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Comparison of Ru- and Mo-Based Chiral Olefin Metathesis Catalysts. Complementarity in Asymmetric Ring-Opening/Cross-Metathesis Reactions of Oxa- and Azabicycles

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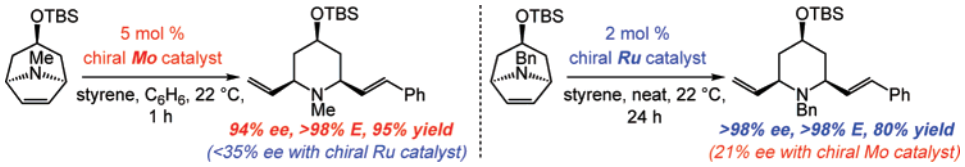
ABSTRACT



A comparative study of chiral Mo- and Ru-based catalysts to promote enantioselective synthesis of 2,6-disubstituted pyrans and piperidines through asymmetric ring-opening/cross-metathesis (AROM/CM) reactions is presented. These studies demonstrate the critical complementarity that exists between the two classes of chiral catalysts.

Ru- and Mo-based catalysts are central to the emergence of olefin metathesis as an indispensable method in chemical synthesis.[1] Detailed studies that compare these catalyst classes are, nonetheless, uncommon, and the limited information available relates to reactivity, not selectivity (particularly enantioselectivity).[2] Herein, we describe the results of our investigations on Ru- and Mo-catalyzed asymmetric ring-opening/cross-metathesis (AROM/CM) reactions of oxa- and azabicycles with aromatic alkenes; these processes afford functionalized pyrans and piperidines in up to >98% ee.[3] We show that, depending on the substrate, one particular catalyst system (Mo- or Ru-based) may provide superior reactivity and/or enantioselectivity.

Chiral Ru (**1**−**2**) and Mo (**3**−**7**) complexes utilized are depicted in Figure 1. The first-generation binaphthyl-based carbenes **1a**,**b**,[4] as well as the more recently developed biphenyl-based complexes **2a**,**b**,[5] were probed. Ru-iodides **1b**[6] and **2b**,[5] although typically less active,[5] have been shown in previous investigations to provide enhanced enantioselectivities (vs chlorides **1a** and **2a**). Chiral Mo alkylidenes, such as biphenolates **3a**−**c**[7] (arylimido) and **6**[8] (adamantylimido), binaphtholates **4a**−**c**[9] (arylimido) and **7**[10] (adamantylimido), as well as partially hydrogenated complexes **5a**,**b**,[11] were examined.

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(1) For reviews on catalytic olefin metathesis, see: *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003.

(2) For example, see: (a) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 257−259. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370. (c) Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R.; Grela, K. *Tetrahedron* **2003**, *59*, 4525−4531. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633.

(3) For a review on catalytic olefin metathesis methods used in the synthesis of heterocycles, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(4) (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954−4955. (b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502−12508. For a brief overview, see: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8−23.

(5) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877−6882.

