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Enantioselective Ruthenium-Catalyzed Ring-Closing Metathesis

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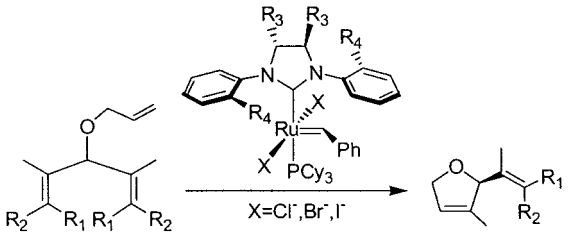
ABSTRACT



The first enantioselective ruthenium olefin metathesis catalysts have been prepared, and high enantiomeric excesses (up to 90%) are observed in the desymmetrization of achiral trienes. A model consistent with the stereochemical outcome of the reactions is described and suggests side-on olefin binding and reorganization of the halide ligands.

Over the past decade, olefin metathesis has emerged as a powerful carbon−carbon bond-forming reaction that is widely used in organic synthesis and polymer science.[1] A major advance in this field was the development of chiral molybdenum catalysts[2] that exhibit high enantioselectivity in a variety of ring-closing[3] and ring-opening[4] metathesis reactions.[5] However, these molybdenum-based systems require specific substrate-to-catalyst matching, necessitating reaction optimization and the availability of a number of catalysts. Additionally, because these systems lack extensive functional group tolerance and require rigorous exclusion of air and moisture, the development of enantioselective metathesis catalysts based on ruthenium is expected to expand dramatically the scope and utility of these transformations. Herein, we report chiral N-heterocyclic carbene (NHC)[6] complexes of ruthenium[7] that exhibit high enantioselectivity (up to 90% ee) in the ring-closing metathesis of achiral trienes.[3b]

In light of studies on the $IMesH_2$/ruthenium system ($IMesH_2$ = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) that suggest that the NHC ligand does not dissociate from ruthenium during metathesis,[8] desymmetrization of the $IMesH_2$ ligand was effected in the development of chiral

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(5) For an in situ preparation of chiral molybdenum catalysts, see: Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452−1456.

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ruthenium metathesis catalysts. Although the mesityl rings of the NHC ligand are readily replaced with chiral substituents through synthesis from commercially available chiral alkylamines, preliminary investigations into the selectivity of these ruthenium complexes are not promising.[9] Alternatively, synthesis of the NHC from commercially available chiral diamines introduces chirality to the imidazole ring, but the stereocenters of the ligand are remote from the metal center. By replacing the mesityl substituents with mono-*o*-substituted aryl groups, a steric effect is expected to more effectively transfer the stereochemistry of the ligand nearer the metal center by placing the *o*-substitutents of the aryl groups in an arrangement *anti* to the substituents on the imidazole ring (Figure 1).

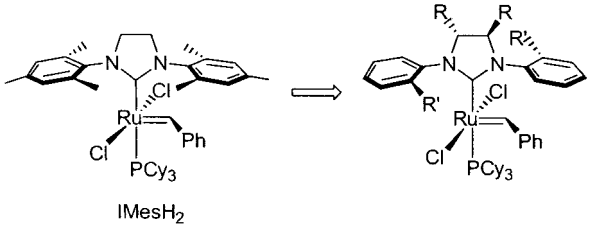
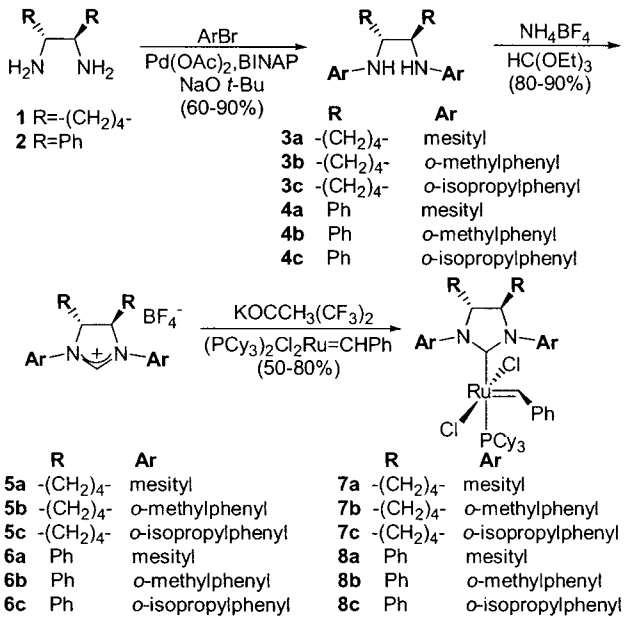


Figure 1. Desymmetrization of the $IMesH_2$/ruthenium system.

