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Chiral Ru-Based Complexes for Asymmetric Olefin Metathesis: Enhancement of Catalyst Activity through Steric and Electronic Modifications

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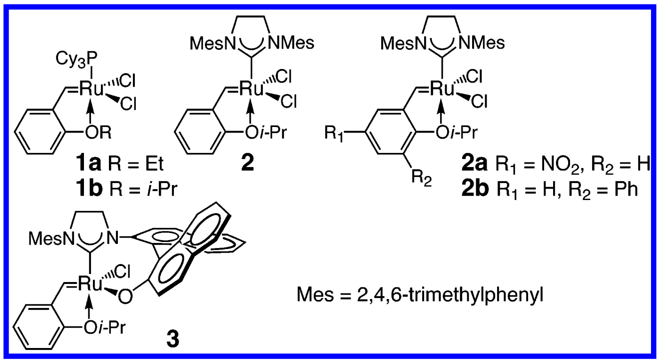
Abstract: Design, synthesis, characterization, and catalytic activity of six enantiomerically pure Ru-based metathesis catalysts are disclosed (**3a**−**3f**). The new chiral catalysts were prepared through steric and electronic alterations of the parent catalyst system (**3**). The present studies indicate that the effect of structural modifications of chiral complex **3** does not always correspond to those of the related achiral complexes. The present findings illustrate that modified Ru complexes (**3e** and **3f**) deliver reactivity levels that are more than 2 orders of magnitude higher than **3**. Reactivity and physical data are provided that shed light on the origin of activity differences. Some members of the new generation of chiral Ru catalysts promote asymmetric ring-opening (AROM) and ring-closing (ARCM) metatheses that cannot be effected by the first generation chiral catalyst (**3**).

Introduction

Since isolation of **1a** in these laboratories in 1996 (Chart 1),[1] we have been involved in the development of a variety of practical Ru-based metathesis catalysts[2] that bear a bidentate styrene ether ligand. Notably, these efforts have led to the synthesis and characterization of recyclable Ru complexes **1b**[3] and **2**.[4] It has also been demonstrated that **2** exhibits reactivity profiles that are unavailable through the related phosphine-containing Ru catalysts.[5] The unique stability and mechanism of action[5k] of **1** and **2** has subsequently resulted in disclosures regarding syntheses of supported variants.[6] While the present studies were in progress, electronically and sterically modified benzylidene ether derivatives **2a**[7] and **2b**[8] were shown to exhibit higher activity than **2**; however, no data were provided regarding the recyclability of these modified catalysts.

Chart 1



In connection to an initiative related to the development of *chiral* variants of Ru catalysts represented by **2**, we recently reported the stereoselective synthesis and activity of optically pure styrenyl ether carbene **3** as a complex that promotes asymmetric olefin metathesis (AOM).[9,10] We demonstrated that asymmetric ring-opening metathesis/cross-metathesis (AROM/

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(1) (a) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488−1489. (b) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

(2) For reviews on catalytic olefin metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833−1836. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (d) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997. (e) Furstner, A. *Top. Catal.* **1997**, *4*, 285−299. (f) *Alkene Metathesis in Organic Synthesis*; Furstner, A., Ed.; Springer: Berlin 1998. (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (h) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (i) Randall, M. L.; Snapper, M. L. *Strem Chemiker* **1998**, *17*, 1−9. (j) Phillips, A. J.; Abell, A. D. *Aldrichchim. Acta* **1999**, *32*, 75−89. (k) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (l) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012−3043. (m) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(3) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799.

(4) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(5) (a) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327−332. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451−1454. (c) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430−432. (d) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796−1797. (e) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692−1693. (f) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595−1606. (g) Lazarova, T.; Chen, J. S.; Hamann, B.; Kang, J. M.; Homuth-Trombino, D.; Han, F.; Hoffmann, E.; McClure, C.; Eckstein, J.; Or, Y. S. *J. Med. Chem.* **2003**, *46*, 674−676. (h) Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927−2930. (i) Nosse, B.; Chhor, R. B.; Jeong, W. B.; Bohm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941−944. (j) Demel, S.; Riegler, S.; Wewerka, K.; Schoefberger, W.; Slugovc, C.; Selzer, F. *Inorg. Chim. Acta* **2003**, *345*, 363−366. For a study shedding light on the mechanistic principles that govern the reactivity of nonphosphine Ru catalysts, see: (k) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4035−4037.

