J|A|C|S
COMMUNICATIONS

Chiral Crown Conformation of Rh_2(*S*-PTTL)$_4$: Enantioselective Cyclopropanation with α-Alkyl-α-diazoesters

Andrew DeAngelis, Olga Dmitrenko, Glenn P. A. Yap, and Joseph M. Fox*
Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

Received April 3, 2009; E-mail: jmfox@udel.edu

Rh(II)−carboxylate catalysts derived from *N*-phthaloylamino acids have emerged as exceptionally powerful tools for asymmetric synthesis. In this series, *tert*-leucine-derived complexes, such as dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, have emerged as highly selective catalysts in asymmetric reactions, including intramolecular C−H insertion,[1] tandem ylide formation/1,3-dipolar cycloaddition,[2] amination,[3] and 2,3-sigmatropic rearrangement.[4] Davies has introduced adamantylglycine analogues of these ligands, which induce even higher levels of enantioselectivity in some reactions.[5]

Previously, Hashimoto determined the crystal structure of the related catalyst dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate], Rh_2(*S*-PTPA)$_4$, in which two phthalimido groups are oriented on each face of the dirhodium tetracarboxylate.[6a] Herein, we provide evidence that Rh_2(*S*-PTTL)$_4$ adopts a considerably different structure, which we call the "chiral crown" conformation. We also demonstrate the effectiveness of Rh_2(*S*-PTTL)$_4$ in intermolecular enantioselective cyclopropanation with selectivity over two competing intramolecular pathways.

We determined the X-ray structure of Rh_2(*S*-PTTL)$_4$ crystals grown from ethyl acetate. As shown in Figure 1, all four *tert*-butyl groups are oriented on the same face of the catalyst, and each C−(*t*-Bu) bond is roughly parallel to the central Rh−Rh bond. This orients the four phthalimido groups on the opposite face of the catalyst in a "chiral crown" structure. If the solvent is ignored, the structure is C_2-symmetric, and the cavity of the catalyst has wide (∼15 Å) and narrow (∼11 Å) dimensions (Figure 1). Calculations also suggest that the chiral crown structure is the lowest-energy conformer of Rh_2(*S*-PTTL)$_4$. Starting from a completely different geometry, we carried out Monte Carlo calculations (MMFF) on Rh_2(*S*-PTTL)$_4$. The lowest-energy conformer was similar to that found in the crystal structure and 2.1 and 3.0 kcal/mol lower in energy than the next-closest conformers. The energies of these three structures were then determined using density functional theory (DFT) calculations (ADF, OLYP/TZP; see the Supporting Information). The chiral crown was lower in energy than the next conformer by 3.8 kcal/mol. We also minimized the energy of Rh_2(*S*-PTTL)$_4$ in conformations similar to that in the crystal of Rh_2(*S*-PTPA)$_4$; the chiral crown was more stable by 8.2 kcal/mol. We propose that Rh_2(*S*-PTTL)$_4$ has a reactive chiral face and that the sterically demanding *t*-Bu groups block the reactivity on the achiral face of the catalyst. Consistent with this hypothesis, only the Rh atom on the chiral face is bound by solvent in the crystal structure (Figure 1a).

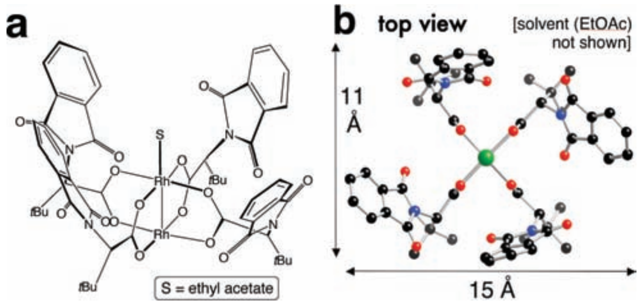
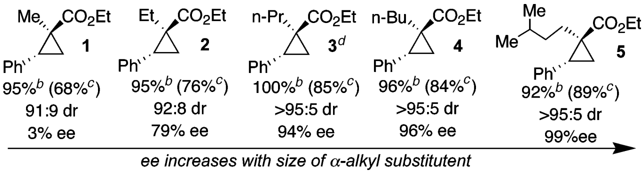


Figure 1. X-ray crystal structure of Rh_2(*S*-PTTL)$_4$ crystallized from ethyl acetate. The unit cell contained two nearly identical (but symmetry-unique) molecules.