The enantiomerically pure ruthenium complexes are easily prepared in three steps from commercially available starting materials (Scheme 1). Diamines **3a**−**c** and **4a**−**c** are synthesized by palladium-catalyzed amination of the appropriate aryl bromides with (1*R*,2*R*)-1,2-diaminocyclohexane (**1**) or (1*R*,2*R*)-diphenylethylenediamine (**2**).[10] The resulting diamines are condensed with triethyl orthoformate and ammonium tetrafluoroborate to produce the corresponding imidazolium tetrafluoroborate salts **5a**−**c** and **6a**−**c**.[11] These salts are treated with potassium hexafluoro-*tert*-butoxide[12] followed by $(PCy_3)_2(Cl)_2Ru{=}CHPh$ to displace a single PCy_3 and generate the desired chiral complexes **7a**−**c** and **8a**−**c** in good yields. Complexes **7a**−**c** and **8a**−**c** are air-stable

Scheme 1



solids and are easily purified on the benchtop by column chromatography.[13] The bromide and iodide analogues of these complexes are generated in situ by the addition of excess LiBr or NaI, respectively.[8c]

Although crystals have not been forthcoming for complexes **8b**,**c**, crystallographic evidence of the conformation of the chiral NHC ligands has been obtained by conversion of complex **8b** to bis(pyridine) adduct **9**.[14] The crystal structure of complex **9** (Figure 2) shows that the NHC ligand

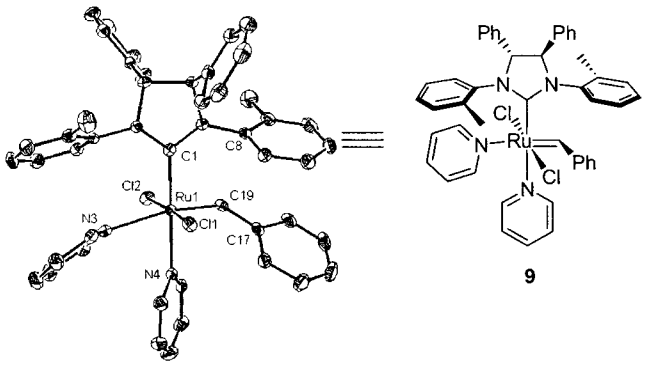


Figure 2. X-ray crystal structure of **9** (50% probability ellipsoids). Selected bond lengths and angles for **9**: Ru(1)−C(19) 1.871 Å, Ru(1)−C(1) 2.031 Å, Ru(1)−N(3) 2.352 Å, Ru(1)−N(4) 2.187 Å, C(8)−C(19) 2.758 Å, Cl(1)−Ru(1)−Cl(2) 175°, C(19)−Ru(1)−N(3) 166°, C(1)−Ru(1)−N(4) 180°, Cl(1)−Ru(1)−C(19)−C(17) 46°.

is approximately C_2-symmetric with the *o*-methyl group oriented *anti* to the phenyl substituent of the imidazole ring. Additionally, the phenyl group of the benzylidene is oriented *anti* to the *o*-methyl substituent of the proximal aryl ring.

121, 2674−2678. (d) Jafarpour, L.; Nolan, S. P. *J. Organomet. Chem.* **2001**, *617*, 17−27. (e) Weskamp, T.; Kohl, F. J.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416−2419. For reactivity studies, see: (f) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903−2906. (g) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (h) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277−1279.

(8) (a) Huang, J. K.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. (b) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162−2187. (c) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543−6554.

(9) Ruthenium complexes of 1,3-diisopinocampheol-4,5-dihydroimidazol-2-ylidene were tested with all substrates reported here, but exhibit only modest selectivity (for ligand synthesis, see ref 6e).

(10) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

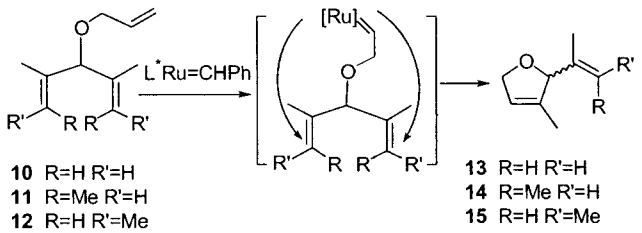
(11) Saba, S.; Brescia, A.-M.; Kaloustain, M. K. *Tetrahedron Lett.* **1991**, *32*, 5031−5034.