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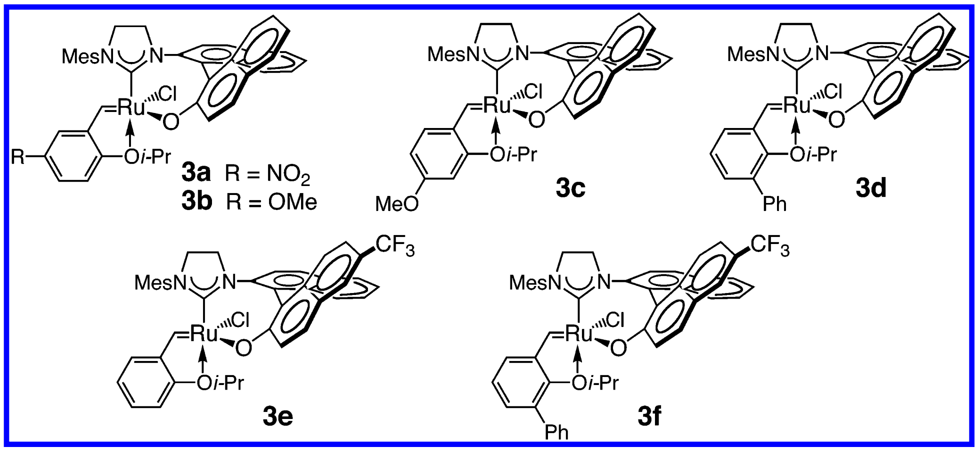
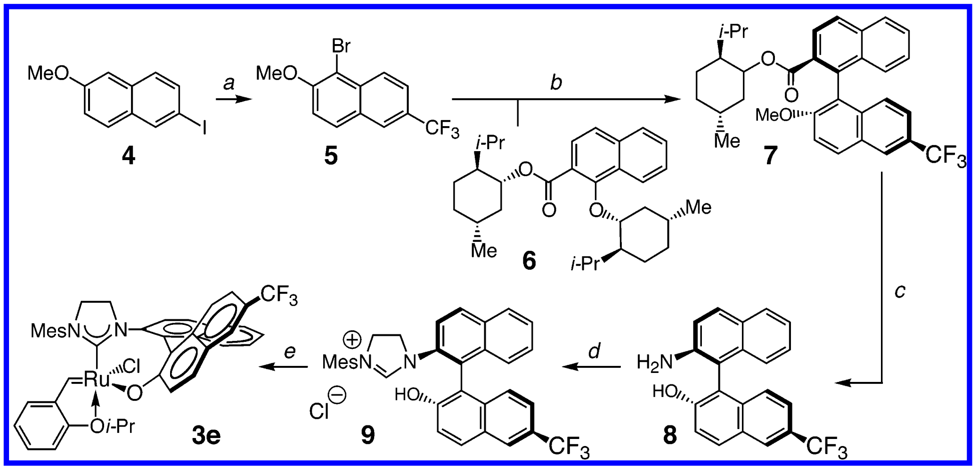
Chart 2. Second Generation Chiral Ru-Based Metathesis Catalysts Bearing Styrene Ether Ligands



Scheme 1



[a] 1. $ClCF_2CO_2Me$, CuI, KF, DMF, 120 °C, 16 h; 78%. 2. NBS, MeCN, 3 h; 82%. [b] Mg, THF, then **6**, C_6H_6, 60 °C, 48 h; 95:5 diastereoselectivity; 84%. [c] 1. KOH, EtOH, 80 °C, 18 h. 2. $EtCO_2Cl$, Et_3N; NaN_3, −15 °C, C_6H_6, 80 °C; KOH; 84% overall. 3. BBr_3, CH_2Cl_2; 90%. [d] 1. MesN(Boc)CH_2CHO, Na$(OAc)_3$BH, 22 °C, 2 h. 2. HCl, MeOH, −78 °C, 5 min. 3. HC$(OEt)_3$, 120 °C, 4 h; 81% overall. [e] PPh_3 (vs PCy_3) derivative of **1b**, Ag_2CO_3, THF, C_6H_6, 75 °C, 30 min; 48%. Mes = 2,4,6-trimethylphenyl.

CM) can be promoted with high enantioselectivity (up to 96% ee) by **3** in cases where such processes are not feasible with chiral Mo-based systems (competitive oligomerization).[11] Furthermore, we showed that reactions may be carried out in air and with commercial grade undistilled solvents. As with complexes **1** and **2**, catalyst **3** can be recovered and reused. Nonetheless, **3** proved to be less reactive than its achiral analogue (**2**) probably as a result of various steric (large chiral ligand) and electronic factors (replacement of a Cl with an aryloxide). To access more active catalysts, we set out to prepare new optically pure Ru carbenes through modifications of the benzylidene and chiral ligands in **3**. Synthesis and metathesis activity of six new enantiomerically pure Ru carbenes are described herein. The present findings illustrate that **3d** and **3f** (Chart 2) deliver reactivity levels that are more than 2 orders of magnitude higher than **3**, and readily promote AOM reactions that cannot be effected by the first generation chiral catalyst. These studies indicate that the effect of structural modifications in chiral complex **3** do not always correspond to those of the achiral complexes, and that stereochemical attributes of a substrate may exert a significant effect on the outcome of a catalytic metathesis process.

Results and Discussion

Initial Mechanistic Considerations and Selection of Modified Chiral Ru Catalysts. For a variety of reasons we decided to prepare the modified chiral catalysts that are shown in Chart 2. We surmised that the electron-withdrawing NO_2 (*para* to the ligating O*i*−Pr) in **3a** would weaken *i*-PrO→Ru chelation and facilitate initiation of the catalytic cycle. A similar influence might also be expected from the electron-releasing OMe (*para* to the Ru═C bond) in **3c** where increased electron donation

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(6) (a) Kingsbury, J. S.; Garber, S. B.; Giftos, J. M.; Gray, B. L.; Okamoto, M. M.; Farrer, R. A.; Fourkas, J. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4251−4255. See also: (b) Grela, K.; Trynowski, M.; Bieniek, M. *Tetrahedron Lett.* **2002**, *43*, 9055−9059. (c) Connon, S. J.; Dunne, A. M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3835−3838. (d) Dowden, J.; Savovic, J. *Chem. Commun.* **2001**, 37−38. (e) Yao, Q. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3896−3898.

