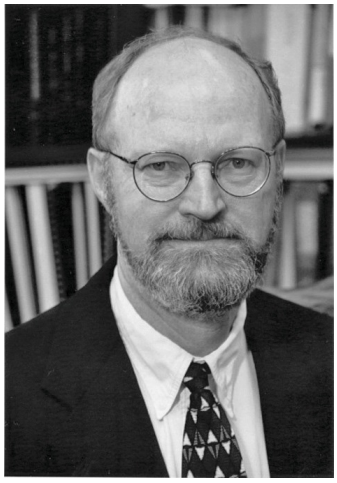
Mechanistic Studies of Enantioselective *N*-aryl, *N*-alkyl NHC Ruthenium Metathesis Catalysts in Asymmetric Ring-Opening Cross-Metathesis

Renee M. Thomas and Robert H. Grubbs*

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA (e-mail: *rhg@caltech.edu*)

About the Author



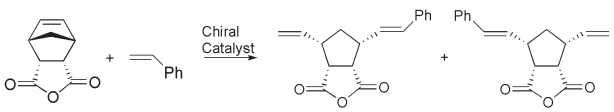
Robert (Bob) H. Grubbs was born in Marshall County Kentucky on February 27, 1942 and gained his high school education at Paducah Tilghman. His BS and MS degrees are from the University of Florida where he worked with the late Prof. Merle Battiste on cyclopropene rearrangements. He transferred to Columbia University for PhD study, which he gained under the direction of Ronald Breslow in 1968. He spent a postdoctoral year with James Collman at Stanford University from where he was appointed to the faculty of Michigan State University. Some nine years later, in 1978, he moved to California Institute of Technology and has remained there since; currently he is the Victor and Elizabeth Atkins Professor of Chemistry.

He was advised that he had been awarded the 2005 Nobel Prize in Chemistry (with Schrock and Chauvin) late on October 5, after having returned to Christchurch (where he was an Erskine Fellow at the University of Canterbury) from giving a lecture at Victoria University in Wellington. His main interests are in catalytic organometallic and synthetic chemistry, where he is especially noted for the olefin metathesis catalysts named after him and for ring-opening metathesis polymerization with cyclic olefins such as norbornene. He also contributed to the development of so-called *living polymerization*.

His numerous awards include an Alfred P. Sloan Fellowship, a Camille and Henry Dreyfus Teacher-Scholar Award, an Alexander von Humboldt Fellowship, the ACS's Benjamin Franklin Medal, Herman F. Mark Polymer Chemistry Award, Herbert C. Brown Award, and Tolman Medal. He was elected to the National Academy of Sciences in 1989 and a Fellowship in the American Academy of Arts and Sciences in 1994. Last year he participated in the US Science and Engineering Festival Lunch and met middle and high school students in an informal conversation with a Nobel Prize winning Scientist over a brown bag lunch.

Introduction

Olefin metathesis is used widely for the construction of carbon-carbon double bonds and has extensive applications in organic and polymer synthesis,[1] as well as materials chemistry.[2] Asymmetric metathesis provides an attractive methodology for synthesizing enantiopure molecules, and significant efforts have been directed toward the development of enantioselective catalysts.[3] *Asymmetric ring-opening cross-metathesis* (AROCM) (Scheme 1) has been employed as the key step in several total syntheses, affording the desired product in excellent enantiomeric excess (ee).[4,5] Applications of AROCM have also been pursued in the synthesis of biologically relevant molecules.[6] Imparting chirality from the catalyst to the substrate is challenging, and has been the focus of catalyst design for this purpose.[7]



Scheme 1. Asymmetric Ring-Opening Metathesis.

Early studies in AROCM focused on molybdenum-based metathesis catalysts, which displayed good selectivity for the reaction of substituted norbornenes with styrene.[8] The enantioselectivities of the molybdenum complexes were substrate dependent, but generally high (>80% ee).[9,10] While AROCM usually yields *E*-olefin products, sterically hindered stereogenic-at-molybdenum catalysts were shown to give excellent *Z*-selectivity, currently unique selectivity to molybdenum catalysts.[11] Ruthenium catalysts were explored owing to their stability to air and moisture, a feature that enables them to be easily handled.[12] Comparison studies showed chiral ruthenium complexes to be comparable, and sometimes superior, to chiral molybdenum catalysts in their enantioselectivity, and the preferred metal was found to be dependent on the particular reaction and substrate.[13]

Chirality has been built into ruthenium complexes primarily in the *N*-heterocyclic carbene (NHC) backbone (see **1**, Fig. 1).[14] Hoveyda and coworkers improved the enantioselectivity of ruthenium catalysts through the synthesis of an *N*-binaphthol NHC with the hydroxyl group chelating to the ruthenium metal (**2**, Fig. 1); however, the catalytic