(12) If potassium *tert*-butoxide is used, the yields of **7** and **8** are dramatically reduced and a *tert*-butoxide adduct of ruthenium forms: Sanford, M. S.; Henling, L. M.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 3451−3453.

This *anti-anti* arrangement suggests that the stereochemistry of the phenyl substituents on the imidazole ring is effectively transferred to the metal center.

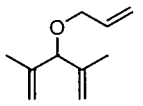
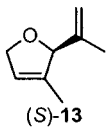
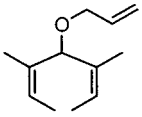
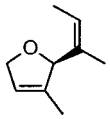
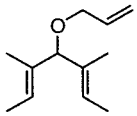
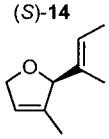
With a series of catalysts in hand, the enantioselective desymmetrization of substrates **10**−**12** to dihydrofurans **13**−**15** is effected (Scheme 2). Substrates **10**−**12** feature a

Scheme 2



monosubstituted central olefin with which the catalyst undergoes the initial metathesis reaction,[15] and two di- or trisubstituted pendant olefins with which the stereochemically defining cyclization step occurs. A preliminary series of reactions, the desymmetrization of substrate **10**, reveals three distinct trends in catalyst selectivity (Table 1). First, catalysts

Table 1. Enantioselective Desymmetrization of Trienes **10**−**12** by Catalysts **8a**−**c**

entry	substrate	catalyst	product	ee(%)[b]	k_{rel}	convn(%)[c]
1		**8a**		13	1.3	57
2		**8b**		23	1.6	95
3		**8c**		23	1.6	96
4		**8b**+NaI		38	2.2	18
5	**10**	**8c**+NaI	(*S*)-**13**	39	2.2	20
6		**8b**+NaI		17	1.4	78
7	**11**	**8c**+NaI	(*S*)-**14**	35	2.1	90
8		**8b**+LiBr		**63**	**4.4**	90
9		**8b**+NaI		**85**	**12.3**	91
10		**8c**+LiBr		**69**	**5.5**	90
11	**12**	**8c**+NaI	(*S*)-**15**	**90**	**19**	82

[a] Conditions: 2.5 mol % of catalyst, 55 mM substrate in CH_2Cl_2, 38 °C. When halide salt is added: 5 mol % of catalyst, 100 mol % of halide salt, 55 mM substrate in THF, 38 °C. [b] Absolute stereochemistry determined by comparison with GLC chromatograms reported in ref 3b. [c] Measured by chiral GLC (Chiraldex GTA Alltech) with toluene as an internal standard.

prepared from (1*R*,2*R*)-diphenylethylenediamine (**8a**−**c**) exhibit higher enantioselectivity (up to 23% ee) than those prepared from (1*R*,2*R*)-1,2-diaminocyclohexane (**7a**−**c**) (<9% ee). Second, replacement of the mesityl groups (**8a**, 15% ee, entry 1) with *o*-methyl- (**8b**, 23% ee, entry 2) or *o*-isopropylaryl groups (**8c**, 23% ee, entry 3) increases the enantioselectivity. Third, changing the halide ligands of catalyst **8c** from Cl^- (23% ee, entry 3) to I^- (39% ee, entry 5) further improves the enantioselectivity. Although the enantioselectivity increases upon changing to the iodide, a marked reduction in the conversion to **13** is observed, presumably due to the instability of the diiodoruthenium methylidene complex[16] generated in the course of this reaction.

To prevent the generation of the methylidene complex and to explore the substrate requirements for high enantioselectivity, trisubstituted substrates **11** and **12** are tested. In the case of the (*Z*)-trisubstituted olefin **11**, conversions are always high, but enantioselectivites are low (<36% ee). However, in the case of (*E*)-trisubstituted olefin **12**, high enantioselectivity and high conversion are achieved (90% ee, entry 11). Importantly, neither solvent (THF, dichloromethane, benzene) nor temperature (−15 °C, 0 °C, 38 °C) has a significant effect on the enantioselectivity of these systems. Additionally, the activity and stability of catalysts **8b** and **8c** are similar to those of the $IMesH_2$/ruthenium system (rigorous exclusion of air and moisture is not required).