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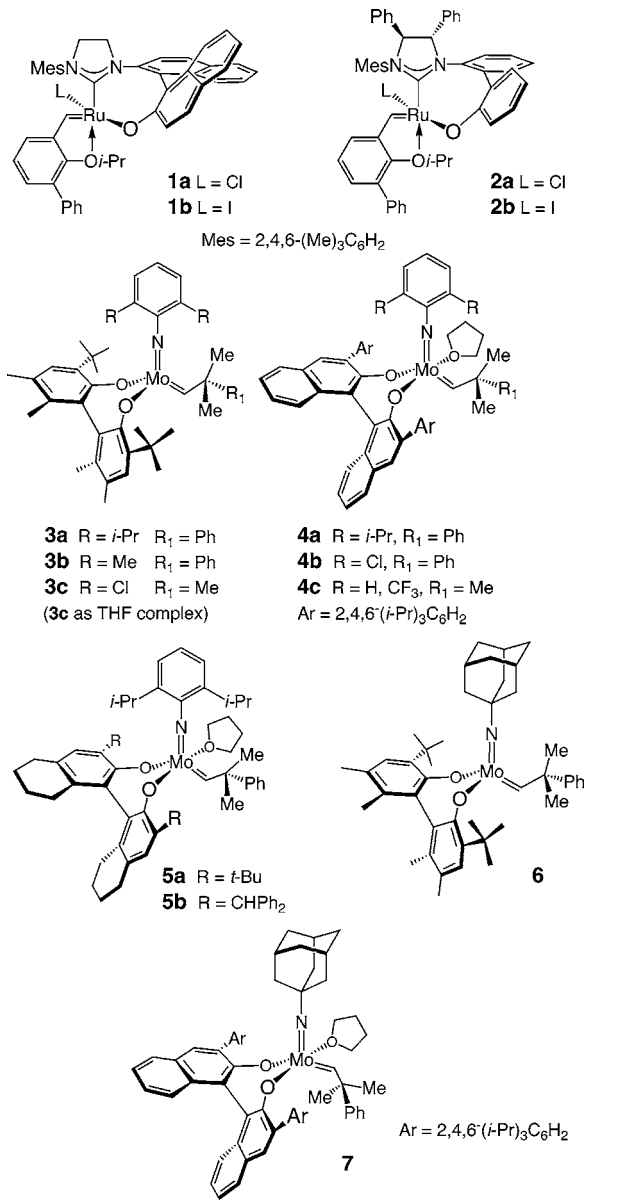
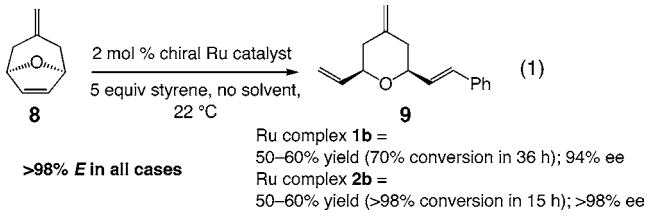


Figure 1. Chiral Ru- and Mo-Based Catalysts for Enantioselective Olefin Metathesis.

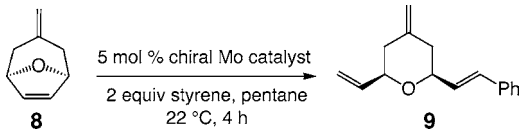
We began our investigations with catalytic AROM/CM of *meso* oxabicycles. We have previously demonstrated that chiral Ru complexes **1a** and **1b** promote this class of enantioselective transformations to afford the desired pyrans as a single alkene isomer (>98% *E*), in up to 98% ee and 91% isolated yield.[6] As illustrated in the representative AROM/CM process in eq 1, reactions can be performed in the absence of solvent, a condition required for transformations with relatively less reactive substrates such as **8**; otherwise, <20% conversion is observed. Consistent with



the previous data, catalyst **2b** is more effective than **1b** (>98% vs 70% conversion) in furnishing **9**.

To probe the feasibility of Mo-catalyzed AROM/CM of oxabicycles, we examined various chiral alkylidenes illustrated in Figure 1. As the data summarized in Table 1

Table 1. Screening of Chiral Mo Catalysts for AROM/CM of **8** with Styrene[a]



entry	Mo catalyst	conv (%)[b]	*E*:*Z*	ee (%)[c]
1	**3a**	>98	nd[d]	nd[d]
2	**3b**	<5		
3	**3c**	50	nd[d]	nd[d]
4	**4a**	<5		
5	**4b**	<5		
6	**4c**	<5		
7	**5a**	<5		
8	**5b**	<5		
9	**6**	**>98**	**>98:<2**	**94**
10	**7**	<5		

[a] Reactions performed under N_2; all conversions are >98%. [b] Determined by 400 MHz ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis (chiralcel OD). [d] Unidentifiable oligomeric products formed, nd = not determined.

indicate, with the exception of adamantyl biphenolate **6** (entry 9), which emerges as a highly effective catalyst, other chiral Mo alkylidenes either do not promote reaction (<5% conv) or, as in the case of **3a** (entry 1) and **3c** (entry 3), generate oligomeric products. Thus, with 5 mol % chiral alkylidene **6**, unsaturated pyran **9** is obtained as a single olefin isomer (>98% *E*) and in 94% ee.

As summarized in entry 3 of Table 2, with C_6H_6 as the solvent, Mo-catalyzed AROM/CM of oxabicycle **8** and styrene generates pyran **9** in 97% ee and ~55% isolated yield[12] (>98% *E*). Comparison of the data shown in entries

(7) (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) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Hoveyda, A. H.; Schrock, R. R. *Tetrahedron Lett.* **2000**, *41*, 9553−9559.

