalyst **22** (2 mg, .002 mmol) was combined with CD_2Cl_2 (.4 ml) in a screw cap NMR tube. The NMR tube was sealed and transferred to a 500 MHz NMR which was warmed to 30 °C. The NMR tube was then ejected, **5** (11 µl, 0.04 mmol) was added and the tube was injected for data collection. A graph of conversion over time follows.

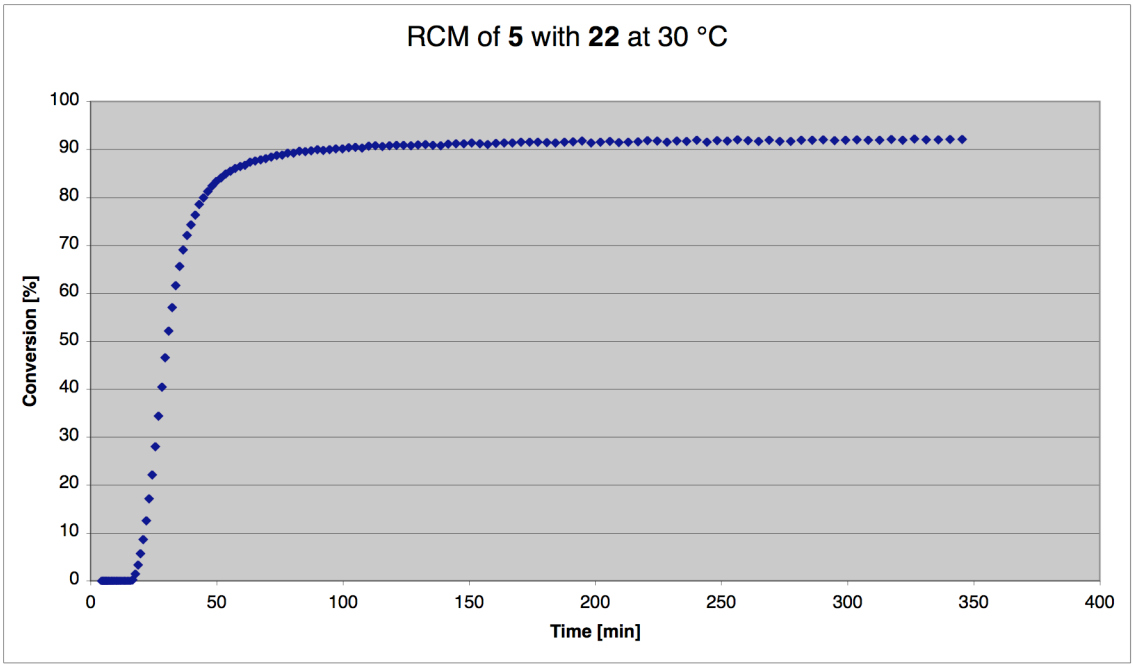
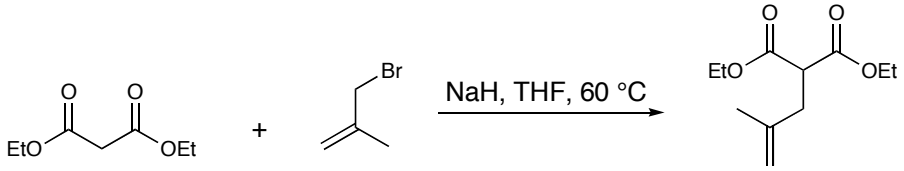


Figure S5.12. RCM to form a tetrasubstituted olefin using **33**.

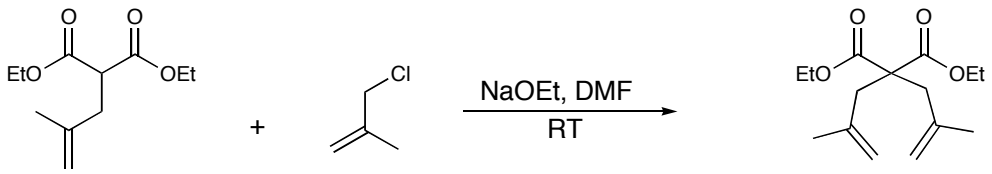
Synthesis of RCM Substrates



S3 **S4** **S5**

Preparation of Diethyl methallylmalonate S5.

