Published in final edited form as:
J Am Chem Soc. 2006 February 15; 128(6): 1840–1846. doi:10.1021/ja055994d.

Highly Active Chiral Ruthenium Catalysts for Asymmetric Ring-Closing Olefin Metathesis

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Abstract

The synthesis of olefin metathesis catalysts containing chiral, monodentate *N*-heterocyclic carbenes and their application to asymmetric ring-closing metathesis (ARCM) is reported. These catalysts retain the high levels of reactivity found in the related achiral variants (**1a** and **1b**). Using the parent chiral catalysts **2a** and **2b** and derivatives that contain steric bulk in the meta positions of the *N*-bound aryl rings (catalysts **3**-**5**), five- through seven-membered rings were formed in up to 92% *ee*. The addition of sodium iodide to catalysts **2a**-**4a** (to form **2b**-**4b***in situ*) caused a dramatic increase in enantioselectivity for many substrates. Catalyst **5a**, which gave high enantiomeric excesses for certain substrates without the addition of NaI, could be used in loadings of ≤1 mol %. Mechanistic explanations for the large sodium iodide effect as well as possible mechanistic pathways leading to the observed products are discussed.

Introduction

The development of well-defined catalysts has made olefin metathesis an important, reliable, and widespread method for constructing carbon-carbon double bonds.[1] Since the initial report of asymmetric olefin metathesis for small molecule synthesis,[2] a variety of chiral, ruthenium- and molybdenum-based alkylidene catalysts have been developed.[3-4] The molybdenum catalysts have been shown to give excellent enantioselectivities in asymmetric ring-closing metathesis (ARCM), asymmetric ring-opening/ring-closing metathesis (ARORCM), and asymmetric ring-opening/cross metathesis (AROCM).[5-6] Our interest in ruthenium-based olefin metathesis catalysts stems from their increased functional group tolerance compared to the molybdenum systems, as well as their stability to air and moisture.[6b] Two classes of chiral ruthenium catalysts have been explored (Chart 1): those containing monodentate *N*-heterocyclic carbenes (NHCs) with chirality in the backbone of the carbene (**2a** and **2b**) developed in our laboratory,[3c] and those containing chiral, bidentate NHC/binaphthyl ligands (**6a** and **6b**) developed by Hoveyda *et al*.[3a-b] While catalysts of the latter type gave good enantioselectivities and yields for AROCM reactions,[7] they exhibited reduced reactivity and selectivity toward ARCM relative to those of the former class.

The ruthenium catalysts containing monodentate, chiral NHC's (**2a** and **2b**) had the same air and moisture stability of the parent catalyst **1a**, as well as a similar level of reactivity.[8] Additionally, we achieved a single example of 90% *ee* using **2b**.[3c] Based on this initial discovery, and because ARCM remains challenging for **6a** and **6b**, we decided to modify **2a** and **2b** to enhance enantioselectivity and expanded the substrate scope of ARCM. The synthesis of new chiral ruthenium catalysts for asymmetric olefin metathesis, as well as their reactivity and selectivity in expanding the scope of ARCM, is reported herein. Catalysts containing

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substitution on the aryl ring para to the *ortho*-isopropyl group (**3a**, **3b**, **4a**, and **4b**) showed very similar enantioselectivities to that of the parent chiral catalysts **2a** and **2b**. However, substitution on the same side of the ring as the *ortho*-isopropyl group (**5a** and **5b**) caused an increase in enantioselectivity to the extent that in a number of substrates, the dichloride catalyst **5a** could be used at very low catalyst loadings to obtain high enantiomeric excesses and conversions.

Results and Discussion

Design and Synthesis of Chiral Ruthenium Catalysts

In our initial study we discovered that NHC's derived from enantioenriched 1,2-diamines could transfer the chirality of the backbone to the *ortho*-substituted *N*-aryl rings.[3c] This “gearing” effect, which results in the *ortho*-subtituent of the unsymmetrically-substituted arene rings to reside on the face opposite to the phenyl groups on the backbone, has been to shown to induce asymmetry in the ring-closing metathesis of prochiral trienes. Using the ring-closing metathesis of **11** to form **12** as a test reaction, we varied the backbone of the NHC as well as the substituent in the *ortho*-position of the *N*-aryl rings and discovered that **2b** was the most successful catalyst, forming dihydrofuran **12** in 90% ee. Based on the success of varying the *ortho*-substitution, we explored catalysts containing substitution in the *meta*-position of the *N*-bound aryl rings.

The synthesis of the chiral dihydroimidazolium salts (**9a**-**9d**) was straight-forward and modular. $Pd_2(dba)_3$/BINAP was used to couple the substituted aryl bromides (**7a-d**) to commercially available (1*R*,2*R*)-diphenylethylenediamine.[9-10] Compound **7b** was used as a mixture of aryl bromides; thus, the diamine coupling reaction was followed by a Pd-catalyzed reduction to yield **8b**. The *para*-methoxy group in aryl bromide **7c** was present as a synthetic handle and was not expected to affect enantioselectivities due to its remote location relative to the Ru center. The chiral diamines were reacted with triethylorthoformate to form dihydroimidazolium BF_4^- salts **9a-d** in good yields over two or three steps. Ligand substitution with bis-phosphine compound **10** gave the desired chiral ruthenium benzylidenes as brown solids.[11] All of these ruthenium compounds were purified using silica gel chromatography with non-degassed solvents, and they were stored in air without significant decomposition over a period of at least three months. Conversions for the ligand substitution step were generally 90%, but challenging chromatographic separations gave varied isolated yields. The analogous catalysts with two iodides bound to the ruthenium (**2b**-**5b**) were generated *in situ* by dissolving the dichloride catalyst in THF in the presence of 25 equivalents of NaI.