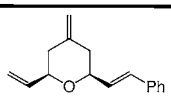
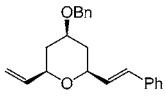
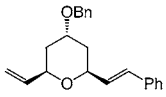
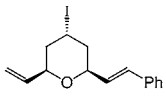
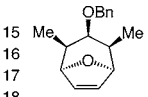
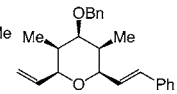
(8) Tsang, W. C. P.; Jernelius, J. A.; Cortez, G. A.; Weatherhead, G. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 2591−2596.

(9) (a) Zhu, S. 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. (b) Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700−3715. (c) Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409−417.

(10) Pilyugina, T. S.; Schrock, R. R.; Müller, P.; Hoveyda, A. H. *Organometallics* **2007**, *26*, 831−837.

(11) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J., Jr.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452−1456.

Table 2. Ru- and Mo-Catalyzed AROM/CM of Oxabicycles and Styrene[a]

entry	substrate	product	catalyst; mol %	equiv styrene	time (h); temp (°C)	yield (%)[b]	ee (%)[c]
1			**1b**; 2	5	36; 22	50–60	94
2			**2b**; 2	5	15; 22	50–60	>98
3	**8**	**9**	**6**; 5	5	1; 22	50–60	97
4			**1a**; 2	5	1; 22	70	96
5			**2b**; 2	5	1; 22	90	88
6			**2b**; 2	5	1; –15	87	91
7	**10**	**11**	**6**; 5	5	1; 22	nd[d]	–
8			**1b**; 2	2	36; 22	85	90
9			**2b**; 2	2	15; 22	70	94
10			**2b**; 2	5	15; –15	84	>98
11	**12**	**13**	**6**; 2	10	1; 22	81	90
12			**1b**; 2	2	5; 22	65	93
13			**2b**; 2	2	5; 22	70	82
14	**14**	**15**	**6**; 5	10	1; 22	76	97
15			**1b**; 5	4	44; 22	44	80
16			**2b**; 5	4	15; 22	56	81
17			**2b**; 2	8	20; –15	64	89
18	**16**	**17**	**6**; 5	10	5; 22	64	67

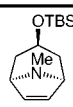
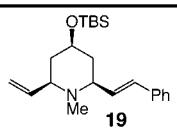
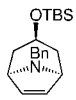
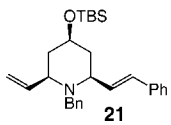
[a] Reactions at 22 °C under N_2. Ru-catalyzed reactions run in the absence of solvent; Mo-catalyzed reactions carried out in C_6H_6. All conversions are >98%, judged by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. >98% *E*:*Z* in all cases. [b] Isolated yields. [c] See Table 1. [d] Oligomeric products formed. nd = not determined.

1−3 of Table 2 suggests that the reaction promoted by Mo complex **6** is more efficient, even though those with Ru carbenes are performed without solvent. The higher activity of **6** proves detrimental in the transformation of the more reactive endocyclic benzyl ether **10** (see entries 4−7,[6] Table 2); only oligomeric products are generated when the Mo complex is used to promote AROM/CM of oxabicycle **10** (entry 7). The less potent Ru carbenes, however, initiate efficient desymmetrizations to deliver **11** in 96% and 88% ee with **1a** and **2b**, respectively (entries 4 and 5, Table 2). With **2b**, the reaction can be carried out at −15 °C to afford **11** in 87% isolated yield and 91% ee (entry 6). Chiral catalyst **6** can be used for AROM/CM of the less reactive exocyclic benzyl ether **12**: reaction proceeds readily, without oligomerization, to afford **13** in 90% ee and 81% isolated yield (entry 11, Table 2). Although more sluggish than Mo-catalyzed processes, transformations promoted by Ru catalysts, shown in entries 8−10, deliver products of higher enantiopurity; as depicted in entry 10 of Table 2, at −15 °C, carbene **2b** gives rise to pyran **13** in 84% isolated yield and as a single olefin isomer (>98% *E*) and enantiomer (>98% ee). Comparison of the data in entries 12 and 14, involving secondary iodide **14** as the substrate, shows that this catalytic AROM/CM can be highly enantioselective with Ru carbene **1b** as well as the more reactive Mo complex **6** (93% and 97% ee, respectively). In contrast, the second-generation Ru iodide **2b** furnishes lower enantioselectivity (82% ee; entry 13).[13] Finally, as illustrated in entries 15−18 (Table 2), formation of a fully functionalized pyran, an intermediate utilized in a recently disclosed enantioselective total synthesis of baconipyrone C,[14] proceeds less readily but more enantioselectively with chiral Ru carbenes than Mo catalyst **6**.