(7) (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4038−4040. For a related more recent disclosure, see: (b) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963−966.

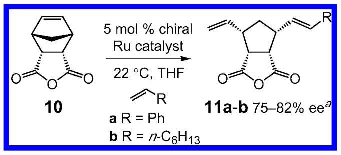
(8) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2403−2405.

(9) VanVeldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954−4955.

(10) For an alternative class of chiral Ru catalysts for olefin metathesis, see: Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225−3228.

(11) As an example, the reaction shown in Tables 1−2 affords only polymerization products in the presence of chiral Mo-based complexes. For an overview of Mo-catalyzed enantioselective olefin metathesis, see: (a) Hoveyda, A. H.; Schrock, R. R. *Chem., A Eur. J.* **2001**, *7*, 945−950. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, in press

Table 1. Relative Efficiency of Chiral Ru Catalysts



catalyst	rel. rate[a] R = Ph	rel. rate[a] R = n-C_6H_{13}
3	1	1
3a	3	3
3b	2	2
3c	1	1
3d	***130***	***110***
3e	3	3
3f	***160***	***140***

[a] See the Supporting Information for details on measurement of relative rates.

into the metal center would reduce its Lewis acidity. The above hypotheses find support in reports regarding the catalytic activity of achiral **2a** (Chart 1);[7a] in addition, the validity of such proposals in relation to chiral Ru complexes would be further substantiated if **3b** proved to be significantly less active than **3**. Complex **3d** would establish whether a recent observation regarding higher activity of its corresponding achiral analogue (cf. **2** in Chart 1) pertains to this class of chiral Ru catalysts.[8] Enantiomerically pure carbenes **3e** and **3f** allow us to determine the significance of reduced electron donation to the Ru center by the aryloxide oxygen.[12]

Synthesis of New Enantiomerically Pure Chiral Ligands and Ru Catalysts. Ru carbenes **3a**−**3f** were prepared in the optically active form by reaction of the requisite chiral imidazolinium salt and an appropriate achiral Ru carbene (e.g., **1b**, Chart 1).[9,13] The more electron deficient chiral ligand **9**, needed for access to complexes **3e** and **3f**, was obtained with excellent diastereoselectivity (>98%) by the route depicted in Scheme 1. All the Ru complexes in Chart 2 are isolated as brownish green solids, and can be purified by silica gel chromatography in air with reagent grade solvents (hexanes and CH_2Cl_2). Chiral Ru carbenes shown in Chart 2 are stable idefinitely under an atmosphere of N_2. Complexes **3b**−**3d** and **3e** are air stable; **3a** and **3f** undergo $\sim$5% decomposition after one week and 48 h, respectively (as judged by 400 MHz ^{1}H NMR analysis).

Relative Reactivity of Various Chiral Ru Catalysts. To examine the relative efficiency of the new chiral Ru catalysts, their activity in promoting the AROM/CM reactions of **10** with styrene and 1-octene was explored. The results of these studies are illustrated in Table 1 and Figure 1 (for reaction of **10** with styrene to afford **11a**). As the data in Table 1 indicate, although the presence of a NO_2 group leads to a chiral catalyst (**3a**) that is three times more active than **3**, enhancement of reactivity is significantly lower than that observed for **2a** (vs **2**).[7] Furthermore, the presence of an electron-donating OMe group in **3b** results in a catalyst that is still twice as active as its parent complex. Our studies indicate that electron donation to the Ru=C in **3c** does not affect its catalytic activity. In contrast to the above-mentioned electronic modifications, the steric alteration that resulted in the highly active achiral catalyst **2b**[8] also seems to enhance significantly the efficiency of chiral complex **3d**, which promotes the AROM/CM of **10** (with styrene or 1-octene) *more than 100 times faster* than **3** (see Table 1).Consistent with extant mechanistic paradigms regarding the significance of the relative Lewis acidity of the Ru center and the facility of the coordination of the olefin substrate to the catalyst,[12] the electronically modified **3e** is three times more potent than **3** in promoting AROM/CM of **10**. As can be seen from the data shown in Figure 1 and Table 1, the positive effects detected for **3d** and **3e** are additive: the doubly modified chiral complex **3f** possesses the highest level of potency among those studied (relative rate = 140−160). It should be noted that all transformations shown in Table 1 proceed with approximately the same levels of enantioselectivity as observed with **3** (75−82% ee).[14] Moreover, product enantiopurities remain unchanged after extended reaction times, indicating that observed selectivities do not arise from kinetic resolution.

