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Desymmetrizations Forming Tetrasubstituted Olefins Using Enantioselective Olefin Metathesis

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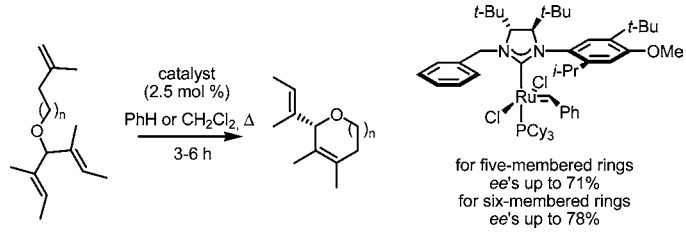
ABSTRACT



Highly reactive chiral Ru-based catalysts possessing C_1-symmetric *N*-heterocyclic carbene ligands adorned with one *N*-alkyl group and one *N*-aryl group were evaluated in asymmetric desymmetrizations to form cyclic products possessing a tetrasubstituted olefin.

Among the current challenges in the field of olefin metathesis, both the synthesis of tetrasubstituted olefins, and the development of asymmetric processes have recently received increasing attention.[1] Although Herrmann and co-workers reported the use of catalyst **1c** to promote cyclizations to form tetrasubstituted olefins almost 10 years ago,[2] the challenges associated with this transformation have recently led to new catalyst developments.[3] Some of the recent developments include the phosphine-containing catalyst **1a**[3b] in which a modified NHC ligand (compared to parent catalysts **1b** and **1c**[4]) has been exploited to improve reactivities (Figure 1, top). Different Hoveyda-type catalysts bearing modified benzylidenes and NHC ligands (including **2a**,[2] **2b**, **2c**,[5] and **2d**[2]) have also shown the propensity to effect the ring-closing metathesis of methallyl-substituted dienes to afford tetrasubstituted olefins to some degree (Figure 1, top).[6,7] Recently, our group reported the synthesis of new chiral Ru-based catalysts bearing C_1-symmetric NHC ligands (Figure 1, bottom).[8] The corresponding catalysts were

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(1) For recent reviews on asymmetric olefin metathesis, see: (a) Hoveyda, A. H. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2,Chapter 2.3. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633. (c) Hoveyda, A. H.; Schrock, R. R. *Chem.—Eur. J.* **2001**, *7*, 945–950. See also: (d) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

(2) Ackermann, L.; Furstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787–4790.

(3) (a) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787. (b) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.

(4) (a) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370–2375. (b) Clavier, H.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 8029–8036. (c) Clavier, H.; Blanco, C. A.; Nolan, S. P. *Organometallics* **2009**, *28*, 2848–2854.

(5) Chung, C. K.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2693–2696.

(6) (a) Gatti, M.; Vieille-Petit, L.; Luan, X.; Mariz, R.; Drinkel, E.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2009**, *131*, 9498–9499. For a stucturally similar catalyst as **6a**, see: (b) Rost, D.; Porta, M.; Gessler, S.; Blechert, S. *Tetrahedron Lett.* **2008**, *49*, 5968–5971. (c) Vorfalt, T.; Leuthäußer, S.; Plenio, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5191–5194.

(7) Backbone substitution of the NHC has also been studied with regard to tetrasubstituted olefin synthesis, see: Kuhn, K. M.; Bourg, J.-B.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313–5320.

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isolated as mixtures of *syn*/*anti* isomers,[9,10] were highly reactive, and produced high enantioselectivities in the desymmetrization of *meso*-trienes without the need for halide additives.[11a] Herein, we report on the first asymmetric desymmetrizations via ring closing metathesis that form tetrasubstituted olefins using catalysts bearing chiral C_1-symmetric NHC ligands.

