

Diastereoselective Construction of *Trans*-Fused Octalone Framework via Ruthenium-Porphyrin-Catalyzed Cycloaddition

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Supporting Information

ABSTRACT: Lewis acid catalyzed cycloaddition of cyclohexenone and butadiene affords *trans*-fused octalone with high regio- and diastereoselectivity. The use of the ruthenium porphyrin complex as the Lewis acid catalyst is key to the reaction. The cycloaddition proceeds in toluene with 1 mol % of the ruthenium catalyst at 25 °C.



O ctalones are among the most versatile building blocks for the synthesis of various natural products such as polycyclic sesquiterpenes and triterpenes. The [4 + 2]cycloaddition of cyclohexenones with butadienes, namely, the Diels-Alder reaction, would be one of the most straightforward synthetic routes to octalones with a *cis*-fused framework (Scheme 1a). This reaction appears to be simple and facile;



however, as a matter of fact it is rather difficult to accomplish due to the low reactivity as a dienophile. Hence, the development of efficient catalysts for the reaction remains a research topic of great interest.¹ Efforts have also been devoted to preparing octalones with a *trans*-fused framework by cycloaddition.^{2,3} Herein, we report that the intermolecular reaction of cyclohexenones with 1,3-butadienes affords *trans*fused octalones in a single step (Scheme 1b); ruthenium porphyrin was found to catalyze the [4 + 2] cycloaddition and isomerization at ambient temperature.^{4–7}

Porphyrins have emerged as useful ligands for transitionmetal catalysts in organic synthesis in cases where the use of other ligands is infeasible.^{8,9} Recently, we developed the ironporphyrin-catalyzed [4 + 2] cycloaddition of aldehydes with 1,3-butadienes to afford dihydropyranes.¹⁰ During the course of our study on metalloporphyrin-catalyzed reactions,¹¹ we postulated that ruthenium porphyrin also catalyzes the cycloaddition of carbonyl compounds with carbon–carbon unsaturated compounds, since both iron and ruthenium complexes show Lewis acidity toward carbonyl compounds and thus efficiently catalyze Diels–Alder-type reactions. To test the hypothesis, we examined the cycloadditions of carbonyl compounds with carbon–carbon unsaturated compounds¹² and found that ruthenium porphyrin complex [Ru(TBPP)-(CO)]SbF₆ (TBPP: *meso*-tetrakis(4-*tert*-butylphenyl)porphyrinate, Figure 1) catalyzed the [4 + 2] cycloaddition of





cyclohexenone with 1,3-butadiene to afford *trans*-fused octalone diastereoselectively in 74% yield regioselectively (Table 1, entry 1).^{13–15} We also examined the effect of counteranions, which would act as axial ligands, on the reactivity of the Ru center. When the triflate anion (TfO⁻) was used, **3aa** was obtained in 35% yield (entry 2) along with the diastereomer **3aa**'. Ruthenium porphyrin [Ru(TBPP)(CO)] did not catalyze the reaction (entry 3).¹⁶

The use of the ruthenium porphyrin $[Ru(TMP)(CO)]SbF_6$ (TMP: *meso*-tetrakis(2,4,6-trimethylphenyl) porphyrinate), which has a sterically hindered *meso*-aryl group near ruthenium, provided octalone **3aa** in 60% yield (entry 4). However, the

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Table 1. [4 + 2] Cycloaddition of Cyclohexenone 1a and 1,3-Butadiene 2a To Afford *Trans*-Fused Octalone $3aa^a$

$\begin{array}{c} H \\ \hline \\ H \\ \hline \\ 1a \\ 2a \\ \end{array} + \begin{array}{c} catalyst (1 \text{ mol } \%) \\ \hline \\ toluene, 25 ^{\circ}C, 12 \text{ h} \\ \hline \\ H \\ 3aa \\ \end{array} + \begin{array}{c} H \\ \hline \\ H \\ \hline \\ H \\ 3aa \\ 3aa \\ \end{array}$	a'
entry catalyst yield (%)	b,c
1 $[Ru(TBPP)(CO)]SbF_6^d$ 74 (99/1)
2 $[Ru(TBPP)(CO)]OTf^d$ 35 (6/1)	
3 $[Ru(TBPP)(CO)]^d$ <1 (-/-)
4 $[Ru(TMP)(CO)]SbF_6^e$ 60 (99/1)
5 RuCl ₃ <1 (-/-)
6 AlCl ₃ <1 (-/-)
7 $BF_3 \cdot Et_2O$ <1 (-/-)
8 MAD^{f} <1 (-/-)
9 AgSbF ₆ <5 (-/-)
10 TfOH <1 (-/-)
11 $[Fe(TPP)]SbF_6$ <1 (-/-)
12 $[Co(TPP)]SbF_6$ <1 (-/-)

^aReaction conditions: catalyst (1 mol %), cyclohexenone **1a** (0.2 mmol), and butadiene **2a** (0.8 mmol) in 0.1 mL of toluene for 12 h. ^bGC yields are given. ^cRatio of diastereomers (**3aa/3aa**'). ^dTBPP: *meso*-tetrakis(4-*tert*-butylphenyl)porphyrinate. ^eTMP: *meso*-tetrakis(2,4,6-trimethylphenyl)porphyrinate. ^fMAD: methylaluminum bis-(2,6-di-*tert*-butyl-4-methylphenoxide).

desired product 3aa was not obtained when using other Lewis acid catalysts such as RuCl₃, AlCl₃, BF₃·Et₂O, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), and AgSbF₆ or when using the Brønsted acid TfOH (entries 5-10). Moreover, nonruthenium metalloporphyrin complexes having iron and cobalt atoms did not show any catalytic activity (entries 11 and 12).