Enantioselectivities and Reactivities of Chiral Ru Catalysts for ARCM

In our previous study we discovered that substrate **11**, derived from (2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-ol, gave the highest enantioselectivities and good conversions, so this substrate and a silyl ether analogue (**13**) were used to examine the reactivities and enantioselectivities of the new catalysts. The presence of trisubstituted alkenes was critical to obtaining high enantiomeric excess using catalyst **2b** with triene **11**. As can be seen in Table 1, catalysts **2a**-**4a** gave relatively similar enantioselectivities and conversions for substrate **11**. In all of these cases, the diiodide catalysts (**2b**-**4b**) caused dramatic increases in the enantioselectivity of the reaction (i.e. 35% *ee* with **2a**, 90% *ee* with **2b**). There is no simple pattern for selectivity based on the steric bulk in the *meta*-position for catalysts **2**-**4**: increasing the size of the *meta* group from H to *t*-butyl caused a sequential decrease in the enantiomeric excess (**2a**-**4a**); but when NaI was added (**2b**-**4b**), it decreased for *meta*-isopropyl but increased again when the larger *t*-butyl group was in the *meta*-position. The largest difference in selectivity was seen when catalyst **5a** was used. An increase of 11% *ee* was observed relative to **2a**, and **5b** gave 90% *ee* just as **2b**. High conversions were obtained with all of the catalysts in 2 h at 40 °C.

When **13** was reacted with these catalysts, higher enantioselectivities were obtained without the need for NaI. As with substrate **11**, selectivity decreased as steric bulk in the *meta*-position increased (catalysts **2a**-**4a**). When the diiodide catalysts **2b**-**4b** were used, enantioselectivities increased for all of the reactions relative to those obtained using **2a**-**4a**. Introducing meta-substitution adjacent to the *ortho*-isopropyl group (catalyst **5a**) resulted in a 92% *ee* for the ring closing of **13** without the need for NaI. This result was the highest enantiomeric excess for ring-closing metathesis we had observed. Moreover, since the dichloride catalysts are generally more reactive than the corresponding diiodide catalysts, complete conversion could be achieved with lower catalyst loadings of **5a**! Conversions with catalysts **2b** and **5b** decreased relative to the reactions with the dichloride catalysts when substitution was on just one side of the *N*-bound aryl rings. On the other hand, conversions remained high for catalysts **3b** and **4b**, which possess substitution on both sides of the aryl rings. This increase in conversion may be due to the substituent in the *meta*-position increasing the steric bulk of the catalyst, and therefore protecting it from various bimolecular decomposition pathways.[12]

Expanded Substrate Scope for ARCM

The ability of the chiral ruthenium catalysts **2**-**5** to give high conversions and enantioselectivities for the ARCM reactions of **11** and **13** encouraged us to examine other substrates which afford 5–8 membered rings upon ARCM. Based on the results from our initial screen, catalysts **2b** and **5a** were used. Two types of prochiral trienes were explored: alkenyl ethers and alkenyl silyl ethers (Table 2). Conversions >90% and 90% *ee*s were obtained when generating 5- and 6-membered rings **12** and **16**. The isolated yields were moderately reduced due to the volatility of the products during the purification procedure. The synthesis of a 7-membered ring from **17** occurred in 85% *ee* when **2b** was used. Unfortunately the formation of the desired product was only ~5%, with the major species being unreacted starting material and homocoupled product. The yield for the same reaction could be drastically increased when catalyst **5a** was used,[13] and because **5a** is more selective than the other catalysts in the absence of NaI (65% *ee* for **18** using **2a**), the desired product could be obtained in 92% yield and 76% *ee*. Synthesis of an 8-membered ring was more challenging, and **2b** catalyzed the ARCM reaction of **19** to **20** in 85% *ee*, but with only a ~2% yield. Attempts to increase the yield using **5a** resulted in a similar yield and a reduced enantiomeric excess. This result was not surprising, as generating 8-membered rings via ring-closing olefin metathesis is a challenging problem.

Silyl ethers proved to be excellent substrates, as both 6- and 7-membered rings (**14** and **22**) formed in good conversions and 92% ee's with **5a**. Catalyst loadings of 1 mol % or less could be used in these reactions. The ring-closing of **13** illustrated that the high yield and enantiomeric excess were maintained when the reaction was scaled up to almost 1 g of substrate. Using the analogous diiodide catalyst **5b** for ARCM of **13** and **21** resulted in 6- and 7-membered rings with the same enantiomeric excesses but lower conversions than with the dichloride catalyst **5a**. Substrate **23**, which placed the prochiral center further from the trisubstituted olefins, also underwent ARCM to form a 7-membered ring in good enantiomeric excess and excellent yield with a substitution pattern different than **22**.

Table 2 provides the best results between catalysts **2b** and **5a**. In most reactions (ARCM of **11**, **13**, **15**, **21**, and **23**), the yields and enantioselectivities are very similar whether catalyst **2b**, **5a**, or **5b** is used. Because both **2b** and **5a** promote the ARCM of 5–7 membered rings, there is no need for specific catalyst/substrate matching.