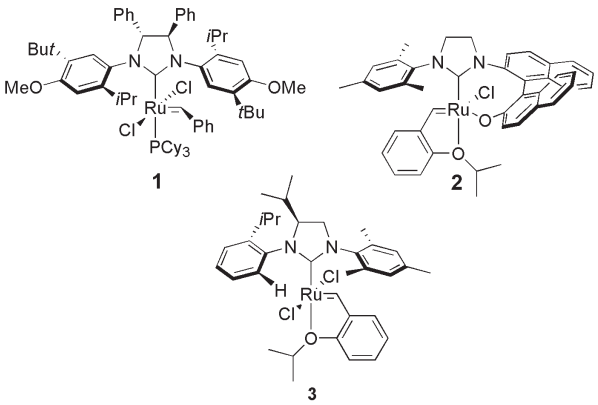
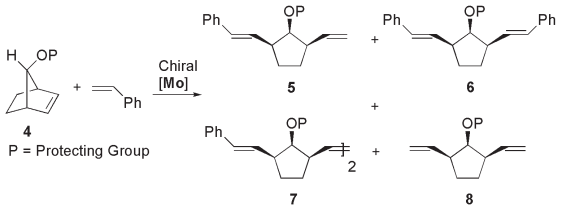


Fig. 1. Ruthenium catalysts reported in AROCM.

activity was decreased.[15,16] The enhanced selectivity of this complex is likely due to the closer proximity of the chiral ligand to the reaction centre, where it can impart a stronger influence on the stereochemistry of the transition state. Recently, Blechert and coworkers reported the synthesis of a chiral mono-substituted NHC backbone that achieved high enantioselectivity while maintaining activity during AROCM of various functionalized norbornenes (**3**, Fig. 1).[17] The NHC backbone substituent, an isopropyl group, was proposed to induce the *N*-aryl ring to twist, creating the desired chiral environment. This is analogous to the mechanism by which the chiral diphenyl NHC backbone catalysts, such as **1**, are believed to impart chirality.[14]



Scheme 2. Side products of AROCM catalyzed by molybdenum complexes.

To the best of our knowledge, there are no detailed investigations of any side products produced during AROCM catalyzed by ruthenium complexes. Schrock and coworkers have disclosed a discussion of possible side products, including the observation of such products, albeit in low yield, for molybdenum catalysts (Scheme 2).[8,9] In addition to product **5**, molybdenum catalysts were noted to give ring-opened products **6** and **8**, as well as homometathesis product **7** in some cases. The authors detail the mechanism leading to the desired **5** and undesired products (**6** and **8**), which has significance for ultimate enantioselectivity, as well as providing information regarding the propagating metal species (alkylidene *vs* methylidene).[9] Product **8** requires ring-opening by a methylidene species. After ring-opening of **4** by a molybdenum methylidene moiety, the styrene cross-partner can react to form either a 2,3- or 2,4-metallacycle to give the major product **5** or product **8**, respectively. However, it is noted that, presuming the catalyst methylidene species has the same facial selectivity as the catalyst alkylidene species, the cross-metathesis reaction with styrene and the methylidene-opened substrate will lead to the opposite enantiomer from that provided by ring-opening with the alkylidene species.[9] This information is valuable for gaining insight into catalyst behaviour, including preference for alkylidene *vs* methylidene propagation and formation of a 2,4- *vs* 2,3-metallacycle. These catalyst attributes are essential to its applications in metathesis reactions.

Herein, we discuss mechanistic studies of chiral *N*-aryl, *N*-alkyl NHC ruthenium catalysts in AROCM. The formation of AROCM side products resulting from metathesis reactions of propagating ruthenium methylidene species was observed. The reaction pathways are discussed, as well as the enantioselectivity of the chiral *N*-aryl, *N*-alkyl NHC complexes studied. Some of the complexes investigated appeared to exhibit unusual preference for methylidene propagation compared to standard second generation ruthenium catalysts. Evidence suggests that these *N*-aryl, *N*-alkyl NHC ruthenium catalysts proceed through both a 2,4-metallacycle and a 2,3-metallacycle during AROCM, accounting for the observed product ratios and distribution. This catalyst behaviour has significant implications for catalyst design and targeted application, as methylidene propagation and metallacycle orientation directly determine product outcome, and can be utilized accordingly.

Results and Discussion

We designed ruthenium catalysts bearing an *N*-aryl, chiral *N*-alkyl NHC, with the goal of bringing ligand chirality in close proximity to the metal centre for increased enantioselectivity during asymmetric metathesis reactions. Since *N*-alkyl, *N*-alkyl NHC ruthenium catalysts are reported to be less active than *N*-aryl, *N*-aryl NHC catalysts,[18] we chose to synthesize *N*-aryl, *N*-alkyl catalysts to ideally maintain good activity while achieving better selectivity.[19] NHC salts **9**-**14** (Fig. 2) were synthesized in an analogous procedure to that outlined by Kotschy and coworkers.[20] The NHC salts were subsequently metallated as previously reported in the literature to give complexes **15**-**20** (Fig. 2).[21]

Complex **15** was initially screened for AROCM, since we anticipated that the large differential in the steric demands of the substituents at the chiral carbon (naphthyl *vs* methyl *vs* H) would provide for a highly enantioselective reaction. Substrate *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**21**) was reacted with 10 equivalents of styrene to yield product **A** in 69% ee over its enantiomer **B** (Scheme 3) after 2 hours at room temperature (99% conversion). Interestingly, side products **C** and **D** were also observed as 17 and 10% of the product mixture, respectively. Therefore, subsequent experiments were directed toward elucidating the pathway to the formation of these two side products. No polymer or homometathesis product was observed in the reaction mixture, although stilbene was formed from the cross-metathesis of styrene. The products all had *trans* stereochemistry, with no detectable *cis* isomers.