The above study demonstrates that chiral Ru and Mo catalysts promote highly selective AROM/CM of oxabicyclic substrates with styrene. Which catalyst class engenders higher enantioselectivity, however, depends on the identity of the particular substrate (e.g., compare entries 12−14 for superior Mo performance and 15−18 for examples of more selective Ru-catalyzed AROM/CM). Although Mo catalysts initiate faster transformations, in cases where the cyclic olefin is highly reactive and competitive oligomerization is a possible complication, Ru carbenes are preferable (e.g., entries 4−7, Table 2). With these results in hand, we carried out a comparative study of the two catalyst systems in AROM/CM of azabicyclic substrates to obtain enantiomerically enriched piperidines.

We recently demonstrated that chiral Mo catalyst **6** readily (>98% conversion in 1 h) promotes AROM/CM of azabicycles bearing an NMe unit (e.g., **18**, Table 3) and a range

Table 3. Comparison of Ru- and Mo-Based Catalysts in AROM/CM of NMe- and NBn-Azabicycles[a]

entry	substrate	product	catalyst; mol %	equiv styrene	time (h)	conv (%)[b]; yield (%)[c]	ee (%)[d]
1			**1a**; 5	20	36	30; nd	33
2			**2a**; 5	20	36	<5; nd	nd
3			**2b**; 5	20	36	<4; nd	nd
4	**18**	**19**	**6**; 5	10	1	***>98; 95***	***94***
5			**1a**; 5	20	24	***>98; 80***	***>98***
6			**2a**; 5	20	24	70; nd	96
7			**2b**; 5	20	24	<5; –	–
8	**20**	**21**	**6**; 5	10	1	>98; 85	21

[a] Reactions at 22 °C performed under N_2. Ru-catalyzed reactions were preformed neat; Mo-catalyzed reactions were carried out in C_6H_6. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c,d] See Table 2. nd = not determined.

of aromatic olefin cross partners in up to 98% ee (>98% *E*).[15] In contrast, Ru carbenes **1a** and **2a**,**b** are ineffective; the data in entries 1−3 of Table 3 are illustrative. Similar general trends were observed for less reactive substrates that carry a carbamate group (e.g., NCbz or NCO_2Et derivative of **18**).

As the data in entries 5−8 of Table 3 illustrate, catalytic AROM/CM of benzyl-protected azabicycles, represented by **20**, follow an entirely different trend compared to methylamines, such as **18**. In stark contrast to unsaturated methyl-

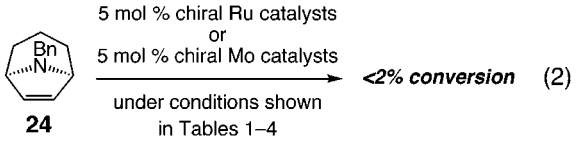
(12) Varying values for isolated yield is due to the volatility of pyran **9**.
(13) Enantioselectivity does not improve when this reaction is carried out at −15 °C.
(14) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860−3864.
(15) Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4534−4538.

amine **18**, with *benzyl*amine **20** as the substrate (entry 5, Table 3), first-generation Ru catalyst **1a** (5 mol %) promotes AROM/CM with styrene (>98% conversion, 80% isolated yield), affording **21** in >98% ee (>98% *E*). As shown in entry 6 of Table 3, unlike a number of previously reported observations,[5] the second-generation chiral carbene **2a** proves to be *less efficient* in this case, giving rise to 70% conversion under identical conditions (vs >98% conversion with **1a**); the less reactive second-generation Ru-iodide (**2b**) is entirely ineffective (entry 7, Table 3). Moreover, unlike reactions of methylamine **18**, chiral Mo alkylidene **6**, optimal for AROM/CM of **18** (94% ee), delivers benzylpiperidine **21** in only 21% ee. These observations underline the versatile complementary nature of chiral Ru and Mo catalysts; seemingly minor variations in substrate structure can render Ru carbenes superior to Mo alkylidenes and vice versa.