Trienes other than those discussed above were also examined in the ARCM reactions (Table 3). Substrates analogous to **13** and **23**, but lacking a terminal methyl group on the olefin (**25** and **27**), formed cyclic products **26** and **28** in reduced enantioselectivities and conversions. When the diiodide catalysts were used, conversions were <20%. The lower conversions using **25** and **27** relative to **11** and **23** may be due to the formation of a ruthenium methylidene versus

a ruthenium ethylidene, respectively. Ruthenium methylidenes are known to decompose more rapidly than other ruthenium alkylidenes, and in these cases decomposition may have occurred more quickly than the cross-metathesis that introduces the ring-closing substrate to the catalyst.[14]

A number of variables other than catalyst and substrate in the ARCM reactions were examined. Using a variety of solvents typical for olefin metathesis, such as CH_2Cl_2, THF, and benzene, had very little affect on the conversions and enantiomeric excesses (Figure 1). The slight reduction in selectivity for ARCM reactions in benzene suggests that solvent coordination to the catalyst is not involved as in the molybdenum systems.[15] Lowering the temperature of the reactions in CH_2Cl_2 to 0 °C led to a small increase (4-5%) in enantiomeric excesses when **2a** and **2b** were used, but catalysts **3b** and **5a** formed the product with slightly reduced (2-3%) enantioselectivities (Figure 2). In all cases the conversions were reduced to no greater than 40% even when 5 mol % of the catalyst was used and the reaction was allowed to proceed for 24h. The reactions which used I^- to form the diiodide catalysts had the best enantioselectivities when NaI in THF was used; NaI in CH_2Cl_2 and $[Bu_4N]I$ in either THF or CH_2Cl_2 resulted in reduced *ee*s and reduced yields. No difference in enantioselectivity or conversion was observed when dry NaI was used in place of ACS-grade NaI stored on the bench top. This fact is a testament to the moisture stability of these ruthenium-based catalysts.

Mechanistic Considerations in Model Determination

In order to rationally design more reactive and selective chiral ruthenium catalysts for olefin metathesis, we must first develop a model which explains the enantioselectivity in these reactions. If the ARCM reaction has a degree of reversibility, a decrease in *ee* over time would be expected. Although this was not observed, further experiments were performed to support the irreversibility of this reaction. When enantioenriched **14** was exposed to achiral catalyst **1a**, no erosion of the enantiomeric excess was observed, which suggests that once the ring is formed, it does not undergo a secondary ring-opening/ring-closing process. The same conclusion was drawn when enantioenriched **12** was heated under 60 psi of ethylene in the presence of **1a** (Figure 3). Under these forcing conditions, the enantiomeric excess of unreacted **12** did not erode, and the ethylenolysis product **28** also retained the stereochemistry from the ARCM reaction.[16]

In the ARCM reactions of the trienes described above, most likely a ruthenium alkylidene derived from the least-substituted olefin initially forms. This species binds one of the diastereotopic olefins, and through a metallacyclobutane intermediate/transition state, forms the ring-closed product. Our initial model[3c] assumed olefin coordination occurred *cis* to the NHC (Scheme 2, lower pathway), on the face opposite the isopropyl group (structure **30**), and that interaction determined the absolute stereochemistry of the product. The interaction of a halide ligand with a substituent on the ring of the cyclic intermediate was also proposed to be an important, stereo-defining interaction.[17] The actual position of the coordinating olefin relative to the NHC is unclear; experimental evidence exists to support olefin binding both *cis* and *trans* to the NHC (Scheme 2).[18] In the most recent report on this issue,[18c] Piers and coworkers provide compelling evidence for the observation of a 14-electron ruthenacyclobutane *trans* to the NHC. Computational studies support olefin binding *trans* to the NHC,[19] and a recent computational study of **2b** reacting with **11** calculated that the diastereotopic olefin coordinated *trans* to the NHC (Scheme 2, upper pathway).[19a] Due to the tilt of the *ortho*-substituted *N*-bound aryl ring,[20] the alkylidene is positioned underneath the isopropyl group (structure **32**), which was found to be the “smaller” side of the aryl ring (Figure 4), instead of underneath the ortho C—H bond (structure **31**). In addition to the position of the alkylidene determining the absolute stereochemistry of the product, the cyclic intermediate formed upon olefin binding is also important. The pendent olefin not involved in the ring-

closing reaction prefers to be in the pseudo-equatorial position of the forming ring. Although the discussion presented here focuses on a substrate that forms a 5-membered ring, substrates that form other ring sizes presumably have an energetically favored ring conformation once olefin binding occurs. Therefore the topics mentioned above can be extended to other ring-closing substrates. The importance of the position of the substituents on the ring in the cyclic transition state could explain the higher enantioselectivities observed for the substrates containing dimethylsilyl groups: there are more non-hydrogen substituents on the ring, and therefore the energy differences for various ring conformations are greater than those for substrates with only methylenes in the ring.

Our initial *cis*-binding hypothesis was supported by the fact that when a larger halide ligand was present, the enantiomeric excess of the product increased. With recent experimental and computational studies providing evidence for olefin binding *trans* to the NHC, we sought to relate our experimental data to the suggested *trans*-binding mechanism. If olefin binding occurs *trans* to the NHC, exchanging the chloride ligands for iodides should not have a major steric impact on the transition state.[21] Instead, the iodide ligands may have an electronic effect. When the chlorides in **1a** were exchanged for iodides (**1b**), phosphine dissociation occurred more rapidly, but the reactivity of the active species did not increase.[14b] In the case of the chiral catalysts **2b**-**4b**, a lower reactivity could increase the enantioselectivity by causing the reaction to proceed through a late, more product-like transition state.[22] The added steric bulk in **5a** may hamper its reactivity enough to mimic the electronic deactivation present in the diiodide catalysts **2b**-**4b**, resulting in a late transition state and higher degree of stereochemical communication between the catalyst and the substrate. Substrates **25** and **27**, which have alkenes with less steric hindrance compared to substrates **13** and **23**, may form products in lower enantiomeric excess due to a higher reactivity with the catalyst. Although recent studies suggest olefin binding occurs *trans* to the NHC, and the observed absolute stereochemistry can be justified using a proposed model based on *trans* binding, the experimental data does not provide enough support to rule out a *cis*-binding mechanism.