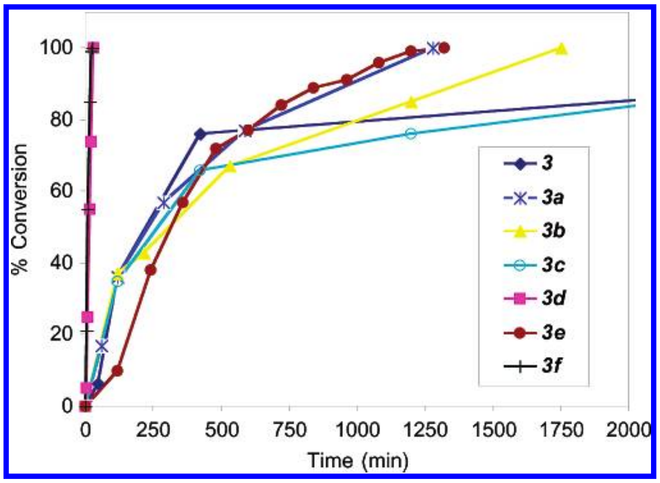


Figure 1. Relative rates of AROM/CM reactions (to afford **11a**) catalyzed by various chiral Ru catalysts (22 °C). (Reactions with catalysts **3** and **3c** require 4000 min to proceed to >98% conv).

Table 2. Comparison of the Activity of Selected Chiral Ru Catalysts[a]

entry	*R*	catalyst	time; conv (%)[b]	yield (%)[c]
1	Ph	**3**	66 h; >98	35
2	Ph	**3e**	22 h; >98	55
3	Ph	**3f**	25 min; >98	85
4	n-C_6H_{13}	**3**	46 h; >98	nd
5	n-C_6H_{13}	**3e**	14 h; >98	74
6	n-C_6H_{13}	**3f**	20 min; >98	54

[a] Enantioselectivities (75−82%) were determined by analysis of the (*R*)-MTPA esters derived from the reduced diols (chiral HPLC; chiralpak AD column). [b] Determined by 400 MHz ^{1}H NMR analysis. [c] Isolated yields after silica gel chromatography. nd = not determined.

The enhanced reactivity of the new generation of chiral catalysts is especially evident by the representative data depicted in Table 2. Reactions with **3e** (entries 2 and 5, Table 2) proceed significantly more efficiently than those promoted by **3** (entries 1 and 4), and the same transformations proceed to completion

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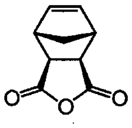
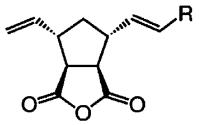
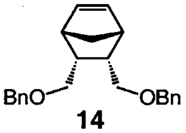
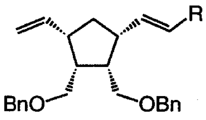
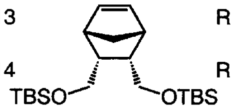
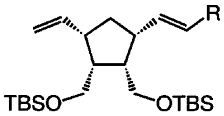
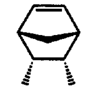
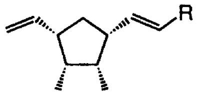
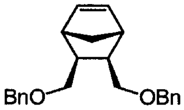
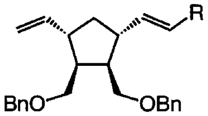
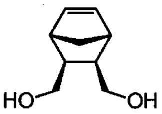
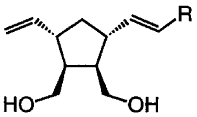
(12) Sanford, M. S.; Henling, L. M.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3451−3453.

(13) See the Supporting Information for experimental details. It should be noted that the electron deficient styrene ether complex related to **3c** (CF_3 instead of OMe) could not be prepared due to susceptibility of the requisite styrene to undergo rapid polymerization.

(14) These are the same enantioselectivities observed with parent complex **3**. In our previous report (ref 9), enantioselectivity values for non-UV-active products from reactions of **10** with 1-heptene and vinylcyclohexane were measured by HPLC/ELSD methods to be >98% ee. Subsequent investigations indicated that ELSD methods are unreliable in measuring ee values (of at least this class of compounds). Alternative approaches led us to determine subsequently that the above reactions proceed in 80−82% ee. *The remaining enantioselectivities in ref 9 are correct as initially reported.*

Table 3. Comparison of the Activity of Chiral Ru Catalysts **3** and **3d**[a]