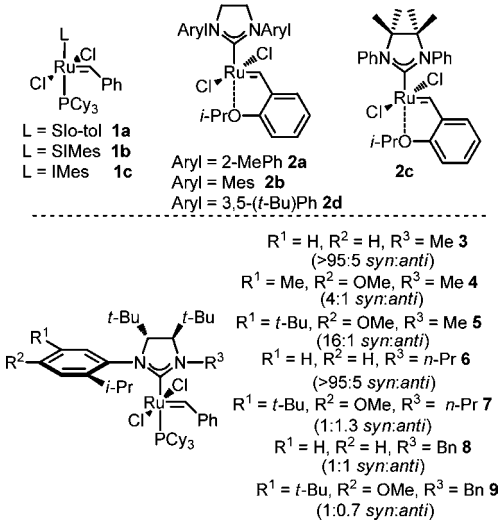
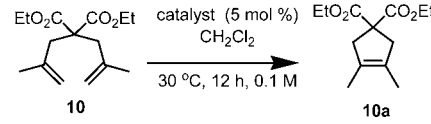


Figure 1. (Top) Olefin metathesis catalysts. (Bottom) Chiral Olefin Metathesis Catalysts Bearing C_1-symmetric NHC ligands.

At the outset of our study, it was reasoned that desymmetrization via asymmetric ring-closing metathesis,[11,12] to form tetrasubstituted olefins would be more challenging than desymmetrizations to form trisubstituted olefins in terms of conversion and enantioselectivity. When considering the former, the *meso*-trienes used for the desymmetrizations possess a prochiral carbon adjacent to a reacting olefin and thus are significantly more sterically demanding than the typical dienes previously studied in the ring-closing metathesis to form tetrasubstituted olefins. Thus, a preliminary study of the ring closing of **10** to form the tetrasubstituted olefin **10a** was conducted (Table 1).[13] When diene **10** was subjected to catalyst **3** and **5** at 30 °C in CH_2Cl_2 for 12 h, only 34% and 55% conversion, respectively, to **10a** were observed.

Table 1. RCM To Form Tetrasubstituted Olefin **10a**



entry	catalyst	convn[a] (%)	entry	catalyst	convn[a] (%)
1	**3**[b]	34	4	**7**	0
2	**5**[b]	55	5	**8**	63
3	**6**[b]	84	6	**9**	38

[a] Determined by ^{1}H NMR of crude reaction mixture. [b] Reaction concentration = [0.055].

Catalysts **8** and **9** afforded 63% and 38% conversions of **10** after 12 h. Catalyst **7** showed only a negligible cyclization of **10** and was clearly inferior to the analogous catalyst **5** (55% conversion after 12 h). Gratifyingly, catalyst **6** showed an improved conversion of **10** (84%) when compared with **3** (34%) after 12 h. To put the above results in context, catalysts **3**−**9** can effectively promote ring-closing metathesis cyclizations to form **10a** and various other tetrasubstituted olefins.[14] With these results in hand, we decided to proceed to investigate the asymmetric desymmetrization to form tetrasubstituted olefins using the Ru-based catalysts **3**−**9**.

The evaluation of catalysts bearing C_1-symmetric NHC ligands (**3**−**9**) in promoting the enantioselective cyclization of a series of *meso*-trienes is summarized in Table 2. The series of *meso*-trienes were chosen to study various aspects of substrate scope including olefin geometry, cyclizations onto 1,1-disubstituted olefins versus 1,1,2-trisubstituted olefins, olefin substitution patterns, and ring size (five- or six-membered rings). It should be noted that all the catalysts bearing C_1-symmetric ligands were isolated as mixtures of *syn* and *anti* isomers. Catalyst **9** was the only catalyst isolated in which a slight separation of the *syn* and *anti* isomers was possible by silica gel chromatography. As such, the cyclization of the various *meso*-trienes were also studied using a sample of catalyst **9** in which the *syn* isomer was the major isomer (1:0.7 *syn*:*anti*) and a sample in which the *anti* isomer is the major isomer (**9anti**, 1:8 *syn*:*anti*).[15]

When the *meso*-triene **11** was treated with catalyst **3** or **5**, excellent conversions were obtained (>95%); however, low enantiomeric excesses (ee's) were observed (8% and 38%,

(8) (a) Fournier, P.-A.; Collins, S. K. *Organometallics* **2007**, *26*, 2945–2949. (b) Fournier, P.-A.; Savoie, J.; Bédard, M.; Stenne, B.; Grandbois, A.; Collins, S. K. *Chem.—Eur. J.* **2008**, *14*, 8690–8695.