Conclusions

We have synthesized novel asymmetric olefin metathesis catalysts, which contain chiral, monodentate NHC ligands, and have shown their use in asymmetric ring-closing metathesis of prochiral trienes containing trisubstituted alkenes. Adding substitution to the position para to the *ortho*-isopropyl group of the *N*-bound aryl rings (**3a** and **4a**) of the parent compound **2a** had a relatively small effect on the enantioselectivities of the ARCM reactions. By exchanging the chloride ligands for iodides, an increase in enantioselectivity was observed for catalysts **2b**-**4b** relative to **2a**-**4a**. In the case of catalyst **5a**, substitution on the same side of the aryl ring results in enantiomeric excesses in up to 92% and very high conversions with low catalyst loadings (less than 1 mol %). Two proposed models for the formation of the observed products have been discussed: if the incoming olefin binds *cis* to the NHC, the stereo-defining interaction is the face of the ruthenium to which the olefin binds; if the incoming olefin binds *trans* to the NHC, the stereo-defining interaction is the position of the alkylidene under the *N*-bound aryl ring. In both cases, the position of the pendent olefin in the forming ring also plays an important role in the transition state.

The general interest in developing ruthenium olefin metathesis catalysts stems from their ease of handling and their different functional group tolerance relative to that of the molybdenum catalysts. Catalysts **2a**-**5b**, much like the achiral analogues, are also stable to air and moisture, making them simple to use. The synthesis of enantioenriched 5–7 membered rings has been illustrated, and although further development is needed to expand the substrate scope of ruthenium-catalyzed ARCM, catalysts containing chiral, monodentate NHC ligands are promising due to their high activity, low catalyst loadings, and ease of handling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the NIH for financial support, Dr. Steven D. Goldberg and Angela Blum for helpful discussions, and Donde Anderson, Dr. Michael Day, and Larry Henling for the crystal structure of the Rh compound.

References

1. For recent reviews on olefin metathesis, see: aHandbook of MetathesisGrubbsRHWiley-VCHWeinheim2003 b Trnka T, Grubbs RH. Acc Chem Res 2001;34:18–29. [PubMed: 11170353] c Fürstner A. Angew Chem Int Ed 2000;39:3012–3043. d Grubbs RH, Chang S. Tetrahedron 1998;54:4413–4450. e Ivin KJ. J Mol Cat A Chem 1998;133:1–16.
2. a Fujimura O, Grubbs RH. J Am Chem Soc 1996;118:2499–2500. b Fujimura O, de la Mata FJ, Grubbs RH. Organometallics 1996;15:1865–1871.
3. Ruthenium catalysts: a Van Veldhuizen JJ, Gillingham DG, Garber SB, Kataoka O, Hoveyda AH. J Am Chem Soc 2003;125:12502–12508. [PubMed: 14531694] b Van Veldhuizen JJ, Garber SB, Kingsbury JS, Hoveyda AH. J Am Chem Soc 2002;124:4954–4955. [PubMed: 11982348] c Seiders TJ, Ward DW, Grubbs RH. Org Lett 2001;3:3225–3228. [PubMed: 11574037]
4. Molybdenum catalysts: a Totland KM, Boyd TJ, Lavoie GG, Davis WM, Schrock RR. Macromolecules 1996;29:6114–6125. b Alexander JB, La DS, Cefalo DR, Hoveyda AH, Schrock RR. J Am Chem Soc 1998;120:4041–4042. c Zhu SS, Cefalo DR, La DS, Jamieson JY, Davis WM, Hoveyda AH, Schrock RR. J Am Chem Soc 1999;121:8251–8259. d Alexander JB, Schrock RR, Davis WM, Hultzsch KC, Hoveyda AH, Houser JH. Organometallics 2000;19:3700–3715. e Aeilts SL, Cefalo DR, Bonitatebus PJ Jr, Houser JH, Hoveyda AH, Schrock RR. Angew Chem Int Ed 2001;40:1452–1456. f Tsang WCP, Schrock RR, Hoveyda AH. Organometallics 2001;20:5658–5669. g Hultzsch KC, Bonitatebus PJ, Jernelius J, Schrock RR, Hoveyda AH. Organometallics 2001;20:4705–4712. h Schrock RR, Jamieson JY, Dolman SJ, Miller SA, Bonitatebus PJ, Hoveyda AH. Organometallics 2002;21:409–417. i Tsang WCP, Jernelius JA, Cortez GA, Weatherhead GS, Schrock RR, Hoveyda AH. J Am Chem Soc 2003;125:2591–2596. [PubMed: 12603147]
5. a Sattely ES, Cortez GA, Moebius DC, Schrock RR, Hoveyda AH. J Am Chem Soc 2005;127:8526–8533. [PubMed: 15941288] b Jernelius JA, Schrock RR, Hoveyda AH. Tetrahedron 2004;60:7345–7351.
6. For reviews of asymmetric olefin metathesis reactions, see: aHoveydaAHHandbook of MetathesisGrubbsRHWiley-VCHWeinheim20032Chapter 23 b Schrock RR, Hoveyda AH. Angew Chem Int Ed 2003;42:4592–4633. c Hoveyda AH, Schrock RR. Chem Eur J 2001;7:945–950.
7. Gillingham DG, Kataoka O, Garber SB, Hoveyda AH. J Am Chem Soc 2004;126:12288–12290. [PubMed: 15453761]Also see ref 7.
8. Scholl M, Ding S, Less CW, Grubbs RH. Org Lett 1999;1:953–956. [PubMed: 10823227]
9. Wolfe JP, Buchwald SL. J Org Chem 2000;65:1144–1157. [PubMed: 10814066]
10. Both enantiomers of 1,2-diphenylethylenediamine are commercially available. See Supporting Information for the synthesis of the aryl bromides **7b-7d** and other experimental details.
11. Although we have been unable to obtain x-ray quality crystals of **2a**-**5b**, the carbene derived from chiral salt **9d** has been bound to $[Rh(COD)Cl]_2$, and an x-ray crystal structure of this complex shows that the isopropyl groups are oriented *anti* to the phenyl rings on the NHC backbone. See Supporting Information.
12. Hong SH, Day MW, Grubbs RH. J Am Chem Soc 2004;126:7414–7415. [PubMed: 15198568]
13. 1 Mol % of **5a** is added at the beginning of the reaction, and then another 1 mol % is added after 2 h, and the 7-membered ring **18** is isolated in 92% yield with a 76%ee. When 2 mol % catalyst **5a** is used at the beginning of the reaction, a 74% yield is obtained. Presumably all of the starting material is homocoupled first, and then a second metathesis reaction forms the ruthenium alkylidene that leads to product. The homocoupling reaction forms a ruthenium methylidene, which may decompose at roughly the same rate as it performs the desired olefin metathesis reaction. Adding fresh catalyst