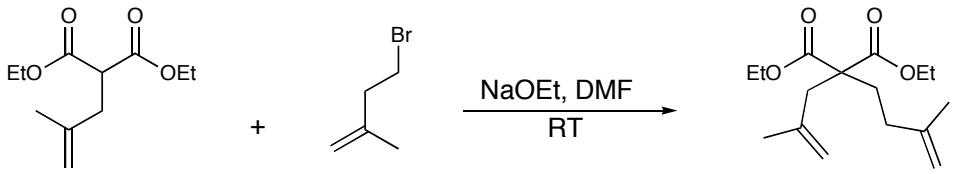
Diethyl methallylmalonate is a known compound: Begley, M. J.; Housden, N.; Johns, A.; Murphy, J. A. *Tetrahedron* **1991**, *47*, 8417, but we report our synthesis for convenience. NaH (238 mg, 9.9 mmol) was suspended in THF (10 ml) and diethyl malonate (1.5 ml, 9.9 mmol) was added dropwise with vigorous bubbling observed. 3-bromo-2-methyl-propene (1 ml, 9.9 mmol) was added dropwise and the reaction was stirred at 60 °C for 24 hours. The reaction was cooled to RT and quenched with water. A copious amount of Et_2O was added and the water layer was removed. The organic fraction was dried with $MgSO_4$, concentrated and purified by column chromatography (10% EtOAc/Hex) to yield 1.481g (70 %) of diethyl methallylmalonate (**S5**). ^{1}H NMR (300 MHz, C_6D_6) δ 4.75 (d, J = 18 Hz, 2H), 4.19 (q, J = 6.9 Hz, 4H), 3.57 (t, J = 7.8 Hz), 2.61 (d, J = 7.8 Hz, 2H), 1.74 (s, 3H), 1.26 (t, J = 7.2 Hz, 6H).



S5 **S6** **5**

Preparation of Substrate 5.

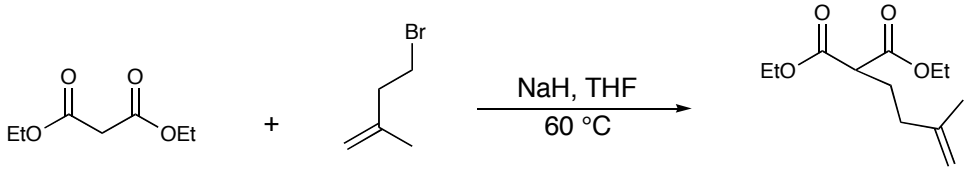
Substrate **5** was prepared from diethyl methallylmalonate (**S5**) as it has been prepared previously in our group: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62,* 7310.



S5 **S7** **21**

Preparation of Substrate 14.

Substrate **14** was prepared from diethyl methallylmalonate (**S10**) as it has been prepared previously in our group: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62,* 7310.

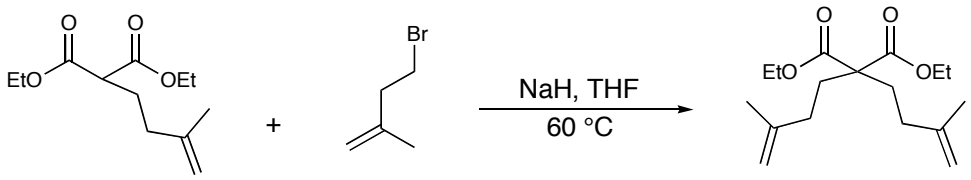


S3 **S8** **S9**

Preparation of Diethyl 2-(3-methylbut-3-enyl)malonate S9.