entry	substrate	RC(H)=CH$_2$	product	catalyst	time (h); conv (%)[b]	yield (%)[c]	trans : cis	rec. cat yield (%)[c]	ee (%)[d]
1	 **12**	R = Ph		**3**	1; >98	63	92 : 8	98	70
2		R = Ph		**3d**	0.25; >98	60	95 : 5	50	70
3		R = *n*-C$_5$H$_{11}$	**13 a–c**	**3**	5; >98	60	90 : 10	85	75
4		R = *n*-C$_5$H$_{11}$	**a** R = Ph	**3d**	0.75; >98	58	96 : 4	10	74
5		R = Cy	**b** R = *n*-C$_5$H$_{11}$	**3**	5; >98	62	90 : 10	90	74
6		R = Cy	**c** R = Cy	**3d**	0.75; >98	57	95 : 5	10	72
7	 **14**	R = Ph		**3**	2; >98	74	>98 : 2	>98	85
8		R = Ph		**3d**	0.5; >98	70	>98 : 2	10	88
9		R = *n*-C$_5$H$_{11}$	**15 a–c**	**3**	5; >98	69	81 : 19	74	90
10		R = *n*-C$_5$H$_{11}$	**a** R = Ph	**3d**	0.1; >98	65	95 : 5	77	91
11		R = Cy	**b** R = *n*-C$_5$H$_{11}$	**3**	5; >98	71	82 : 18	82	89
12		R = Cy	**c** R = Cy	**3d**	0.1; >98	77	95 : 5	38	88
13	 **16**	R = Ph	 **17**	**3**	5; >98	79	>98 : 2	73	78
14		R = Ph		**3d**	0.5; >98	>98	>98 : 2	66	80
15	 **18**	R = Ph	 **19**	**3**	24; <2	nd	nd	nd	nd
16		R = Ph		**3d**	24; <2	nd	nd	nd	nd
17	 **20**	R = Ph	 **21**	**3**	1; >98	80	96 : 4	90	10
18		R = Ph		**3d**	0.25; >98	75	>98 : 2	30	10
19	 **22**	R = Ph	 **23**	**3**	1; >98	48	97 : 3	38	11
20		R = Ph		**3d**	0.25; >98	40	>98 : 2	<2	10

[a] Conditions: 5 mol % catalyst, 2 equiv terminal olefin, 22 °C, THF, under N$_2$ atm. [b] Determined by analysis of 400 MHz ^{1}H NMR of the upurified mixture. [c] Isolated yields after silica gel chromatography. [d] Determined by chiral HPLC and 400 MHz ^{1}H NMR analysis of the derived (*R*)-MTPA esters. nd = not determined.

within minutes in the presence of chiral catalyst **3f** (entries 3 and 6).

Additional cases of Ru-catalyzed AROM/CM are shown in Table 3. In all instances, reactions with chiral complex **3d** are notably more facile than those promoted in the presence of Ru catalyst **3**. As the data in entries 3−6 and 9−12 of Table 3 illustrate, such rate differences are more pronounced when aliphatic olefin partners are involved. Several other issues regarding the data presented in Table 3 merit mention:

(1) In all cases, the less reactive chiral catalyst **3** is recovered more efficiently than complex **3d** (see below for a more detailed discussion on catalyst recovery).

(2) Relative stereochemistry within a disubstituted olefin substrate can exert a profound influence on enantioselectivity of the Ru-catalyzed AROM/CM. For example, as depicted in Table 3, although reactions of *exo*-anhydride **12** are only slightly less selective than those with *endo*-anhydride **10**, reactions of *endo* **14** (85−88% ee; entries 7−8 of Table 3) are significantly more enantioselective than similar transformations carried out with *exo* substrate **20** (10% ee; entries 17−18 of Table 3).

(3) The stereochemical identity of the more substituted AROM/CM substrate can significantly alter the efficiency of the metathesis process. As shown in entries 15−16 and 19−20 of Table 3, whereas *endo* diol **18** is recovered unreacted even

after 24 h, the derived *exo* substrate **22** readily undergoes reaction (>98% conv in 0.25 to 1 h) albeit with minimal enantioselectivity. The high reactivity of **22**, and the fact that reaction of **10** with styrene proceeds in the presence of one equiv of *n*-octanol with identical efficiency and selectivity (with 5 mol % **3** or **3d**), indicate that the positioning of the Lewis basic sites relative to Ru carbene (formed through reaction of the catalyst with the strained olefin) determines whether a neighboring alcohol function inhibits the AROM/CM.

(4) Ru-catalyzed AROM/CM can be effected in air (vs under an N_2 atm) to afford the desired products in similar yields and selectivities, but with lower yield of recovered catalyst. As an example, the reaction shown in entry 7 (5 mol % **3**) of Table 3 delivers **15a** in 74% yield and 85% ee along with recovered **3** in 52% isolated yield (>98% conv in 2 h at 22 °C). When Ru complex **3d** (10 mol %)[15] is used in air (cf. entry 8), reaction proceeds to >98% conv in 30 min and the desired product (**15a**) is isolated in 60% yield and 77% ee (<10% recovered **3d**).

Possible Origins of Higher Catalytic Activity. In connection to studies regarding electronically modified achiral catalyst **2a** (see Chart 1), it has been suggested[7a] that the higher activity of **3d** and **3f** may be the result of faster initiation of the catalytic cycle due to a more facile release[1] of the sterically demanding phenyl-substituted benzylidene. This proposal finds credence in the X-ray structure of **3d**, illustrated in Figure 2. The presence of the benzylidene's phenyl group appears to restrict the space available to the adjacent O*i*−Pr, causing an increase in the $C_{37}-C_{38}-O-C_{39}$ dihedral angle and Ru−O bond length in **3d** (vs **3**).[16] The congested steric environment of the phenyl-substituted benzylidene in **3d** is further manifested in the upfield shift of its O*i*−Pr methine proton ($C_{39}-H$ in Figure 2: δ 4.77 in **3** vs δ 4.10 in **3d**). This likely arises from restricted conformational mobility of O*i*−Pr and phenyl groups in **3d**, situating the methine C−H over the face of the adjacent aromatic ring.