allows most of the remaining unreacted starting material and homocoupled product to proceed to the desired 7-membered ring.

14. a Ulman M, Grubbs RH. J Org Chem 1999;64:7202–7207. b Sanford MS, Love JA, Grubbs RH. J Am Chem Soc 2001;123:6543–6554. [PubMed: 11439041](c) reference 12.
15. Teng X, Cefalo DR, Schrock RR, Hoveyda AH. J Am Chem Soc 2002;124:10779–10784. [PubMed: 12207534]
16. See Supporting Information for more details.
17. Allowing the hydrogen instead of the non-metal bound vinyl group to interact with the iodide also puts the vinyl group in the pseudo-equatorial position of the ring (see **30**).
18. Evidence for *cis*-coordination: a Trnka TM, Day MW, Grubbs RH. Organometallics 2001;20:3845–3847. Evidence for *trans*-coordination: b Tallarico JA, Bonitatebus PJ Jr, Snapper ML. J Am Chem Soc 1997;119:7157–7158. c Romero PE, Piers WE. J Am Chem Soc 2005;127:5032–5033. [PubMed: 15810833]
19. a Costabile C, Cavallo L. J Am Chem Soc 2004;126:9592–9600. [PubMed: 15291563] b Adlhart C, Chen P. J Am Chem Soc 2004;126:3496–3510. [PubMed: 15025477] c Fomine S, Vargas SM, Tlenkopatchev MA. Organometallics 2003;22:93–99. d Cavallo L. J Am Chem Soc 2002;124:8965–8973. [PubMed: 12137552] e Vyboishchikov SF, Bühl M, Thiel W. Chem Eur J 2002;8:3962–3975.
20. The x-ray crystal structure of an analogue of **2a** in reference 3c shows that the plane of the *N*-bound aryl ring is not orthogonal to the plane of the NHC. QM/MM calculations in reference 19a concluded that the *N*-bound aryl rings of a substrate-bound ruthenium alkylidene also are not orthogonal to the plane of the NHC.
21. Computations suggest that as the halide ligand increases in size (van der Waals radii) from Cl^- to I^-, the X—Ru—X bond angle also increases. A larger bond angle positions the halides closer to the Ru=CHR moiety (a smaller angle means the halides are pulled away from the alkylidene), which puts the halides in closer proximity to the reacting olefin, creating a smaller pocket, and therefore a more selective reaction. See reference 19a.
22. Palucki M, Finney NS, Pospisil PJ, Güler ML, Ishida T, Jacobsen EN. J Am Chem Soc 1998;120:948–954.

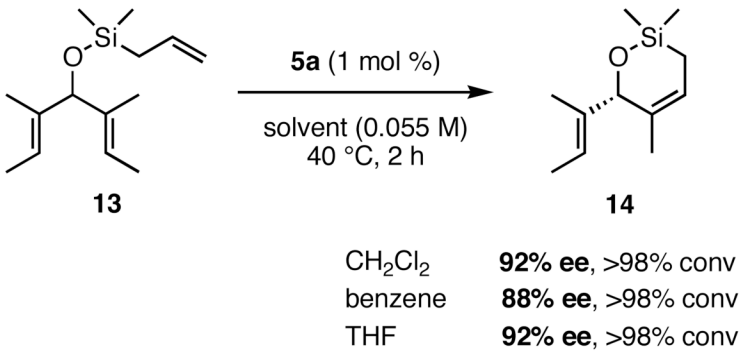


Figure 1.
Solvent Effect on Enantioselectivity of ARCM.