NaH (523 mg, 21.8 mmol) was suspended in THF (10ml) and diethyl malonate (1.5 ml, 9.9 mmol) was added dropwise with vigorous bubbling observed. The reaction was heated to 60 °C and 4-bromo-2-methyl-1-butene[12] (2.33 ml, 21.8 mmol) was added dropwise. The reaction was stirred for 20 hours, cooled to RT, quenched with water and copious Et_2O was added. The organic layer was separated, dried with $MgSO_4$, concentrated and purified by column chromatography (5% EtOAc/Hex) to yield 715 mg (32%) of **S9.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, J = 18 Hz, 2H), 4.19 (q, J = 7.2 Hz,

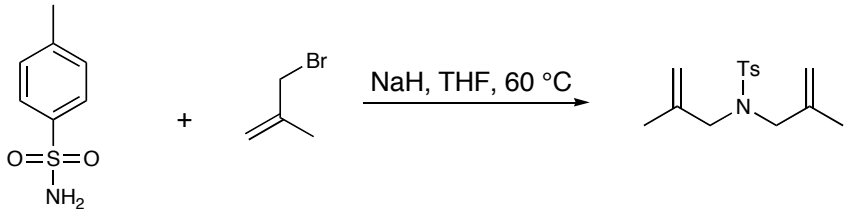
4H), 3.36-3.30 (m, 1H), 2.05-2.04 (m, 4H), 1.72 (s, 3H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 169.7, 144.3, 11.4, 61.6, 51.6, 35.5, 26.9, 22.4, 14.3.



S9 **S8** **22**

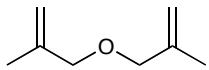
Preparation of substrate 22.

NaH (82 mg, 3.4 mmol) was suspended in THF (5 ml) and **22** (715 mg, 3.1 mmol) was added dropwise. The reaction was heated to 60 °C and vigorous bubbling was observed. 4-bromo-2-methyl-1-butene[1] (336 μl, 3.1 mmol) was added dropwise. The reaction was stirred for 20 hours, cooled to rt, quenched with water and copious Et_2O was added. The organic layer was separated, dried with $MgSO_4$, concentrated and purified by column chromatography (5% EtOAc/Hex) to yield 412 mg (45%) of **22.** ^{1}H NMR (300 MHz, C_6D_6) δ 4.76 (d, J = 19.8, 4H), 3.93 (q, J = 7.2 Hz, 4H), 2.33-2.29 (m, 4H), 2.07-2.02 (m, 4H), 1.59 (s, 6H), 0.87 (t, J = 6.9 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 171.3, 144.9, 110.7, 60.9, 57.4, 32.6, 31.2, 22.4, 14.0. HRMS (EI+) calc for $C_{17}H_{29}O_4$, 297.2066, found 297.2069.



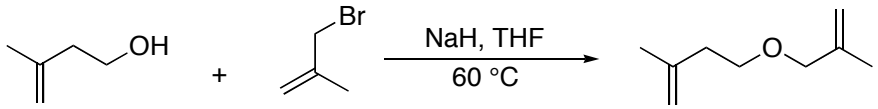
S10 **S4** **23**

Preparation of 23. NaH (1.39 g, 58 mmol) was suspended in THF (130 ml) at 0 °C and p-toluenesulfonamide (**23**) (5 g, 29 mmol) was added in THF (10 ml). The reaction was warmed to rt and heated to 60 °C, whereupon the reaction started to foam vigorously. The reaction was cooled to rt and stirred for 15 minutes. 3-bromo-2-methylpropene (8.8 ml, 87 mmol) was added in THF (10 ml) and the reaction was heated to 60 °C again. The reaction stirred for 24 hours and was then quenched with water. The organic layer was removed, dried over $MgSO_4$, concentrated, and purified by column chromatography (20% EtOAc/Hex) to yield 2 g (25 %) of diene **23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1, 2H), 4.81 (d, J = 24.6 Hz, 4H), 3.70 (s, 4H), 2.42 (s, 3H), 1.60 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 143.3, 140.3, 137.7, 129.7, 127.5, 114.8, 53.3, 21.8, 20.2. HRMS (EI+) calc for $C_{15}H_{22}NO_2S$, 280.1371, found 280.1373.



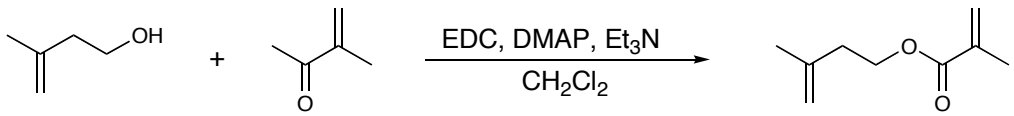
24

Diene **24** was purchased from "Monomer and Polymer, and Dajac Labs" and used as received.