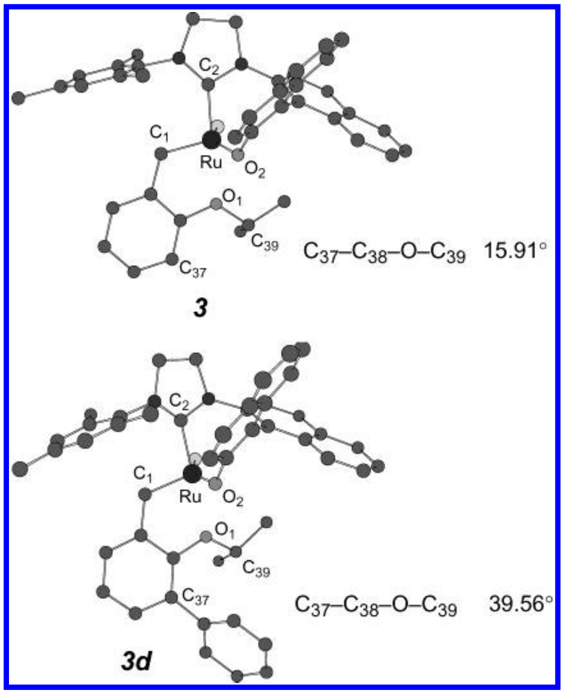
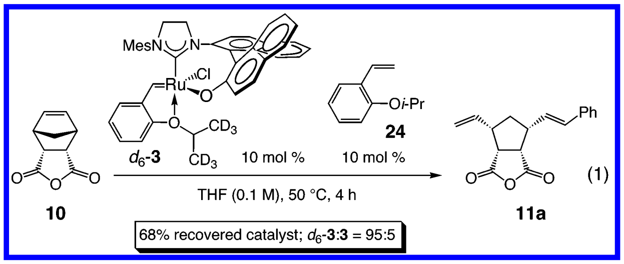


Figure 2. X-ray crystal structure of chiral Ru complex **3** and **3d**.

Efficiency of Catalyst Recovery and Its Mechanistic Implications. As illustrated in Table 4, the two most active catalysts (**3d** and **3f**) are recovered less efficiently. Therefore, it may be argued that factors which influence the release of the active Ru catalyst may also reduce the facility with which the styrene ether reassociates with the active Ru system (e.g., Ru-methylidene) to regenerate the original chiral complex. It could be suggested that, due to increased steric bulk of the chiral ligand, and in contrast to complex **2**, there is minimal regeneration of the styrene ether Ru complex. That is, higher catalyst activity resulting from more facile release of styrene ether could lead to lower yield of chiral catalyst recovery.[17]

To address the above questions, a crossover experiment involving deuterium-labeled chiral Ru catalyst *d*$_6$-**3** was carried out. We established that, as illustrated in eq 1, when catalytic AROM/CM of **10** leading to **11** is affected in the presence of an equivalent amount of nondeuterated styrene ether **24**, 95% of the recovered catalyst remains deuterated (as judged by 400 MHz ^{1}H NMR analysis; >98% conversion after 4 h at 50 °C). This finding suggests that, in the case of chiral Ru complexes such as **3**, the catalyst recovered at the end of a metathesis reaction for the most part represents the *unreleased* chiral Ru complex (**11a** obtained in ~80% ee), and that return of the styrene ether ligand is inefficient (otherwise, the presence of **24** would result in recovery of some amount of **3**).[18] Several related points should be mentioned: (1) Treatment of *d*$_6$-**3** with 1 equiv of **24** in the absence of substrate (0.01 M solution in THF; 4 h, 50 °C) leads to recovery of the deuterated catalyst in 90% yield without any detectable amount of **3** (<2% by 400 MHz ^{1}H NMR). (2) Subjection of the more active **3d** to one equivalent of **24** in the absence of substrate (0.01 M) results in a relatively more facile rate of exchange to afford **3** (~10% after 6 h at 22 °C). (3) Similar studies regarding achiral carbene **2** clearly indicate that, in contrast to the more sterically hindered chiral catalysts, efficient return of the released ligand does occur.[4]



Utility of the New Chiral Ru Catalysts in Efficient AOM. 1. Ru-Catalyzed AROM/CM. The enhanced activity of aforementioned chiral catalysts allow for Ru-catalyzed AROM/CM reactions to proceed with significantly lower catalyst loadings. For example, formation of **11a** is complete within 2 h in the presence of only 0.5 mol % **3f** at 22 °C (65% isolated yield), whereas with 5 mol % **3** reaction is complete (>98% conv) after 66 h.