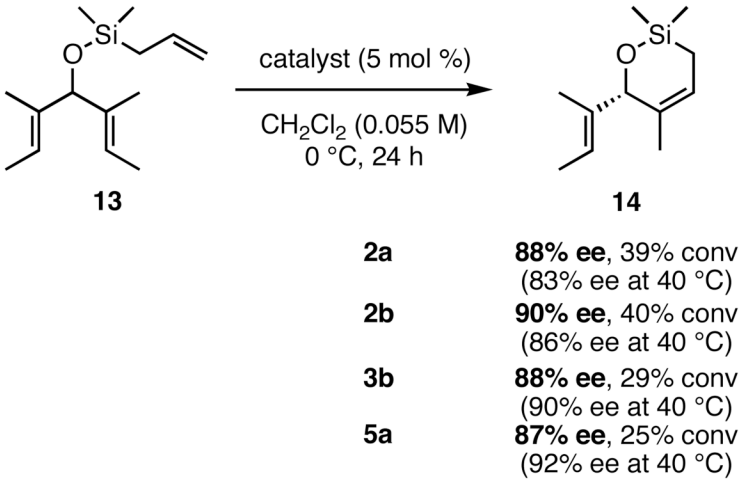


Figure 2.
Temperature Effect on Enantioselectivity of ARCM.

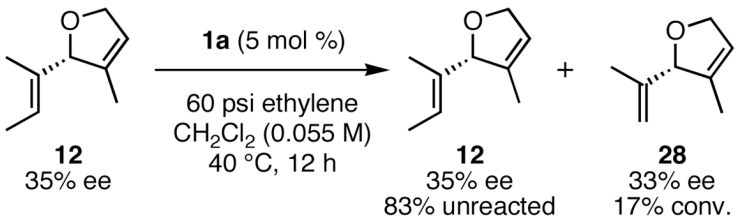


Figure 3.
Ethylenolysis of **12**.

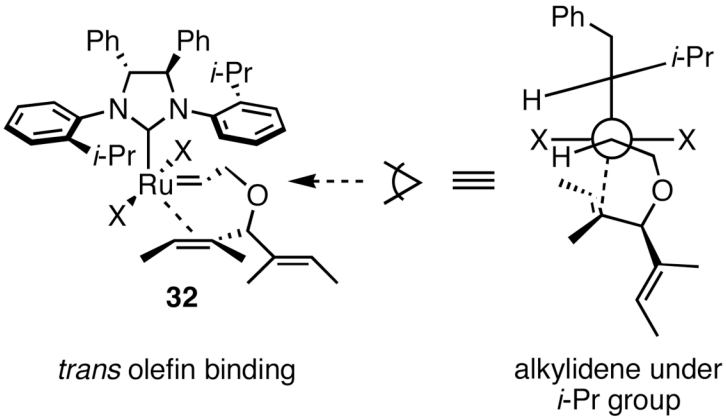
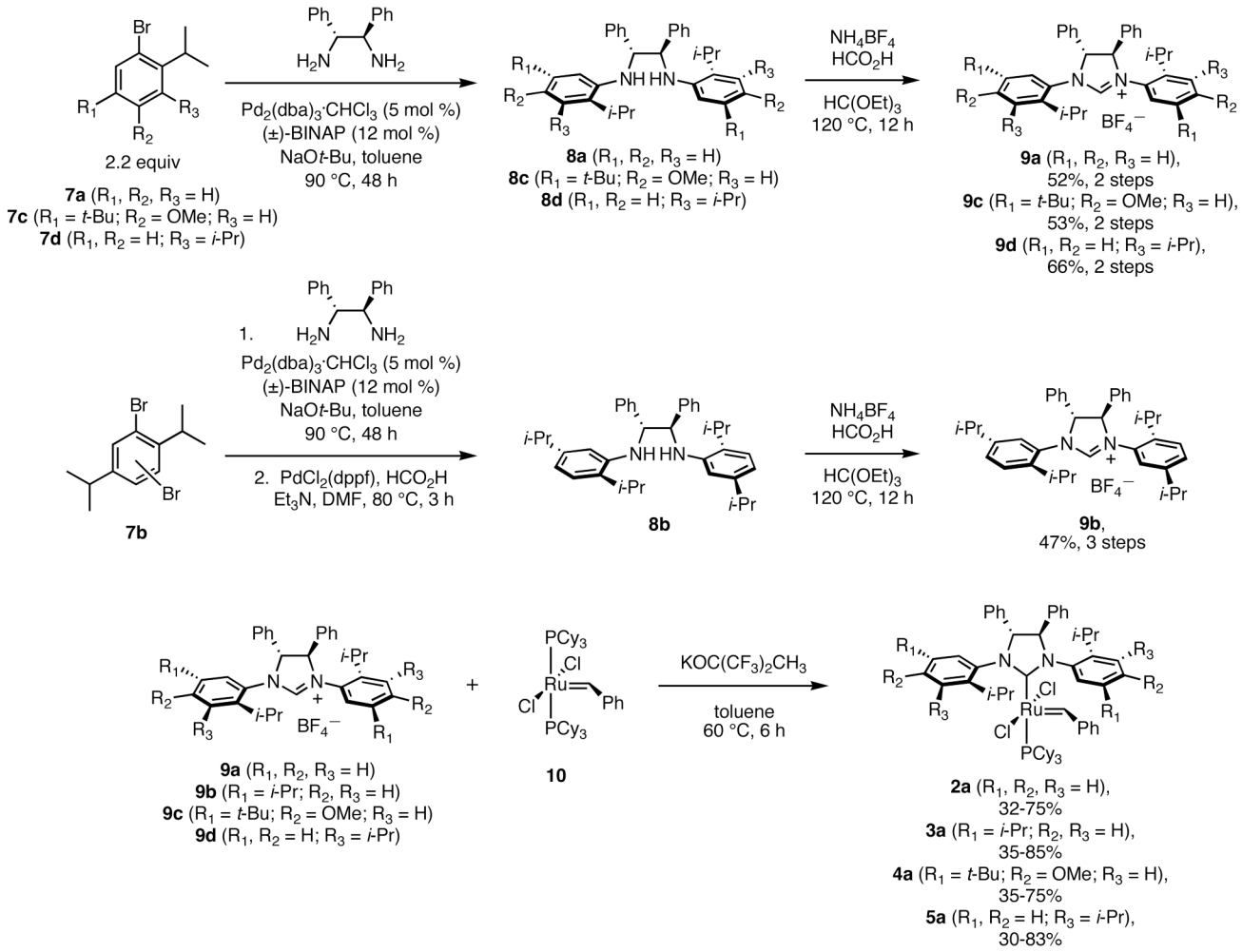
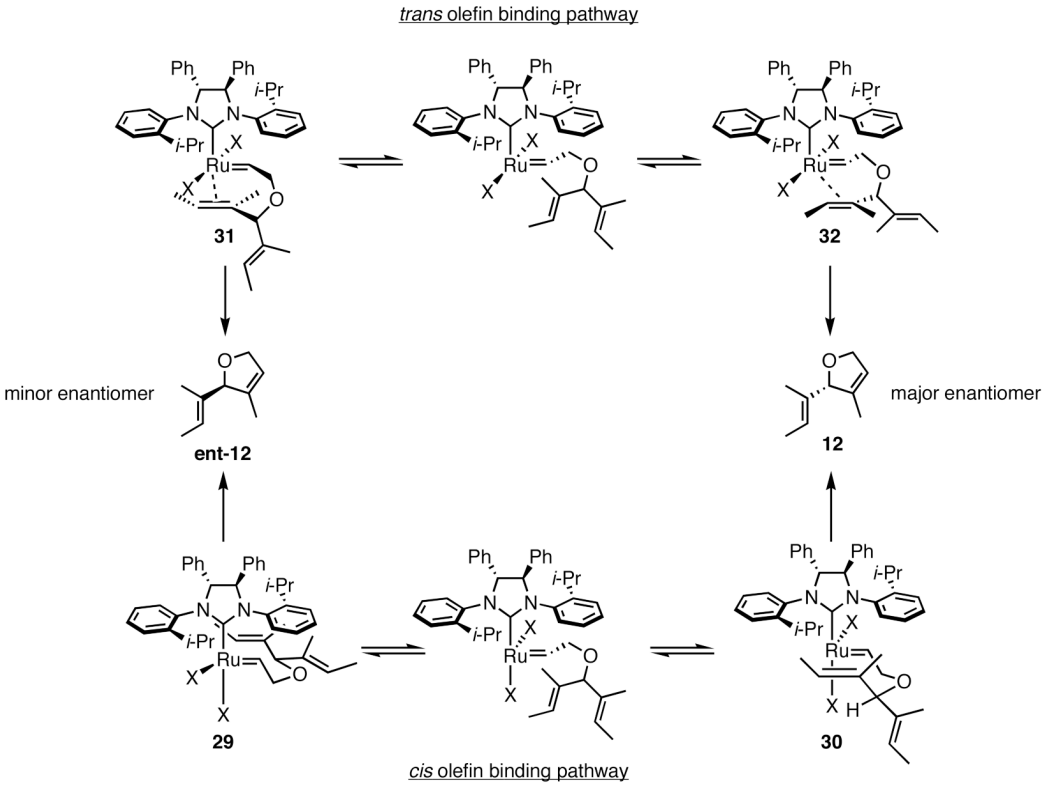