Previous studies suggest a 14-electron, four-coordinate species as the active intermediate in the metathesis cycle,[17] but the geometry of this intermediate and the subsequent olefin complex intermediates remains unknown. Three different conformations of the intermediate olefin complex have been proposed (Figure 3):[18] **A**, in which one halide ligand

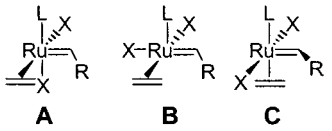


Figure 3. Possible geometries of olefin complex.

is bound *trans* to the L-type ligand; **B**, in which the chlorides adopt a *cis* arrangement in the alkylidene−halide−olefin plane; and **C**, in which the olefin binds *trans* to the L-type ligand. Of these conformations, only **C** is inconsistent with the observed stereochemical outcome of the desymmetrization of substrates **10**−**12**. Although geometry **B** cannot be

(13) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799.
(14) Similar results are observed in achiral NHC/ruthenium bis(pyridine) complexes, see: (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H., submitted. (b) Sanford, M. S. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2001.
(15) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484−2489.
(16) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202−7207.
(17) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749−750.
(18) (a) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics* **2001**, *20*, 3845−3847. (b) Tallarico, J. A.; Bonitatebus, P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157−7158. (c) Hinderling, C.; Baumann, H.; Chen, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2685−2689. (d) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204−8214. (e) Bianchini, C.; Lee, H. M. *Organometallics* **2000**, *19*, 1833−1840. (f) Moers, F. G.; Langhout, J. P. *J. Inorg. Nucl. Chem.* **1977**, *39*, 591−593. (g) Brown, L. D.; Barnard, C. F. J.; Daniels, J. A.; Mawby, R. J.; Ibers, J. A. *Inorg. Chem.* **1978**, *17*, 2932−2935. (h) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897.

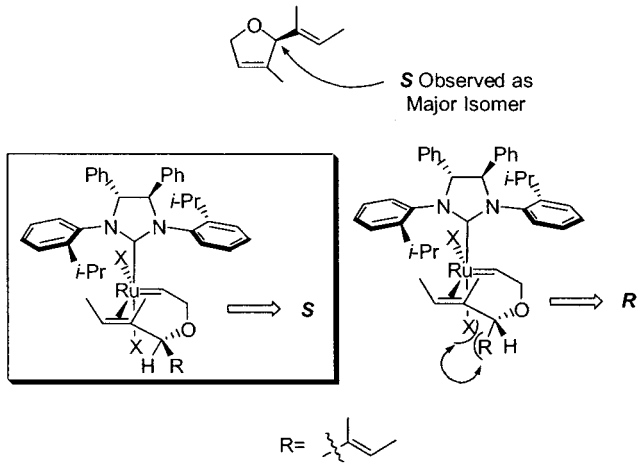


Figure 4. Stereochemical model of catalyst **8c** (configuration of dihydrofuran **15**).

discounted, geometry **A** appears to be most consistent with the observed ligand effects and stereochemical outcome of these reactions. Geometries similar to that of **A** have been observed crystallographically[18a] and computationally,[18d] and three key features of stereochemical model **A** are consistent with the observed selectivity (Figure 4). First, the alkylidene substituent is oriented *anti* to the bulky NHC ligand. Second, the tethered olefin binds to the front face of the complex to avoid a steric interaction with the bulky *o*-isopropyl group of the NHC ligand. Third, the unbound olefin (R in Figure 4) occupies the distal position relative to the apical halide; this proposed steric interaction between the unbound olefin and apical halide is further consistent with the dramatic increase in enantioselectivity observed upon changing the halide from Cl^- to Br^- to I^-.

In conclusion, the first enantioselective ruthenium olefin metathesis catalysts have been prepared, and high enantioselectivities (up to 90% ee) are observed in the desymmetrization of achiral trienes. A model consistent with the stereochemical outcome of the reactions is described and suggests side-on olefin binding and reorganization of the halide ligands. An understanding of the olefin complex geometry has implications in general mechanistic understanding and for the further development of enantioselective metathesis catalysts and reactions. Furthermore, the ease of handling and anticipated functional group tolerance of the described ruthenium catalysts are expected to expand the utility of enantioselective olefin metathesis in organic synthesis by allowing access to a wide range of substrates.

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Supporting Information Available: Experimental details for all new complexes, GC traces, and a complete table of enantiomeric excesses for all substrates and catalysts. This information is available free of charge via the Internet at http://pubs.acs.org.

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