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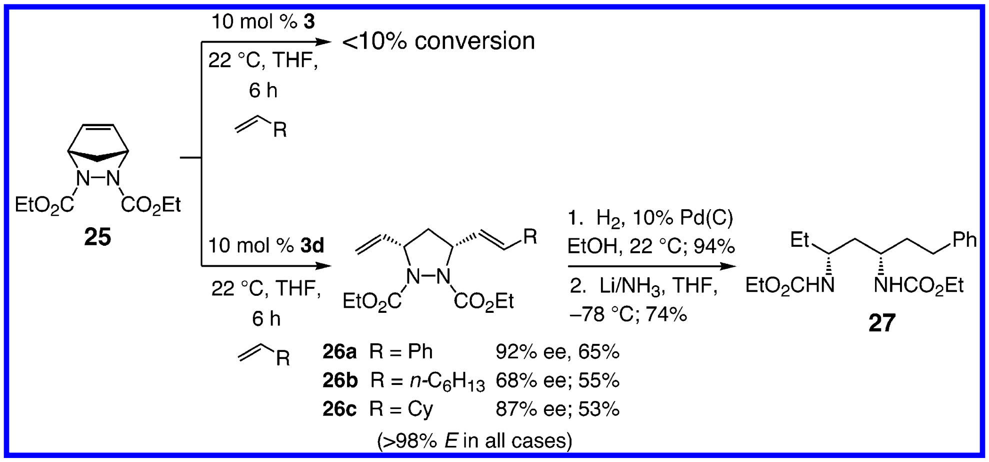
(15) Reaction in air with 5 mol % **3d** proceeded to 50% conv after one h, presumably due to instability of the more reactive and sensitive catalyst.

(16) Consistent with the above hypotheses, X-ray crystal structures of **3** and **3d** indicate that the $Ru-O_1$ bond length is slightly longer in **3d** than in **3**. Thus, $Ru-O_1$ bond length is 2.252 Å in **3** and for **3d** the two molecules in the unit cell show bond lengths of 2.267 and 2.294 Å, respectively.

(17) The low recovery yield for **3a** might be the result of less favorable reassociation of the less Lewis basic *p*-NO_2 styrene ether.

(18) Accordingly, the significantly lower yield of recovery of **3f** (cf. data in Table 3) is likely due to a combination of inefficient styrene ether return and lower stability of the CF_3-bearing Ru carbene. Moreover, recovery of the fluorinated Ru catalysts, including **3e**, is more cumbersome than the derived nonfluorinated analogues.

Scheme 2



Scheme 3. Ru-Catalyzed ARCM Reactions

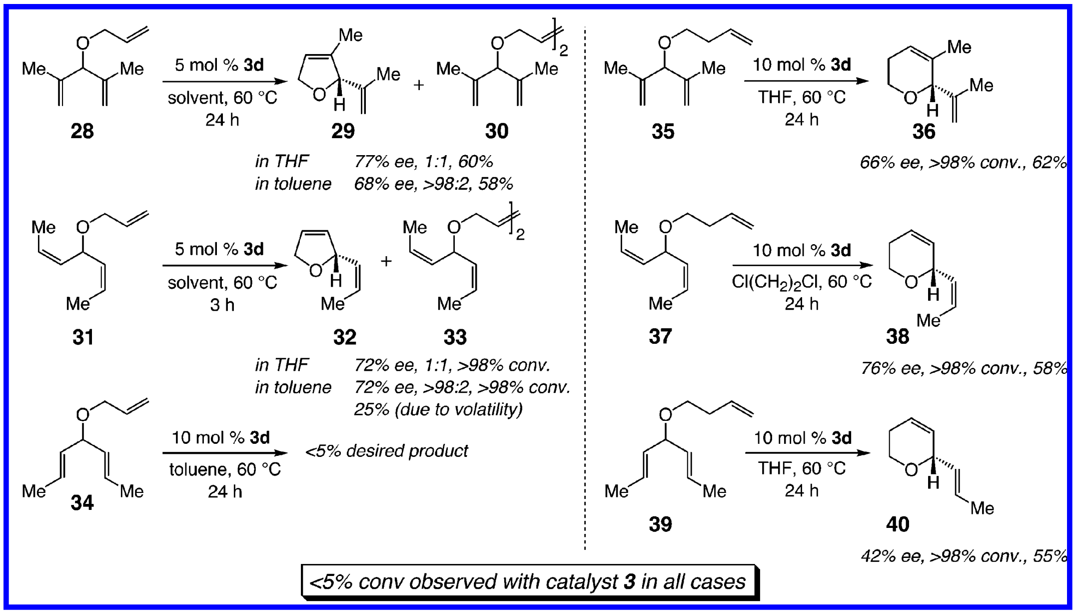


Table 4. Relative Efficiency of Chiral Catalyst Recovery from Synthesis of **11A**[a]

entry	catalyst	time (h)[b]	yield (%)[c]	rec. cat. yield (%)[c]
1	**3**	66	35	90
2	**3a**	21	74	65
3	**3b**	29	83	92
4	**3c**	58	94	92
5	**3d**	0.5	82	65
6	**3e**	22	55	88
7	**3f**	0.4	85	<20

[a] Conditions: 5 mol % catalyst, THF, 22 °C. [b] Time required for >98% conv. [c] Isolated yield after silica gel chromatography.