Formation of product **C** could result from the cross-metathesis reaction proceeding *via* a 2,3-metallacycle, and/or by secondary metathesis of products **A** and **B** with styrene. Breakdown of the 2,3-metallacycle to yield product **C** generates a ruthenium methylidene species, whereas reaction *via* a 2,4-metallacycle to afford the major products **A** and **B** gives a ruthenium alkylidene species (Scheme 4). Secondary metathesis of products **A** and **B** with styrene, reacting *via* a 2,3-metallacycle, also generates a ruthenium methylidene species (Scheme 5). Accordingly, formation

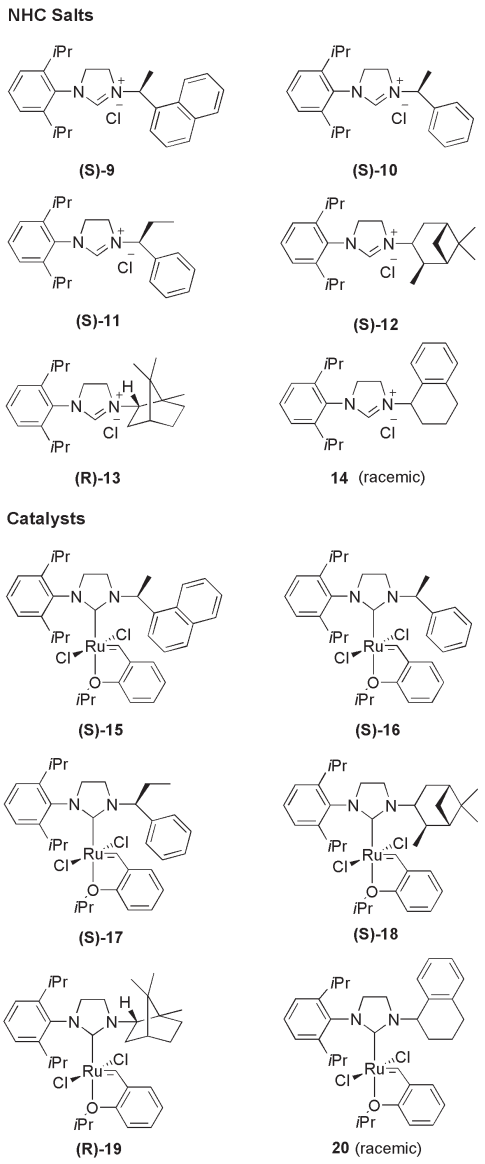
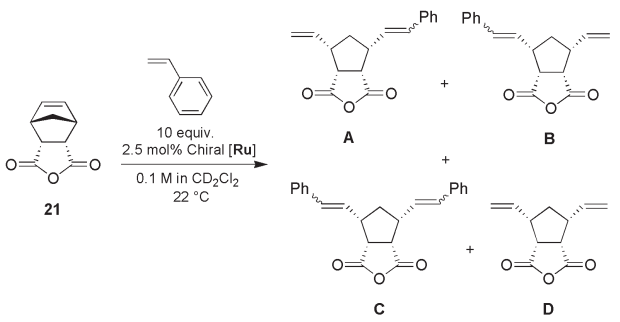


Fig. 2. NHC salts and catalysts synthesized.

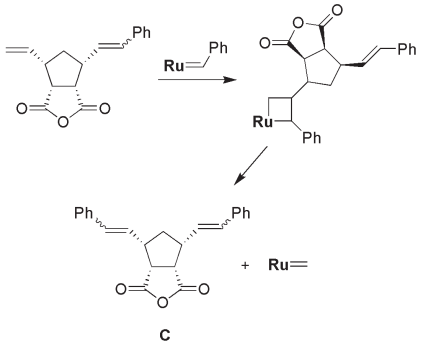
of product **C** results in production of a ruthenium methylidene species, regardless of which pathway is taken.