We envisaged that Rh_2(*S*-PTTL)$_4$ and related catalysts could prove useful for intermolecular reactions of α-alkyldiazo compounds that ordinarily give products of *β*-hydride elimination.[7] Recent studies by our group have demonstrated that several intermolecular Rh-catalyzed processes can be favored over *β*-hydride elimination when sterically demanding carboxylate ligands and low reaction temperatures are employed.[8] For intermolecular cyclopropanation, Rh_2TPA_4[6b] is an effective catalyst.[8d] Recently, Hashimoto reported that Rh_2(*S*-PTTL)$_4$ catalyzes intramolecular C−H insertion reactions in preference over *β*-hydride elimination and that lowering the temperature had a positive effect on the selectivity over *β*-hydride elimination: 99:1 selectivity was observed at −78 °C vs 82:18 selectivity at 0 °C.[1a]

Rh_2(*S*-PTTL)$_4$ in hexanes at −78 °C led to cyclopropanes with high diastereoselectivity and yield. The enantioselectivity was highly sensitive to the structure of the diazoester, and larger α-alkyl substituents led to increasingly higher ee (Scheme 1). The diastereoselectivity also increased with the size of the α-alkyl substituent. The distinction between ethyl α-diazopropionate (3% ee) and ethyl α-diazobutanoate (79% ee) was most striking. In the best case, 99% ee and >95:5 dr was observed in the reaction of styrene with ethyl 2-diazo-5-methylhexanoate. The highest yields were obtained when an excess (3 equiv) of readily available diazoesters was used. However, good yields could be obtained when the alkene and diazo compound were used in 1.1:1 stoichiometry.

Scheme 1. Effects of α-Alkyl Substitution on Stereoselectivity[a]

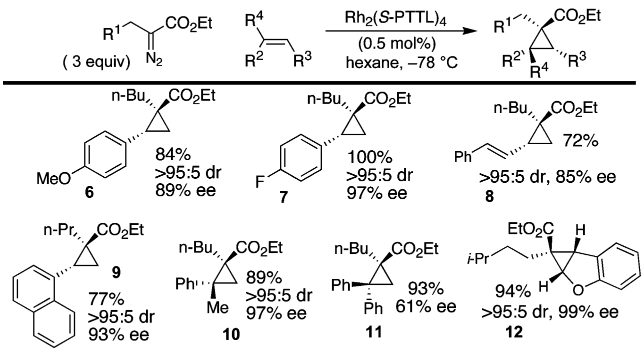


[a] In general, reactions were carried out in hexane at −78 °C with 0.5 mol % Rh_2(*S*-PTTL)$_4$. [b] Isolated yield with 3 equiv of diazo compound and limiting alkene. [c] Isolated yield with 1.1 equiv of alkene and limiting diazo compound. [d] The yield and ee of **3** dropped in reactions carried out with 3.0 equiv of diazoester at 0 °C (54%, 88% ee) and 25 °C (43%, 85% ee).

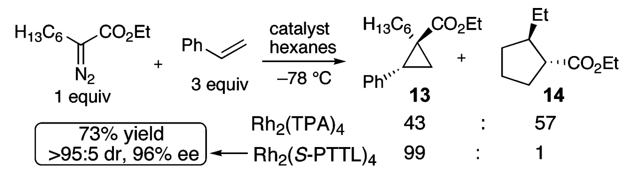
The scope of the cyclopropanation reaction was studied (Scheme 2). High diastereoselectivity and enantioselectivity were achieved in cyclopropanation reactions with styrenes, α-methylstyrene, 1-vinylnaphthalene, benzofuran and (*E*)-1-phenylbutadiene. Moderate enantioselectivity (61% ee) was observed in the reaction between 1,1-diphenylethylene and ethyl α-diazohexanoate. Enantioselective cyclopropanation of styrene with ethyl α-diazooctanoate was selective over intramolecular C−H insertion[1a,5,7b] (Scheme 3). Thus, the Rh_2(*S*-PTTL)$_4$-catalyzed reaction gave cyclopropane **13** (99:1

10.1021/ja9026852 CCC: $40.75

Scheme 2. Enantioselective Cyclopropanation with α-Alkyl Diazoesters



Scheme 3. Catalyst-Dependent Selectivity over C−H Insertion



dr, 96% ee) with 99:1 selectivity over C−H insertion product **14**. The analogous Rh_2TPA_4-catalyzed reaction showed poor selectivity, giving a **14**/**13** ratio of 57:43.

To explain the enantioselectivity, we propose a model (Figure 2a) in which the carbene is aligned with the wide dimension of the C_2-symmetric chiral cavity (see Figure 1). This leaves the *Si* face of the carbene accessible for reaction with the alkene via end-on[9] approach. We propose that when the α-alkyl substitutent is small (Me or Et), there is competing reactivity on the *Re* face via a conformation in which the carbene is aligned with the narrow dimension of the chiral cavity (Figure 2b). DFT calculations were used to support this hypothesis.

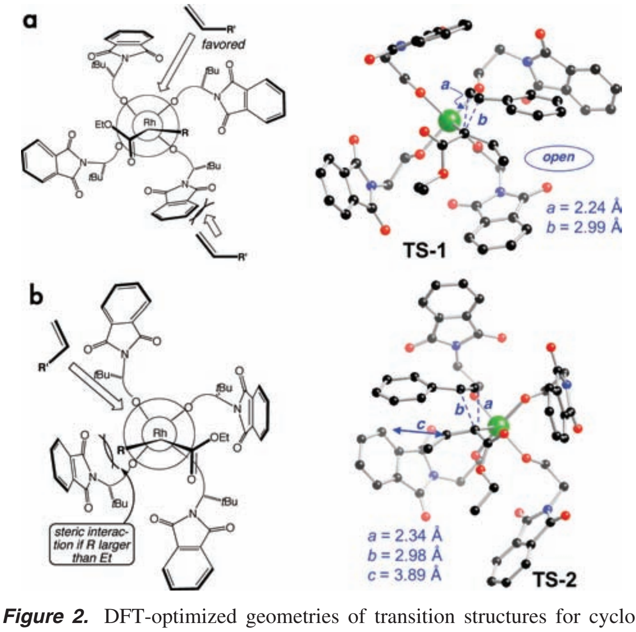


Figure 2. DFT-optimized geometries of transition structures for cyclopropanation by attack on the (a) *Si* and (b) *Re* faces.