(9) Throughout this paper, *syn* refers the *N*-alkyl group of the NHC ligand being on the same side as the Ru carbene. Isomer mixtures for catalysts **4**, **5**, and **7**−**9** were inseparable by silica gel chromatography. After repeated attempts, partial separation of the *syn*/*anti* isomers of catalyst **9** was possible.

(10) For a discussion of carbene lifetimes, see: Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 72037207..

(11) For examples of desymmetrizations : (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. (c) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591–7595.

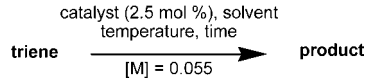
(12) For examples in tandem ring-opening/cross-metathesis processes: (a) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem* **2004**, *2*, 8–23. (b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

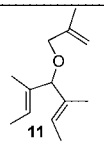
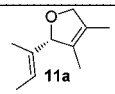
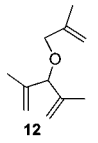
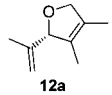
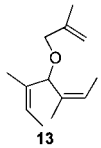
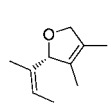
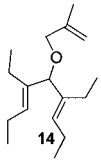
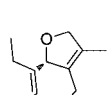
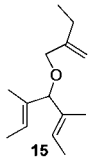
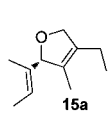
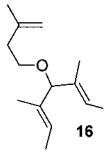
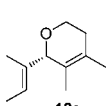
(13) For a full comparison of the ring closing of **10** with other Ru-based catalysts, see the Supporting Information.

(14) See the Supporting Information for a list of other five- and six-membered rings containing tetrasubstituted olefins that were cyclized using catalysts **3**−**9**.

(15) Catalysts **3**−**9** were all heated in an NMR tube in toluene-d_8 to 60 °C. Catalysts **3**−**5** rapidly decompose, while catalysts **6**−**9** are stable for up to 4 h before the solution slowly darkened and the benzylidene peaks in the ^{1}H NMR slowly began to decrease in intensity. In addition, 2D EXSY experiments of catalysts **6**−**9** conducted in NMR tubes in toluene-d_8 at 40 or 50 °C revealed no rotation of the NHC in the precatalyst.

Table 2. ARCM Desymmetrization Reactions Forming Tetrasubstituted Olefins



entry	triene	product, solvent, temp (°C) time (h)	cat.	ee (%)[a]	convn (%)[b], yield (%)[c]
1	 11	 11a CH_2Cl_2, 30, 3	**3**	8	95
			5	38	95
			6	43	95;82
			7	54	60;42
			8	52	90;85
			9	50	86;63
			9anti	59	46
2	 12	 12a C_6D_6, 60, 6	**5**	36	24
			8	57	31
			9	61	33
			9anti	26	76, 52
3	 13	 13a CH_2Cl_2, 30, 3	**8**	56	>95, 67
			9anti	71[c]	50
			5	31	>95, 84
4	 14	 14a PhH, 60, 6	**8**	6	13
			9anti	12	46
5	 15	 15a C_6D_6, MW 100, 0.25	**9anti**[d]	49	49
6	 16	 16a PhH, 60, 6	**9anti**	78	47

[a] The absolute configuration of **11a** and **12a** has been determined (see the Supporting Information). The configuration of the remaining products is assumed on the basis of **11a** and previous desymmetrizations of *meso*-trienes. [b] Conversion determined by ^{1}H NMR spectrum of crude reaction mixture. Yields are following purification via silica gel chromatography. The products are volatile and yields can sometimes vary greatly. [c] The ee is an estimate, due to a irremovable impurity. See the Supporting Information. [d] A second portion of catalyst (2.5 mol %) was added after 10 min. MW = microwave irradiation.

respectively). Catalysts **6** and **7** afforded mediocre ee's (43 and 54%, respectively), although catalyst **7** (60% conv, 42% yield) was again less reactive than **6** (95% conv, 82% yield). Catalysts **8** and **9** also afforded similar results, (52 and 50% ee, respectively).[16]

Interestingly, the best ee for cyclizations of **11** was observed using the catalyst **9anti** (59% ee), although the conversion to heterocycle **11a** (46%) was significantly less than with catalyst **9**. When the triene **12** was cyclized with **9**, the conversion was low (33%), but a 61% ee of the product was obtained. When the cyclization of triene **12** was attempted with catalyst **9anti** a low ee (26%) was observed, although a higher conversion (76%, 52% yield) to the corresponding tetrasubstituted olefin **12a** was observed in comparison with catalyst **9**.