Reaction kinetics can be used to determine the likely pathway through which the catalyst proceeds to generate product **C**. If formation of product **C** is solely the result of secondary metathesis, then the ratio of product **C** relative to products **A** and **B** would be expected to depend on



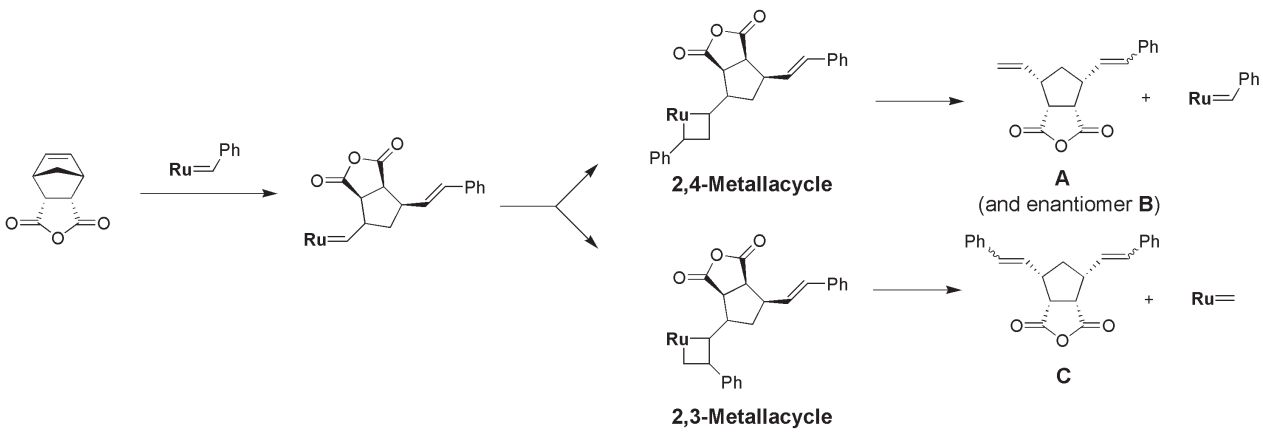
Scheme 3. AROCM catalyzed by ruthenium complexes: observation of side products.

conversion. This would be an indication of the production of **C** depending on the concentration of **A** and **B** in the reaction. With increasing concentration of **A** and **B** (through conversion of substrate), the relative amount of **C** would be expected to increase. Thus, a graph of the ratio of **C** relative to **A** and **B** as a function of conversion should have an upward slope if secondary metathesis were the primary mechanism. However, if formation of **C** were the result of the catalyst proceeding through a 2,3-metallacycle, then the ratio of **C** relative to **A** and **B** would be expected to be constant, reflecting the inherent preference of the catalyst for a 2,4-metallacycle *vs* a 2,3-metallacycle. Thus, plotted as a function of conversion, the ratio of product **C** relative to products **A** and **B** should be a horizontal line.

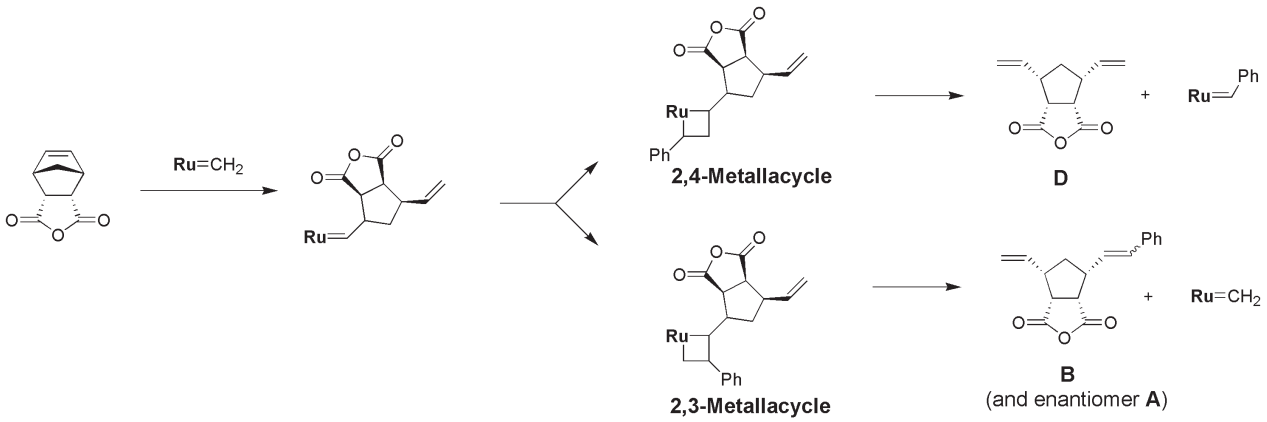


Scheme 5. Mechanism for the formation of product C via secondary metathesis.

Accessing product **D** requires ring-opening of **21** by a ruthenium methylidene species to generate the first terminal olefin, followed by reaction with styrene through a 2,4-metallacycle to give the second terminal olefin (Scheme 6). Product **D** could be formed by the ethenolysis of products **A** and **B**, although this mechanism of forma-



Scheme 4. Mechanism for the formation of product C via a 2,3-metallacycle.



Scheme 6. Formation of product D: ring-opening of 21 via a ruthenium methylidene species.

tion is highly unlikely, considering the low concentration of ethylene in solution. If product **D** were made by the ethenolysis of **A** and **B**, then the ratio of **D** relative to products **A** and **B** would be expected to be dependent on the concentration of ethylene in solution. If the ratio of **D** relative to **A** and **B** is independent of ethylene concentration, then presumably **D** is formed by ring-opening of **21** with a ruthenium methylidene species.