The results of studies on catalytic AROM/CM of azabicycle **22** with styrenyl cross partners are summarized in Table 4. In addition to the low selectivities that would be expected (see Table 3), such transformations cannot be performed with Mo alkylidenes due to the free hydroxyl group. As the observations in Table 4 indicate, Ru-catalyzed AROM/CM reactions with electron-deficient (entries 3−4, 7, and 10) as well as electron-rich (entries 8 and 9) substituents proceed readily and with high enantioselectivity (96% to >98% ee). The facile reactions shown in entries 5 and 6, involving sterically hindered *o*-methylstyrene, are noteworthy. Comparison of data in entries 1−2, 3−4, 5−6, and 8−9 further indicates that first-generation Ru catalyst **1a** is superior to complex **2a** in promoting such processes.

This study furnishes the first comparative study of chiral Ru- and Mo-based catalysts in promoting a useful class of asymmetric olefin metathesis reactions. Our investigations provide evidence for the significance of catalyst diversity on different levels. In certain cases involving AROM/CM of oxabicycles, it is the Ru catalysts that perform more effectively. In other instances, Mo complexes generate more attractive results. Strikingly, in reactions of azabicycles, when the amine unit carries a methyl or a carbonyl group, Mo alkylidenes deliver high activity and selectivity, whereas with benzyl-protected azabicycles, Ru catalysts are superior.

In spite of the advances rendered possible by the availability of chiral catalysts,[16] such as those illustrated in Figure 1, notable issues of reactivity and selectivity remain unaddressed in asymmetric olefin metathesis. For example, the reaction shown in eq 2 cannot be promoted by any of the complexes depicted in Figure 1.



Another critical point is that catalytic AROM/CM processes are largely limited to aromatic alkenes as cross partners. Aliphatic olefins readily undergo homocoupling, causing formation of highly reactive methylidenes that compete with alkyl-substituted Ru carbenes or Mo alkylidenes, leading to diminution of enantioselectivities.[17] One solution may arise through the recently reported strategy involving cross partners that carry metal-coordinating groups (enoates and ynoates), which stabilize the resulting carbenes and can exist predominantly as one carbene stereoisomer.[18]

Investigations directed toward development of new catalysts, strategies, and methods that address such unresolved problems are in progress.

Acknowledgment. Financial support was provided by the NSF (CHE-0213009 to A.H.H.) and the NIH (GM-59426 to R.R.S. and A.H.H.). G.A.C. was an NIH predoctoral fellow (F31 GM-73556) and C.A.B. a Fulbright Scholar. We thank D. G. Gillingham (Boston College) for performing the reactions in entries 15−17 of Table 2 and for many helpful discussions.

Supporting Information Available: Experimental procedures and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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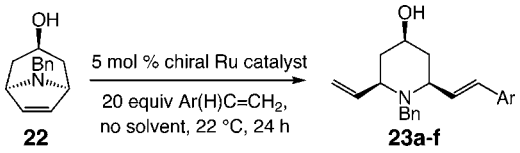
Table 4. Ru-Catalyzed AROM/CM of NBn-Azabicycles[a]



entry	Ar	product	Ru catalyst	conv (%)[b]; yield (%)[c]	ee (%)[d]
1	C_6H_5	**23a**	**1a**	>98; 82	>98
2	C_6H_5	**23a**	**2a**	80; 65	94
3	*o*-BrC_6H_4	**23b**	**1a**	63; 55	97
4	*o*-BrC_6H_4	**23b**	**2a**	27; nd	nd
5	*o*-MeC_6H_4	**23c**	**1a**	>98; 81	98
6	*o*-MeC_6H_4	**23c**	**2a**	95; 60	98
7	*o*-FC_6H_4	**23d**	**1a**	87; 70	>98
8	*p*-$OMeC_6H_4$	**23e**	**1a**	87; 67	>98
9	*p*-$OMeC_6H_4$	**23e**	**2a**	50; 38	96
10[e]	*p*-$CF_3C_6H_4$	**23f**	**1a**	>98; 78	97

[a] Reactions at 22 °C performed under N_2 in the absence of solvent. [b−d] See Table 3. [e] Reaction performed with 5 equiv of the cross partner, and catalyst was added in two batches (see the Supporting Information for details). nd = not determined

(16) For another class of chiral Ru catalysts (monodentate NHC), see: (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225−3228. (b) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840−1846. These catalysts have thus far proven to be less effective in promoting AROM/CM (1.4−1:1 *E*:*Z*, 33−80% ee); see: (c) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591−7595.

(17) For a discussion regarding the effect of competing methylidene complexes on catalytic AROM/CM reactions, see: La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767−7778.

(18) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824−3825.