In light of these results, we investigated whether high conversions and enantioselectivities could be obtained using triene **13**, in which the geometry of the double bonds is changed with respect to triene **11**. When triene **13** was treated with catalyst **9anti**, the product was again obtained in good ee (71%) and in moderate conversion (50%). These results are similar to what was observed in the desymmetrization of trienes **11** and **12**. Ring closing of triene **13** with catalyst **5** gave excellent conversion (>95%, 84% yield) but poor ee (31%). Catalyst **8** provided the five-membered ring product **13a** in 56% ee and in excellent conversion (>95%, 67% isolated yield). The above results demonstrate that the terminal Me group in trienes **11**−**13** affect both the conversion and the observed enantioselectivity in the cyclizations.

We then attempted to cyclize the more challenging substrates, trienes **14** and **15**, to afford the corresponding products **14a** and **15a**. Almost all cyclizations to form tetrasubstituted olefins to date have formed an olefin with two Me groups as substituents,[17] and no cyclizations to form tetrasubstituted olefins bearing both a Me and Et group have been reported. While **8** afforded only traces of the desired product **14a** in low ee (6%), **9anti** gave a 46% conversion of **14**, albeit in low ee (12%). Given that the cyclization onto the Et-substituted olefins of **14** was difficult to achieve, we next investigated the cyclizations of triene **15** in which the Et-substituted olefin is expected to react first with the catalyst. Cyclization using the standard conditions provided only traces of the desired product. However, rapid heating using microwave irradiation proved helpful.[18] Treating **15** with catalyst **9anti** in C_6D_6 at 100 °C afforded the desired product **15a** in 49% conversion and 49% ee after 15 min. The best ee for a desymmetrization forming a tetrasubstituted olefin was observed in the cyclizations of a six-membered ring using the **9anti** catalyst. The cyclization of *meso*-triene **16** afforded the tetrasubstituted olefin **16a** in 47% conversion and 78% ee with catalyst **9anti**.

The results obtained with catalyst **9** and **9anti** in the desymmetrizations demonstrate the importance of understanding the origin of enantioselectivity in catalysts possessing C_1-symmetric NHC ligands. As such, we performed preliminary DFT calculations using Gaussian 03 in order to

(16) The influence of perfluorinated solvents on challenging RCM reactions has been documented. Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun.* **2008**, *47*, 6282–6284. Curiously, when **11** was treated with **5** in C_6F_6, identical conversions were obtained but the ee decreased from 38% to 0%.

(17) For traditional tetrasubstituted olefins bearing two Me groups, see: Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339–1342. (b) For an example of a tetrasubstituted olefin formed with a Cl and a Me substituent, see: White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811.

(18) Microwave heating was not used for the other substrates. For an example of microwave-assisted RCM, see :Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2923–2926.

gain a deeper insight into the enantiodescriminating transition-state structures responsible for asymmetric ring closure of *meso*-triene **11** with catalyst **9**. In this vein, the ONIOM[19] (Our Own N-Layered Integrated Molecular Orbital + Molecular Mechanics Method) theoretical approach at the HF[20]/LANL2MB:[21]UFF[22] level was employed for initial optimization of transition state structures, followed by the implementation of single-point B3LYP[23]/LANL2DZ calculations to gain more accurate final energies (i.e., B3LYP/LANL2DZ//HF/LANL2MB:UFF) (Figure 2). Gratifyingly, these calculations lead to the location of enantiodetermining TS-**9**-S and TS-**9**-R, corresponding to the respective transition states responsible for the formation of the major *S*- and minor *R*-enantiomeric products observed experimentally.[24] The predicted energetic difference between these two first order saddle points was computed to be 0.91 kcal/mol, which corresponds to a predicted ee of 65%. It is worth noting that this computed energetic difference, comparatively speaking, is a value well in line with the experimentally observed ee of 50%.