Figure 4.
Suggested Alkylidene Position in *trans*-Binding Transition State.



Scheme 1.
Synthesis of Chiral Ruthenium Olefin Metathesis Catalysts.



Scheme 2.
Proposed Pathways Leading to the Desired Product.

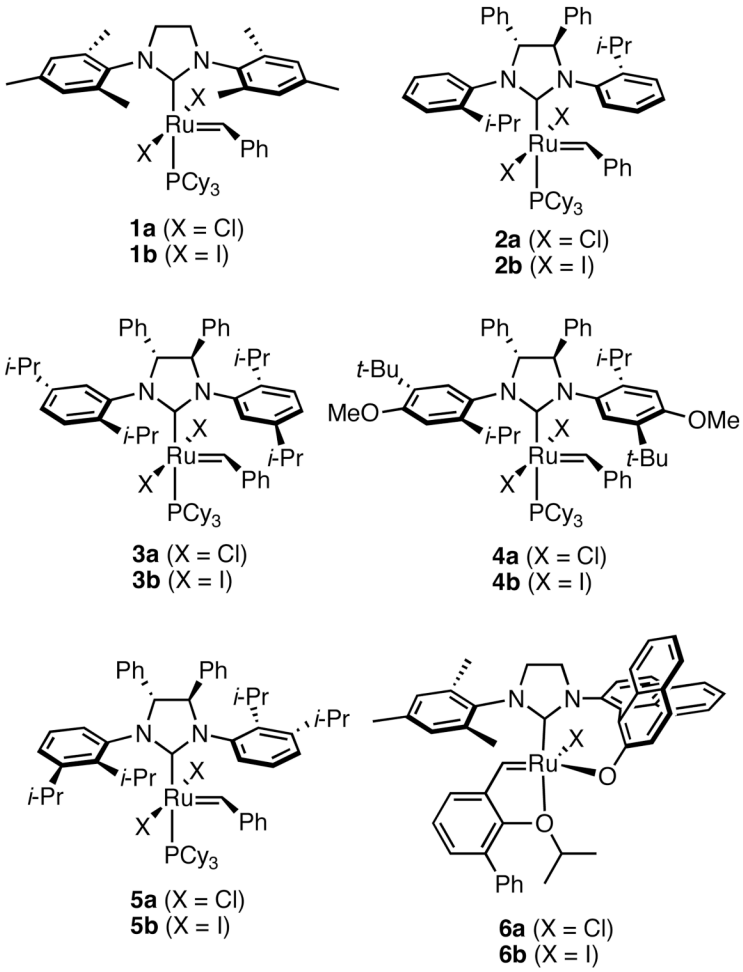
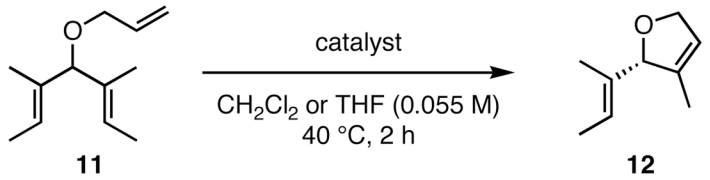