Kinetic studies were carried out with catalyst **15** (Fig. 2) to elucidate the pathways to products **C** and **D**. The ratio of product **C** relative to products **A** and **B** was followed with conversion by proton NMR and is shown in Fig. 3. This ratio is constant (0.16:1.0) up to complete consumption of substrate **21**, indicating that product **C** is formed as a result of formation and breakdown of the 2,3-metallacycle. After complete conversion of substrate **21**, the ratio of product **C** relative to products **A** and **B** increases, indicating that secondary metathesis is occurring, but primarily only after **21** has completely reacted. Hence, during the reaction product **C** is formed as a result of the catalyst proceeding *via* a 2,3-metallacycle, and after the reaction is complete, secondary metathesis of products **A** and **B** generates more product **C** (Fig. 3).

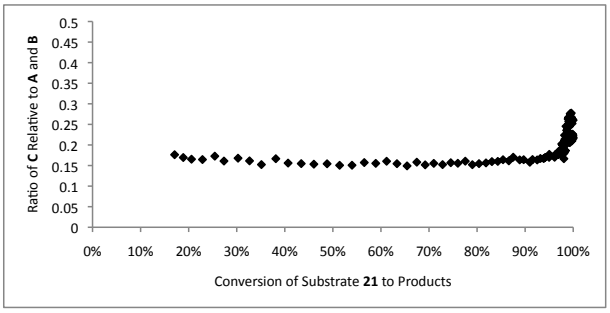


Fig. 3. Ratio of product **C** relative to products **A** and **B** as a function of conversion catalyzed by **15**.

The ratio of product **D** relative to products **A** and **B** was constant as a function of conversion (Fig. 4), suggesting ring-opening of **21** by a methylidene species, followed by reaction of styrene through a 2,4-metallacycle. No dependence was observed on the concentration of ethylene in solution, indicating that ethenolysis of products **A** and **B** is not a major contributing pathway to the formation of compound **D**. Therefore, the production of **D** indicates propagation of a ruthenium methylidene species. This ruthenium methylidene species can be generated by several reactions, including self-metathesis of styrene and formation of product **C**.

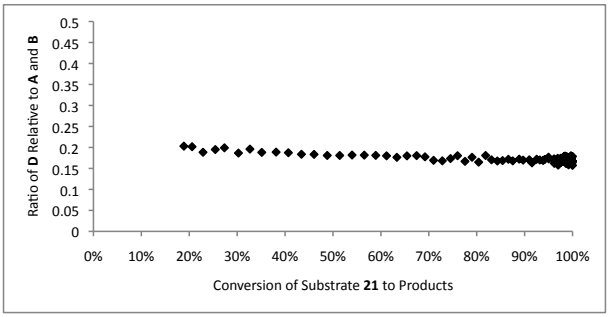


Fig. 4. Ratio of product **D** relative to products **A** and **B** as a function of conversion catalyzed by **15**.

Complexes **16-20** (Fig. 2) were also screened to determine their enantioselectivity and to see if they afforded products **C** and **D** in addition to products **A** and **B**. The reactions were monitored by NMR to determine when they were complete. The mixtures were worked-up immediately to prevent any secondary metathesis from potentially eroding or enhancing the ee of the products. As discussed, complex **15** gave good enantioselectivity at 69% ee of **A** (Table 1, entry 1). Interestingly, **16** gave 14% ee of the opposite enantiomer **B**, despite having the same stereochemistry as **15** (both *S* configuration). The most plausible explanation is that **16** is less enantioselective than **15**; additionally, the ring-opening of **21** by the methylidene species of **16**, followed by formation of the 2,3-metallcycle, occurs at a high enough frequency to ultimately favour enantiomer **B**. Since the methylidene species presumably has the same facial selectivity as the alkylidene species (leading to the formation of the opposite enantiomer of product), (*S*)-**16** could afford **B** as the major enantiomer (Table 1, entry 2), compared to enantiomer **A** yielded by (*S*)-**15**. Complex **17** also gave **B** in 9% ee, probably for the aforementioned reasons (Table 1, entry 3). While the different structural features of the chiral *N*-alkyl groups of the same stereochemical configuration could spatially alter which enantiomer they select for, complexes **15-17** seem similar enough to render this unlikely to be the cause of the difference in the preferred enantiomer.

By comparison to **15**, catalyst **18** showed only moderate enantioselectivity, affording product **A** in 33% ee (Table

Table 1. Enantioselectivity of catalysts **15-19** in AROCM of substrate **21**.

Entry[a]	Catalyst	Time (h)	Conv. (%)[b]	Yield (%)[c]	ee (%)[d]
1	**15**	5.5	60	60	69 (**A**)
2	**16**	0.5	99	69	14 (**B**)
3	**17**	0.5	99	73	9 (**B**)
4	**18**	5.5	98	65	33 (**A**)
5[e]	**19**	10.5	98	54	82 (**A**)

[a]Catalyst loading of 2 mol%; [**21**]: 0.2 M in dichloromethane; T: 22 °C. [b]Conversion determined by ^{1}H NMR spectroscopy using disappearance of **21**. [c]Isolated yield. [d]Enantiomeric excess determined by chiral HPLC. [e]Catalyst loading of 3 mol%.