The availability of highly effective chiral complexes gives rise to new possibilities in catalytic AOM. The examples shown in Scheme 2 are illustrative. Whereas Ru-catalyzed AROM/CM of **25**[19] leads to <10% conversion with **3** (and likely result in rapid polymerization with chiral Mo catalysts),[20] in the presence of 10 mol % **3d**, diamide **26a** is generated in 92% ee and 65% isolated yield. As illustrated in Scheme 2, with this class of heterocyclic olefin substrates enantioselectivity varies depending on the steric requirements of the terminal alkene partner; use of vinylcyclohexane leads to the formation of **26b** in 87% ee but with 1-octene **26c** is obtained in 68% ee. The enantiomerically enriched N-containing products can be functionalized in a variety of manners, as exemplified by the stereoselective formation of **27**.

2. Ru-Catalyzed ARCM. Another important class of AOM reactions examined are asymmetric ring-closing metathesis (ARCM) processes.[21] Several examples from our initial studies

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(19) Ellis, J. M.; King, S. B. *Tetrahedron Lett.* **2002**, *43*, 5833−5835.

(20) For representative reports on Mo-catalyzed AROM/CM, see: (a) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829. (b) La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767−7778. (c) Tsang, W. C. P.; Jernelius, J. A.; Cortez, G. A.; Weatherhead, G. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2591−2596.

(21) For representative reports on Mo-catalyzed ARCM, see: (a) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041−4042. (b) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720−9721. (c) Zhu, S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R., *J. Am. Chem. Soc.* **1999**, *121*, 8251−8259. (d) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553−9559. (e) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139−3140. (f) Kiely, A. F.; Jernelius, J.; A.; Schrock, R.; R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868−2869. (g) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991−6997.

in this area are outlined in Scheme 3. Noteworthy points regarding the Ru-catalyzed ARCM transformations are:

(1) In all cases shown, in the presence of chiral catalyst **3**, <5% conversion to the desired product is observed.

(2) The present class of chiral Ru catalysts are more efficient in effecting RCM of 1,6-dienes (to dihydrofurans) than 1,7-dienes (to unsaturated pyrans); reactions of 1,7-dienes require 10 mol % catalyst loading to proceed to completion (45−50% conv under identical conditions with 5 mol % **3d**). It should be noted that similar catalyst dependency has been observed in Mo-catalyzed ARCM reactions[20a,c] and likely points to significantly different structural requirements for the binding pockets of chiral catalysts that effect five- vs six-membered ring closures.[22]

(3) In reactions of 1,6-dienes (**28**, **31**, and **34** in Scheme 3) leading to five-membered ring products significant amounts of homodimeric products (**30** and **33**) are formed when reactions are carried out in THF. In contrast, reactions of 1,7-dienes (**35**, **37**,[23] and **39** in Scheme 3), although less efficient, do not generate any homodimers in THF (<2% as judged by analysis of 400 MHz ^{1}H NMR).

(4) As illustrated in Scheme 3 (left column), ARCM of 1,6-dienes in THF lead to the formation of significant amounts of homodimeric compounds. When reactions are carried out in toluene, <2% of these byproducts are formed with small or no reduction in enantioselectivity.

(5) In contrast to triene **31** which bears cis olefins, attempted ARCM of **34** in the presence of 5 mol % **3d** leads to complete recovery of the starting material (22 to 60 °C after 24 h in THF or toluene). The remarkable difference in reactivity between trienes **31** and **34**, which incidentally does not exist in the case of trienes **37** and **39**, suggests strict geometrical constraints in the binding cavity of the chiral Ru complex; further mechanistic details must await the outcome of additional studies.

Conclusions

We have prepared and examined the catalytic activity of several sterically and electronically modified chiral Ru-based catalysts for AOM. The chemistry of Ru carbenes **3a**−**3f** and the available crystallographic data shed light on various mechanistic aspects of this class of nonphosphine Ru carbenes. Furthermore, enhanced catalytic activities give rise to significantly more efficient asymmetric processes (lower catalyst loadings) and offer new possibilities for the development of practical and synthetic protocols that cannot be promoted by the alternative chiral metathesis catalysts.

Given the stability of Ru carbenes (reactions can often be carried out in air and with undistilled solvents) and their functional group stability (complementary to Mo-based catalysts),[11] asymmetric Ru-catalyzed olefin metathesis promises to make available practical protocols for useful methods in enantioselective synthesis. Toward this end, as the present studies indicate, additional classes of chiral Ru-based metathesis catalysts must be designed and developed. Processes that promote the formation of a wide range of cyclic structures through efficient Ru-catalyzed ARCM likely receives priority. This will probably be feasible only if an array of chiral catalysts[21] are made available that can be selected for particular applications.

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Supporting Information Available: Additional experimental procedures and crystallographic data (53 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] For a discussion of the concept of "catalyst generality", see: Hoveyda, A. H. In *Handbook of Combinatorial Chemistry* Nicolaou, K. C.; Hanko, R.; Hartwig, W., Eds.; Wiley-VCH: Weinheim; 2002; pp 991−1016.

[23] The reaction of triene **37** in THF affords **38** in 65% ee; subsequent brief solvent screening proved dichloroethane to be a superior medium.