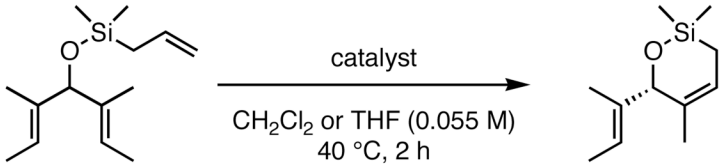
Chart 1.
Ruthenium Olefin Metathesis Catalysts.

Table 1

Relative Reactivity and Selectivity of Asymmetric Ruthenium Catalysts.



11 **12**



13 **14**

catalyst	11 to 12[a]		13 to 14[a]	
	ee(%)[b]	conv[c] (%)	ee (%)[b]	conv[c] (%)
2a	35	>98	83	>98
3a	31	>98	81	>98
4a	30	>98	75	>98
5a	46	>98	92	>98
2b	90	>98	86	68
3b	84	>98	90	>98
4b	87	>98	85	>98
5b	90	>98	92	58

[a] Reactions with **2a**-**5a** (2 mol %) run in CH_2Cl_2; catalysts **2b**-**5b** generated by stirring **2a**-**5a** (4 mol %) in THF with 25 equiv NaI.

[b] Enantiomeric excesses determined by chiral GC; see supporting information for chromatograms and proof of absolute stereochemistry.

[c] Determined by ^{1}H NMR spectrum of crude reaction mixture.

Table 2

ARCM Reactions with Chiral Ruthenium Catalysts.[a]

triene	product	catalyst (mol %)	ee (%)[b]	conversion (%)[c]	yield (%)
 **11**	 **12**	**2b** (4)	90	>98	64
 **15**	 **16**	**2b** (4)	90	>98	77
 **17**	 **18**	**2b** (4) **5a** (2)[d]	85 76	5 93	nd 92
 **19**	 **20**	**2b** (4)	85	~2[e]	nd
 **13**	 **14**	**5a** (0.8)	92	>98	77[f]
 **21**	 **22**	**5a** (1)	92	65	64
 **23**	 **24**	**2b** (4)	78	>98	98

[a] Conditions for reactions with **2b**: NaI (25 equiv relative to catalyst) and **2a** in THF (0.055 M in triene) for 1h at rt, then add triene and stir for 2h at 40 °C; conditions for reactions with **5a**: triene, CH_2Cl_2 (0.055 M in triene), and **5a** for 2h at 40 °C.

[b] Enantiomeric excesses determined by chiral GC; see supporting information for chromatograms and proof of absolute stereochemistry.

[c] Determined by ^{1}H NMR spectrum of crude reaction mixture.

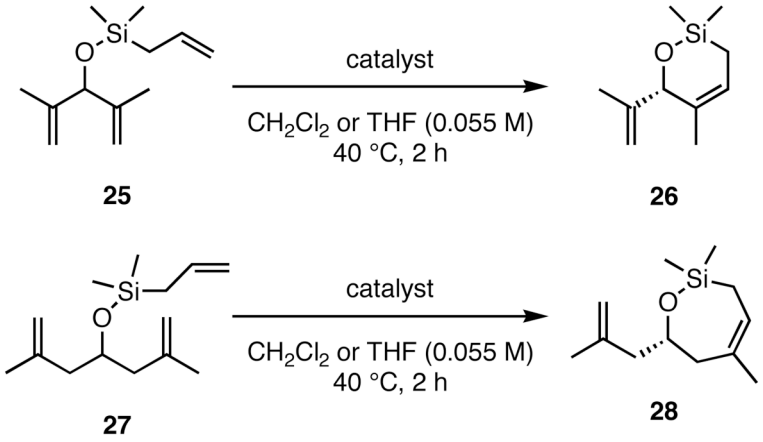
[d] See footnote 13.

[e] Never isolated as a pure compound.

[f] Reaction done on a 4 mmol (0.95 g) of **13** scale. nd = not determined

Table 3

Challenging ARCM Substrates.



catalyst	25 to 26[a]		27 to 28[a]	
	ee (%)[b]	conv[c] (%)	ee (%)[b]	conv[c] (%)
2a	16	72	−5	>98
3a	45	92	−5	>98
5a	30	93	−8	>98
2b	nd	<2	3	15
3b	nd	6	15	18

[a] Reactions with **2a**-**5a** (2 mol %) run in CH_2Cl_2; catalysts **2b** and **3b** generated by stirring **2a** and 3a (4 mol %) in THF with 25 equiv NaI.

[b] Enantiomeric excesses determined by chiral GC; see supporting information for chromatograms and proof of absolute stereochemistry.

[c] Determined by ^{1}H NMR spectrum of crude reaction mixture. nd = not determined