1, entry 4). Complex **19** showed the highest selectivity at 82% ee of **A**, comparable to the best ruthenium catalysts reported to date for this particular substrate (Table 1, entry 5). Although complex **19** (*R* configuration) yields the same enantiomer as complex **15** (*S* configuration), we believe the *N*-alkyl structures are unique enough that a direct comparison between these catalysts cannot be made. Complex **19** was significantly slower than the other catalysts screened, but showed no signs of decomposition throughout the reaction. Only the *trans* products were observed in all cases.

The effect of temperature on enantiomeric excess for AROCM catalyzed by **15** was studied and, as expected, the ee increased with decreasing temperature and decreased with increasing temperature (Table 2). Complex **15** gave up to 72% ee of **A** at 0 °C, and afforded only 42% ee of **A** at 60 °C. The reaction was also noticeably slower at lower temperatures, reaching only 50% conversion after 4 hours at 0 °C, compared to 99% conversion at 50 °C in 3.5 hours.

Table 2. Effect of temperature on the enantioselectivity of 15.

Entry[a]	Time (h)	Temp (°C)	Conv. (%)[b]	ee (%)[c]
1	4.0	0	50	72
2	7.0	22	99	69
3	3.5	40	99	51
4	3.5	50	99	50
5	3.5	60	99	42

[a]Catalyst loading of 2.5 mol%; T: 22 °C; [**21**]: 0.1 M in dichloromethane. [b]Conversion determined by ^{1}H NMR spectroscopy. [c]Enantiomeric excess was determined by chiral HPLC.

Complexes **16-20** also gave side products **C** and **D** during the AROCM of **21** (Table 3). Since complex **20** is racemic, its product distribution should not be affected by any potential enantiospecificity of a reaction step. With the exception of complex **19**, the catalysts generated approximately the same amount of product **C** relative to major products **A**/**B**, indicating that the inherent preference for a 2,4-metallacycle *vs* a 2,3-metallacycle is similar for these *N*-aryl, *N*-alkyl NHC catalysts. Complex **19**, however, proceeds almost exclusively by a 2,4-metallacyle, as shown by its low ratio of **C** to **A** and **B** (0.08:1). The ratio of product **D** relative to products **A** and **B** varied significantly for the different catalysts. Complex **19** gave an unusually high ratio of product **D** relative to **A** and **B** (0.43:1), suggesting that this complex has a high propensity to propagate *via* a methylidene species (Table 3, entry 5).

Table 3. The amount of side products C and D formed by different catalysts.

Entry[a]	Catalyst	Time (h)	Conv. (%)[b]	%**C**[c]	%**D**[d]
1	**15**	1.0	99	16	12
2	**16**	0.5	99	15	19
3	**17**	0.25	99	14	23
4	**18**	1.0	99	12	18
5	**19**	6.0	82	8	43
6	**20**	0.5	99	17	18

[a]Catalyst loading of 2.5 mol%; [**21**]: 0.2 M in dichloromethane. [b]Conversion determined by ^{1}H NMR spectroscopy. [c]Percent **C** relative to **A** and **B**. [d]Percent **D** relative to **A** and **B**.

In order to confirm that product **C** was being formed as a result of the catalysts proceeding *via* a 2,3-metallacycle as a general principle, and not unique to complex **15**, the ratio of **C** relative to **A** and **B** was plotted as a function of conversion for catalysts **17**, **18**, and **20** as well. In all cases, the ratio of **C** to **A** and **B** was constant up to complete consumption of substrate **21**, after which secondary metathesis occurred to increase the amount of **C** in the reaction mixture. Similarly, the ratio of product **D** to products **A** and **B** was shown to be constant throughout the reaction, confirming that these pathways are general to the complexes investigated in this study.

The ratios of **C** to **A**/**B** and **D** to **A**/**B** were calculated as a function of temperature in order to determine the effect of temperature on alkylidene *vs* methylidene propagation and the formation and breakdown of the 2,4-metallacycle *vs* 2,3-metallacycle. Complex **15** was used as the catalyst at a loading of 2.5 mol%, and the respective ratios were determined upon completion of the AROCM of **21** (0.1 M in dichloromethane) by proton NMR spectroscopy. With higher temperature, the amount of both products **C** and **D** formed in the reaction increased (Fig. 5). This is possibly a result of the higher temperature providing the necessary energy for the reaction to proceed down the less favourable pathways, thereby giving more of the end-products of those pathways, **C** and **D**.