Previously, DFT calculations on cyclopropanation reactions with carbenoids of $Rh_2(O_2CH)_4$ were carried out with Gaussian 03 using the hybrid B3LYP functional with the LANL2DZ basis set and effective core potential for Rh atoms and the 6-311+G(d) basis set for the other atoms.[9a] However, such calculations would have been intractably slow for the large carbenoids from $Rh_2(S\text{-PTTL})_4$. Accordingly, we turned to calculations at the OLYP/TZP (small frozen core) level of theory using ADF. The cyclopropanation of styrene by a model carbenoid $[(CO_2Et)(Et)C{=}Rh_2(O_2CH)_4]$ was used for calibration: transition structures with similar geometries were found in the OLYP/TZP calculations (using ADF) and in the B3LYP/LANL2DZ/6-31G(d) calculations (using Gaussian 03). For the OLYP-optimized geometries, single-point B3LYP/LANL2DZ/6-31G(d) energy calculations were carried out to better estimate the barriers of the transition structures.[10a]

For the $Rh_2(S\text{-PTTL})_4$-catalyzed reaction to form **2**, two[10b] similar-energy[11] transition structures (**TS-1** and **TS-2**) were located with a barrier of 11 kcal/mol (Figure 2). The C_2 symmetry of the chiral cavity of the catalyst is retained in **TS-1** and **TS-2**. In **TS-2**, where the carbene is aligned along the narrow dimension of the chiral cavity, the α-ethyl group is only 3.89 Å away from a phthaloyl moiety. Inspection of the model indicates that simple replacement of the α-ethyl group by a larger *n*-alkyl group would result in a significant steric interaction. In contrast, the space around the α-alkyl group of **TS-1** is open and able to support larger alkyl groups. We believe that reaction via **TS-2** competes when R is Me or Et but that **TS-1** is dominant when R is larger than Et.

In summary, a chemoselective, enantioselective, and diastereoselective protocol for intermolecular $Rh_2(S\text{-PTTL})_4$-catalyzed cyclopropanation is described for reactions of alkenes with α-alkyl-α-diazoesters. Calculations and X-ray crystallography support a "chiral crown" conformation for $Rh_2(S\text{-PTTL})_4$ in which the catalyst has a reactive chiral face and an unreactive achiral face.

Acknowledgment. We thank the NIH (GM068640) for support.

Supporting Information Available: Full experimental and computational details, ^1H and ^{13}C NMR spectra, stereochemical assignments, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483. (b) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817. (c) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

(2) (a) Shimada, N.; Anada, M.; Nakamura, S.; Nambu, H.; Tsutsui, H.; Hashimoto, S. *Org. Lett.* **2008**, *10*, 3603. (b) Tsutsui, H.; Shimada, N.; Abe, T.; Anada, M.; Nakajima, M.; Nakamura, S.; Nambu, H.; Hashimoto, S. *Adv. Synth. Catal.* **2007**, *349*, 521.

(3) (a) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559. (b) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561.

(4) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361.

(5) (a) Denton, J. R.; Cheng, K.; Davies, H. M. L. *Chem. Commun.* **2008**, 1238. (b) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312. (c) Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013. (d) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437.

(6) (a) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109. (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.

(7) (a) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908. (b) Taber, D. F.; Joshi, P. V. *J. Org. Chem.* **2004**, *69*, 4276.

(8) (a) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22. (b) DeAngelis, A.; Panne, P.; Yap, G. P. A.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 1435. (c) DeAngelis, A.; Taylor, M. T.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 1101. (d) Panne, P.; DeAngelis, A.; Fox, J. M. *Org. Lett.* **2008**, *10*, 2987.

(9) (a) Nowlan, D. T.; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902. (b) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348.

(10) (a) OLYP/TZP calculations (ADF) overestimate the barrier relative to B3LYP/LANL2DZ/6-311+G(d) (Gaussian 03). However, the geometries of the transition structures were similar. (b) A third, higher-energy structure, **TS-3**, shown in the Supporting Information, was also located and corresponds to attack on the "southern" face of the carbenoid as shown in Figure 2a.

(11) **TS-2** was lower in energy than **TS-1** by 1.4 kcal/mol at the OLYP/TZP level of theory; their energies were reversed (**TS-1** lower by 0.3 kcal/mol) after a single-point calculation at the B3LYP/LANL2DZ/6-31G(d) level. We consider these energetic differences to be within the margin of error for these levels of theory.

JA9026852