S11 **S4** **25**

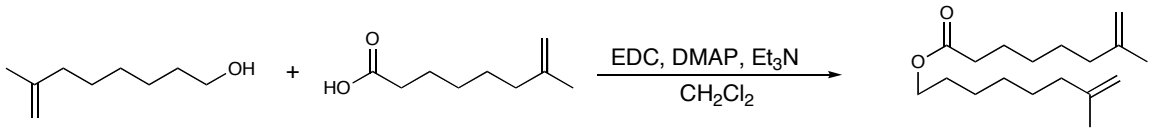
Preparation of 25. NaH (264 mg, 11 mmol) was suspended in THF (10 ml) at 0 °C and 3-methylbut-3-en-1-ol (**S11**) (1.11 ml, 11 mmol) was added dropwise. The solution bubbled and turned yellow. The solution was heated to 60 °C and 3-bromo-2-methylpropene (1ml, 9.9 mmol) was added. The reaction was stirred for 48 hours, cooled to rt and quenched with water. The reaction was extracted 4x with Et_2O and the combined organic fractions were dried with $MgSO_4$, concentrated and purified by column chromatography (5% Et_2O/Pent). The column fractions were concentrated to **25** using a rotovap with an ice bath. This gave 1.22 g (88%) of diene **25**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (d, J = 21.9, 2H), 4.75 (d, J = 12.9, 2H), 3.88 (s, 2H), 3.51 (t, J = 6.9 Hz, 2H), 2.31 (t, J = 6.9 Hz, 2H), 1.74 (d, J = 6 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 143.2, 142.6, 112.2, 11.7, 75.1, 68.7, 38.1, 22.9, 19.7; HRMS (EI+) calc for $C_9H_{16}O$, 140.1201, found 140.1199.



S11 **S12** **26**

Preparation of 26. 3-methyl-3-buten-1-ol (853 mg, 9.9 mmol), methacrylic acid (853 mg, 9.9 mmol) and DMAP (120 mg, .99 mmol) were dissolved in CH_2Cl_2, the solution was cooled to 0 °C, flushed with argon, and EDC (1.898 mg, 9.9 mmol) was added. Then Et_3N (2.67 ml, 19.8 mmol) was added and the reaction was stirred for 24 hours. Precipitates were observed and 50 ml of Et_2O was added. The solution was washed with water, 1N HCl, water and brine, dried over $MgSO_4$, concentrated and purified by column

chromatography (10% EtOAc/Hex) to yield 703 mg (46%) of substrate **26**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09-6.08 (m, 1H), 5.54-5.53 (m, 1H), 4.80 (s, 1H), 4.74 (s, 1H), 4.25 (t, J = 6.6 Hz, 2H), 2.37 (t, J = 6.6 Hz, 2H), 1.92 (s, 3H), 1.76 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 146.9, 142.0, 136.6, 125.6, 112.5, 63.1, 36.9, 22.7, 18.5; HRMS (EI+) calc for $C_9H_{14}O_2$, 154.0994, found 154.0994.



S13 **S14** **27**

Preparation of 27. Primary alcohol **S13**[13] (747 mg, 4.78 mmol), carboxylic acid **S14** (747 mg, 4.78 mmol) and DMAP (58 mg, .478 mmol) were dissolved in CH_2Cl_2, the solution was cooled to 0 °C, flushed with argon, and EDC (916 mg, 4.78 mmol) was added. Then Et_3N (1.3 ml, 9.6 mmol) was added and the reaction was stirred for 24 hours. Precipitates were observed and 50 ml of Et_2O was added. The solution was washed with water, 1N HCl, water and brine, dried over $MgSO_4$, concentrated and purified by column chromatography (5% EtOAc/Hex) to yield 1.115 g (83%) of substrate **27**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (d, J = 8.7 Hz, 4H), 4.05 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.00 (t, J = 7.8 Hz, 2H), 1.70 (s, 6H), 1.68-1.28 (m, 14H); ^{13}C (75 MHz, $CDCl_3$) δ 148.0, 146.3, 146.2, 131.9, 110.0, 109.9, 64.6, 37.9, 37.8, 34.6, 29.1, 29.0, 28.8, 27.7, 27.4, 26.1, 25.1, 22.6; HRMS (EI+) calc for $C_{18}H_{32}O_2$, 280.2402, found 280.2390.