Conclusion

Complexes **15-20** yield side products during AROCM reactions resulting from the catalysts proceeding through a 2,3-metallacycle in addition to a 2,4-metallacycle, as well as propagating by a methylidene species, and these pathways were found to be general to this class of ruthenium catalysts investigated. The inherent preference of a given catalyst for the formation and breakdown of a 2,4-metallacycle *vs* a 2,3-metallacycle affects its product distribution, and this catalyst behaviour can be utilized to target products and particular applications. It also can be considered in new catalyst design, as the ligand structure was shown to have an effect on the propensity of the catalyst to undergo a 2,3- *vs* 2,4-metallacycle. Similarly, high pref-

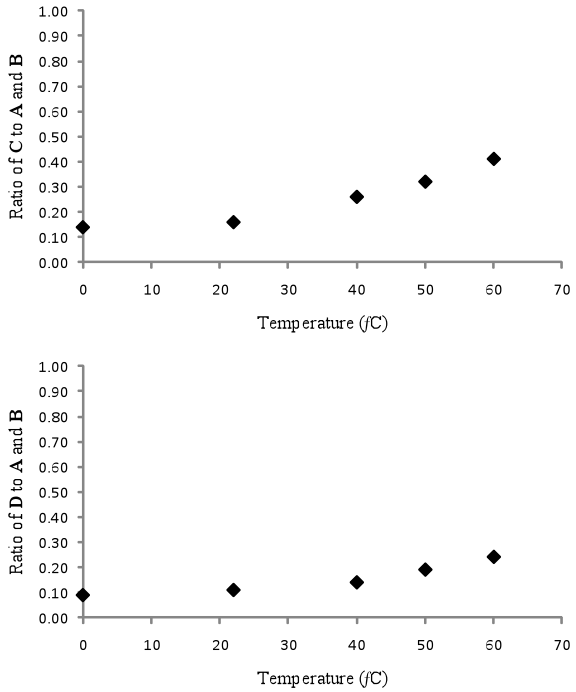


Fig. 5. Effect of temperature on the conversion to products **C** and **D**.

erence for methylidene propagation alters product ratios and can be used for applications where this is a desirable pathway. Additionally, methylidene propagation generally shortens catalyst lifespan, a necessary consideration in the choice of catalyst for a given reaction. Catalysts **15** and **19** gave high enantioselectivities, with catalyst **19** showing comparable enantioselectivity to the best ruthenium catalysts reported to date. Future research directions are focused toward exploited these catalyst properties for targeted reactions.

Experimental Section

General Considerations

All manipulations of air- or water- sensitive compounds were carried out under dry nitrogen using a glovebox or under dry argon utilizing standard Schlenk line techniques. NMR spectra were recorded on a Varian Mercury (^{1}H, 300 MHz), Varian Inova 400 (^{1}H, 400 MHz), or a Varian Inova 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometer and referenced to residual protio solvent. Enantiomeric excesses were determined by chiral HPLC. Column: chiralcel AD; Solvent system: 8% isopropanol in hexanes. Flow rate: 0.75 mL per min.

Materials

Deuterated dichloromethane was dried over calcium hydride and vacuum distilled, followed by three cycles of freeze-pump-thawing. *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**21**) was obtained from Aldrich and used without further purification. Styrene was purchased from Aldrich and filtered through a silica gel plug prior to use.

Representative AROCM reaction of **cis***-5-norbornene-***endo***-2,3-dicarboxylic anhydride with styrene.*

Substrate *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (60 mg, 0.36 mmol) was added to a 100 mL round bottom flask containing a vacuum adaptor, and the flask was placed under an argon atmosphere. Dry dichloromethane (6 mL) was added *via* syringe, followed by styrene (0.42 mL, 3.6 mmol). Catalyst **15** (6.5 mg, 2.5 mol%) was then added, and the reaction was stirred for 4 h. The mixture was concentrated, and a proton NMR taken to calculate the relative ratios of products **A**/**B**, **C**, and **D**. The products were purified by column chromatography (silica gel, 50% ether in pentane). Stillbene came off with an R_f of 0.91. Product **D** came off with an R_f of 0.43 and was recovered in trace amounts. Product **A**/**B** had an R_f of 0.33 (49 mg, 47% yield) and product **C** had an R_f of 0.27 (12 mg, 10% yield). Enantiomeric excess was determine by chiral HPLC, with enantiomer **A** showing a retention time of 28.95 min, and enantiomer **B** showing a retention time of 32.98 min. Product **A** was obtained in 69% ee over product **B**. The enantiomers were identified by comparison to the retention times under the same chiral HPLC conditions outlined in reference 14.

^{1}H NMR of product **A**/**B** ($CDCl_3$, 500 MHz): δ 7.42–7.35 (m, 2H), 7.35–7.29 (m, 2H), 7.25–7.21 (m, 1H), 6.52 (d, J = 15.8 Hz, 1H), 6.30 (dd, J = 15.8, 8.0 Hz, 1H), 6.03–5.90 (m, 1H), 5.23 (d, J = 1.1 Hz, 1H), 5.20 (dt, J = 7.5, 1.3 Hz, 1H), 3.61–3.47 (m, 2H), 3.22–3.11 (m, 1H), 3.10–2.99 (m, 1H), 2.14 (dt, J = 12.8, 5.5 Hz, 1H), 1.57 (q, J = 12.9 Hz, 1H) ppm. ^{13}C NMR of product **A**/**B** ($CDCl_3$, 125 MHz): δ 170.79, 136.84, 134.99, 132.48, 128.81, 127.96, 126.68, 126.57, 117.62, 50.06, 49.62, 47.00, 46.43, 36.78 ppm.