Perhaps the most interesting geometrical difference between the two transition states is where the alkylidene is placed with respect to the substituents on the NHC ligand. In TS-**9**-S, the ring closing event takes place "underneath" the *N*-Bn substituent of the NHC ligand. Consequently, the alkylidene resides underneath the *N*-Bn group and the *pro*-*S* olefin of the substrate beneath the aryl group. Inspection of TS-**9**-S and TS-**9**-R suggests that a predominant factor contributing to enantioselectivity is the position of the alkylidene with respect to the NHC ligand. In the former, the alkylidene resides "beneath" the aryl group, placing a methyl hydrogen on the prochiral olefin within 2.49 Å of the *tert*-butyl moiety. In the latter, the alkylidene is beneath the *N*-Bn group and thus brings the *t*-Bu group within 2.29 Å of the furan methylene hydrogens; this creates van der Waals repulsions that raise the energy of the TS enough for the reaction to favor one stereochemical outcome over the other. It is possible then that the observed differences between **9** and **9anti** are due to the rotational barrier of the NHC ligand at various points of the catalytic cycle, and computational investigations are being continued in hopes of unveiling such mechanistic nuances.

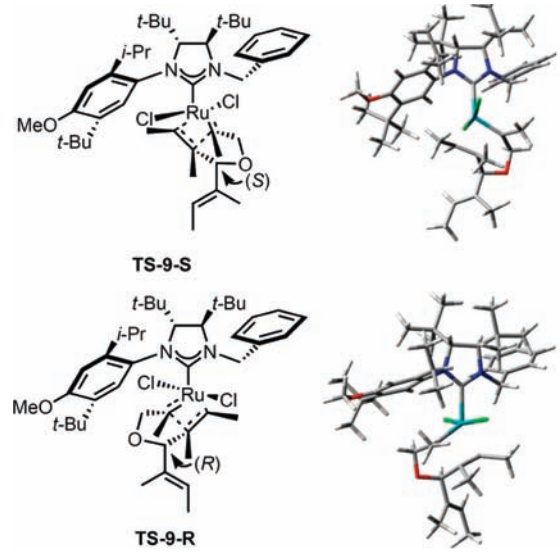


Figure 2. Transition states (TS) for the ring-closing of *meso*-triene **11** with catalyst **9**. (Top) TS calculated for the major enantiomer. (Bottom) TS calculated for the minor enantiomer. (*S*)-TS is 0.91 kcal/mol less in energy than (*R*)-TS.

In summary, the cyclization to produce tetrasubstituted olefins is possible using Ru-based olefin metathesis catalysts bearing chiral C_1-symmetric NHC ligands with small *N*-alkyl groups such as *n*-Pr or Bn. In addition, the desymmetrization of *meso*-trienes to afford tetrasubstituted olefins afforded five-membered rings with up to 71% ee and six-membered rings with up to 78% ee. Computational studies suggest a new model for the origin enantioinduction in the formation of the major enantiomer via desymmetrization. We continue to study new enantioselective processes through the use of these catalysts; we aim to gain a better understanding of the importance of ligand dynamics through molecular modeling.

Acknowledgment. We thank the NSERC (Canada), FQRNT (Québec), CFI (Canada), Boehringer Ingelheim (Canada) Ltd., Merck Frosst Centre for Therapeutic Research, and the Université de Montréal for generous financial support. We thank Prof. R. H. Grubbs and Dr. I. C. Stewart (Caltech) for a sample of **2a**.

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

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(24) It should be noted that although only the two lowest energy transition states are shown here, a total of 96 geometrically distinct transition structures were considered, including the enantiomorphic TSs of those shown in Figure 2. See Table S1 in the Supporting Information for the energetic data for all TSs examined.