RCM with 3, 18, 20.

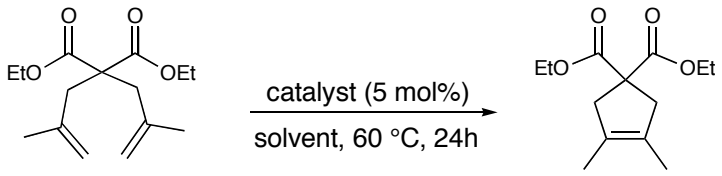
Standard RCM Procedure for Table 5.1.

For conversions: Catalyst **3** (12.5 mg, .02 mmol) or catalyst **18** (15 mg, .02 mmol) was weighed into a 2 ml volumetric flask that was taken into the glove box. C_6D_6 (2 ml) was added and then 0.4 ml of the solution (.004 mmol of catalyst) was transferred to a screw cap NMR tube. The solution in the NMR tube was diluted with 0.4 ml of C_6D_6 and the tube was sealed with a screw cap that had a built in septa. The NMR tube was removed from the glove box, the substrated (.08 mmol) was injected and the tube was heated to 60 °C in an oil bath. After 24 hours, the tube was removed and an NMR was taken to determine conversion.

Conversions for catalyst **20** were obtained using a slightly different procedure because **20** is insoluble in benzene. Instead, catalyst **20** (18.5 mg, .03 mmol) was dissolved in $CDCl_3$ (5.92 ml) and then 0.8 ml of the solution (.004 mmol of catalyst) was transferred to a screw cap NMR tube, which was sealed with a screw cap that had a built in septa. The NMR tube was removed from the glove box, the substrated (.08 mmol) was injected and the tube was heated to 60 °C in an oil bath. After 24 hours, the tube was removed and an NMR was taken to determine conversion.

For isolated yields: Catalyst **18** (7 mg, .009 mmol) was weighed into a 1 dram vial. A stirbar was added and the vial was taken into the glove box where C_6D_6 (1.8 ml) was

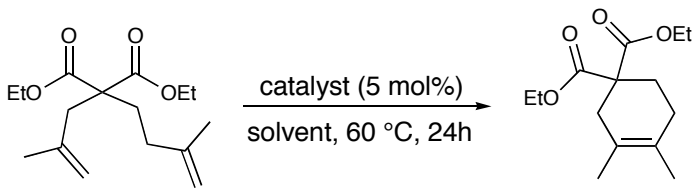
added. The vial was sealed with a screw cap that had a built in septa and removed from the box. The substrate (0.185 mmol) was injected and the vial was heated to 60 °C in an oil bath. After 24 hours, the solution was concentrated and the product was purified by column chromatography.



5 **6**

For conversion: The SM methylene signal at 2.99 ppm was compared to the product signal at 3.14 ppm.

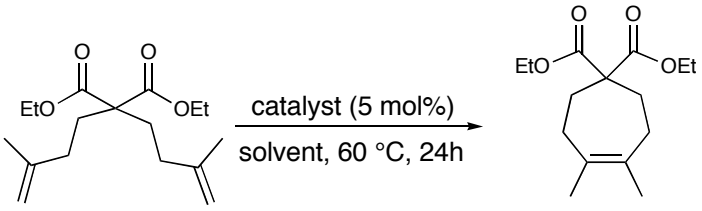
For isolated yield: 50 μl of **5** was used. The rxn was columned in 5% EtOAc/Hex to yield 38.5 mg (86 %). Product **6** is a known compound and our spectral data matches the published data: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62,* 7310.



21 **S15**

For conversion: The SM methylene signal at 2.72 ppm was compared to the product signal at 2.63 ppm.