^{1}H NMR of product **C** ($CDCl_3$, 500 MHz): δ 7.39 (m, 4H), 7.35–7.29 (m, 4H), 7.24 (m, 2H), 6.55 (d, J = 15.8 Hz, 2H), 6.31 (dd, J = 15.7, 8.0 Hz, 2H), 3.63–3.56 (m, 2H), 3.22 (m, 2H), 2.22 (dt, J = 12.7, 5.4 Hz, 1H), 1.66 (q, J = 12.9 Hz, 1H) ppm. ^{13}C NMR of product **C** ($CDCl_3$, 125 MHz): δ 170.77, 134.98, 132.55, 128.82, 127.98, 126.70, 126.54, 50.00, 46.57, 37.55 ppm.

^{1}H NMR of product **D** ($CDCl_3$, 500 MHz): δ 6.01–5.91 (m, 2H), 5.23–5.20 (m, 2H), 5.19 (dt, J = 10.0, 1.2 Hz, 2H), 3.54–3.44 (m, 2H), 3.06–2.94 (m, 2H), 2.07 (dt, J = 12.9, 5.5 Hz, 1H), 1.49 (q, J = 13.0 Hz, 1H) ppm. ^{13}C NMR of product **D** ($CDCl_3$, 125 MHz): δ 170.74, 135.00, 117.59, 49.68, 46.90, 36.04 ppm.

Representative kinetic experiment for the pathway to the formation of products C and D.

In a nitrogen atmosphere glovebox, an NMR tube was charged with *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (20 mg, 0.12 mmol) and 0.5 mL of deuterated dichloromethane. The NMR tube was sealed with a septum cap and brought out of the glovebox. Styrene was added via syringe through the septum cap, and a proton NMR spectrum (CD_2Cl_2, 500 MHz) was taken for time = 0. An NMR array was set up with pad increments of 10 sec, 16 scans per spectrum, 200 spectra. Catalyst solution (**15** in 0.25 mL dry CD_2Cl_2; 1.7 mg, 2 mol%) was injected by syringe into the NMR tube, and the sample was inserted into the spectrometer. The data were collected and analyzed using MestReNova software.

Acknowledgement

This research was supported by the National Science Foundation through a Graduate Research Fellowship to Renee Thomas. The authors acknowledge Dr. Scott Virgil for helpful discussions. We thank the NSF and NIH for funding.

References

1. (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003 and refs cited; (b) Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, 2010.
2. (a) Mutlu, H.; de Espinosa, L. M.; Meier, M. A. R. *Chem. Soc. Rev.* **2011**, *40*, 1404-1445; (b) Buchmeiser, M. R. *Macromol. Symp.* **2010**, *298*, 17-24; (c) Khaja, S. D.; Lee, S.; Murthy, N. *Biomacromol.* **2007**, *8*, 1391-1395; (d) Grubbs, R. H.; Trnka, T. M. *Ruthenium in Org. Synth.* **2004**, 153-177.
3. (a) Hoveyda, A. H.; Schrock, R. R. *Comp. Asym. Cat. Suppl*. **2004**, *1*, 207-233; (b) Connon, S. J.; Blechert, S. *Topics Organomet. Chem.* **2004**, *11*, 93-124; (c) Hoveyda, A. H.; Schrock, R. R. *Org. Synth. Highlights V* **2003**, 210-229.
4. Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 3860-3864.
5. Takao, K.; Yasui, H.; Yamamoto, S.; Sasaki, D.; Kawasaki, S.; Watanabe, G.; Tadano, K. *J. Org. Chem.* **2004**, *69*, 8789-8795.
6. Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 4534-4538.
7. (a) Savoie, J.; Stenne, B.; Collins, S. K. *Adv. Synth. & Catal.* **2009**, *351*, 1826-1832; (b) Fournier, P. A.; Savoie, J.; Stenne, B.; Bedard, M.; Grandbois, A.; Collins, S. K. *Chem. Eur. J.* **2008**, *14*, 8690-8695; (c) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840-1846.
8. La, D. S.; Ford, J. G.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603-11604.
9. La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767-7778.
10. Pilyugina, T. S.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics* **2007**, *26*, 831-837.
11. Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844-3845.
12. (a) Mol, J. C. *J. Mol. Cat. A: Chem.* **2004**, *213*, 39-45; (b) Kuhn, K. M.; Bourg, J. –B.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313-5320.
13. Cortez, G. A.; Baxter, C. A.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 2871-2874.
14. Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7591-7595.
15. Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954-4955.
16. Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288-12290.
17. Tiede, S.; Berger, A.; Schlesiger, D.; Rost, D.; Lühl, A.; Blechert, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 3972-3975.
18. Grisi, F.; Costabile, C.; Gallo, E.; Mariconda, A.; Tedesco, C.; Longo, P. *Organometallics* **2008**, *27*, 4649-4656.
19. Vehlow, K.; Maechling, S.; Blechert, S. *Organometallics* **2006**, *25*, 25-28.
20. Paczal, A.; Bényei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969-5979.
21. Kuhn, K. M.; Bourg, J. B.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313-5320.