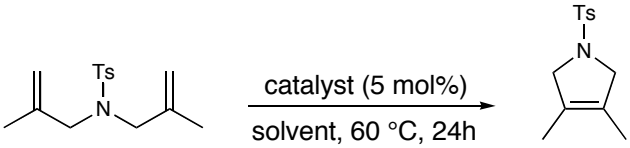
For isolated yield: 52 μl of **21** was used. The reaction was columned in 5% EtOAc/Hex to yield **S15** quantitatively. Product **S15** is a known compound and our spectral data matches the published data: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62,* 7310.



22 **S16**

For conversion: The SM methyl group signal at 1.59 ppm was compared to the product signal at 1.50 ppm.

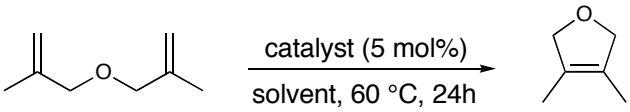
For isolated yield: 55 μl of **22** was used. The rxn was columned in 5% EtOAc/Hex to yield 23 mg (47 %). Product **S16** is a known compound and our spectral data matches the published data: Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.



23 **S17**

For conversion: The SM methyl group signal at 3.62 ppm was compared to the product signal at 3.84 ppm.

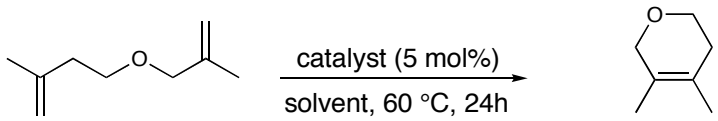
For isolated yield: 52 μl of **23** was used. The reaction was columned in 25% EtOAc/Hex to yield **S17** quantitatively. Product **S17** is a known compound and our spectral data matches the published data: Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255.



24 **S18**

For conversion: The SM methylene signal at 3.68 ppm was compared to the product signal at 4.45 ppm.

For isolated yield: Product **S18** was not isolated due to its high volatility. Product **S18** is a known compound and our spectral data matches the published data: Ripoll, J.-L. *Tetrahedron Lett*. **1974**, *15,* 1665. A ^{1}H NMR is reported here for convenience: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 4H), 1.23 (s, 6H).



25 **S19**

For conversion: The SM methylene signal at 3.51 ppm was compared to the product signal at 3.76 ppm. The impurity has a signal at 4.26 ppm.

For isolated yield: An isolated yield was not obtained for **S19** due to its high volatility. A sample was isolated by column chromatography (5% Et_2O/Hex) but the solvent could not be fully removed for the ^{1}H NMR so the methyl groups could not be rigorously identified. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 2H), 3.76 (t, J = 6 Hz, 2H), 2.01 (s, 2H).

[1] (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (b) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416. (c) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (d) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236.

[2] (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (b) Clavier, H.; Audic, N.; Guillemin, J.-C.; Mauduit, M. *J. Organomet. Chem.* **2005**, *690*, 3585. (c) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236. (d) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318. (e) Fürstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000. (f) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (g) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Hermann, W. A. *Tet. Lett.* **1999**, *40,* 4787. (h) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tet. Lett.* **1999**, *40*, 2247. (i) Jafarpour, L.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 4075. (j) Louie, J.; Grubbs, R. H.

Angew. Chem., Int. Ed. **2001**, *40*, 247. (k) Yao, Q. *Org. Lett.* **2002**, *4*, 427. (l) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126,* 74. (m) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517. (n) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875. (o) Yao, Q.; Motta, A. R. *Tet. Lett.* **2004**, *45*, 2447.

[3] Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. *Organometallics*, **2006**, *25*, 5740.

[4] (a) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (b) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591.

[5] (a) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546-2558.

[6] Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

[7] This synthesis has been improved by Alexandre Pletnev at Materia, Inc. The improved synthesis makes use of oxalyl chloride and is presented in the experimental section.

[8] Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11768.

[9] In reference 2f, it was reported that **26** could be ring-closed in 43% yield using the variant of **3** where the NHC is unsaturated. Despite efforts to reproduce this result under identical conditions to those reported, I never observed any conversion at all.

[10] Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

[11] Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

[12] Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763.

[13] Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673.