With the optimized reaction conditions in hand, we briefly examined the $[Ru(TBPP)]SbF_6$ -catalyzed [4 + 2] cycloaddition to afford trans-fused octalones 3. The results are summarized in Scheme 2. Not only the symmetrically substituted 1,3butadiene 2a but also unsymmetrically substituted 1,3-dienes such as isoprene 2b, 2-benzyl-1,3-butadiene 2c, and myrcene 2d participated in the reaction with cyclohexenone to afford the correspondingly substituted octalones 3ab, 3ac, and 3ad in good to moderate yields with high regio- and diastereoselectivity. Aryl-substituted 1,3-butadienes, which tend to oligomerize in the presence of a strong Lewis acid or Brønsted acid, also reacted with cyclohexenone to provide the corresponding octalones. For examples, phenyl- and tolyl-substituted 1,3butadienes 3e and 3f reacted with cyclohexenone to afford the correspondingly substituted otcalones 3ae and 3af in 65% and 64% yields, respectively. Aryl-substituted 1,3-butadienes having electron-withdrawing groups such as chloride, fluoride, and trifluoromethyl also participated in the cycloaddition to give 3ag, 3ah, and 3ai in moderate yields. However, aryl-substituted 1,3-diene possessing an electron-donating methoxy group failed to react with cyclohexenone because it underwent rapid oligomerization. Butadiene 2j possessing an acetyl group also participated in the reaction to give 3aj in 27% isolated yield, along with the dimer of 2j. However, cyclohexenones 1b and 1c did not participate in the reaction with 2a. The molecular structures of trans-fused octalones 3aa and 3ag were confirmed through X-ray crystal structure analysis (Figure 2).

The cycloaddition of cyclohexenone 1a with 2a provided *trans*-fused octalone 3aa in 74% yield after 12 h, while a shorter



^{*a*}Reaction conditions: catalyst (1 mol %), cyclohexenone 1 (0.2 mmol), and butadiene 2 (0.8 mmol) in 0.1 mL of toluene for 12 h. Isolated yields are given. ^{*b*}Reaction time, 24 h. ^cButadiene (0.4 mmol). ^{*d*}Reaction temperature, 50 °C. ^{*c*}*cis*-3ca' was isolated in 55% yield.



Figure 2. ORTEP drawings of 3aa and 3ag.

reaction time (30 min) afforded *cis*-fused octalone **3aa'** in 11% yield (Scheme 3). Furthermore, epimerization of *cis*-fused octalone **3aa'** to *trans*-fused octalone **3aa** was efficiently catalyzed by the ruthenium porphyrin, within 4 h (Scheme 4). These results indicated that the ruthenium-porphyrin-catalyzed cycloaddition proceeded to initially afford a *cis*-fused octalone, which underwent epimerization to the *trans*-fused octalone.¹⁷

In summary, we have demonstrated the rutheniumporphyrin-catalyzed reaction of cyclohexenones with 1,3butadienes to afford *trans*-fused octalones regio- and stereoselectively. The ruthenium porphyrin effectively catalyzed (1) the [4 + 2] cycloaddition to provide *cis*-octalones and Scheme 3. Ruthenium-Porphyrin-Catalyzed [4 + 2] Cycloaddition of Cyclohexenone 1a and Butadiene 2a



Scheme 4. Ruthenium-Porphyrin-Catalyzed Epimerization of *cis*-3aa' to *trans*-3aa



subsequent (2) epimerization to the *trans*-isomer. Detailed studies to elucidate the mechanism underlying the unique reactivity of the ruthenium porphyrin catalyst and efforts to improve the scope of the reaction are underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures including spectroscopic and analytical data of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Schmidt, R. K.; Müther, K.; Mück-Lichtenfeld, C.; Grimme, S.; Oestreich, M. J. Am. Chem. Soc. **2012**, 134, 4421. (b) Klare, H. F. T.; Bergander, K.; Oestreich, M. Angew. Chem., Int. Ed. **2009**, 48, 9077. (c) Lee, J. H.; Kim, W. H.; Danishefsky, S. J. Tetrahedron Lett. **2009**, 50, 5482. (d) Ryu, D. H.; Corey, E. J. J. Am. Chem. Soc. **2003**, 125, 6388. (e) Eklund, L.; Axelsson, A.-K.; Nordahl, Å.; Carlson, R. Acta Chem. Scand. **1993**, 47, 581. (f) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, F. Tetrahedron Lett. **1986**, 27, 4945.

(2) (a) Jones, J. B.; Dodds, D. R. Can. J. Chem. 1987, 65, 2397.
(b) Hart, D. J.; Kanai, K. J. Am. Chem. Soc. 1983, 105, 1255.

(3) Bartlett, P. D.; Woods, G. F. J. Am. Chem. Soc. 1940, 62, 2933.
(4) Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. J. Am. Chem. Soc. 2010, 132, 5625.

(5) (a) Peng, F.; Grote, R. E.; Danishefsky, S. J. *Tetrahedron Lett.* **2011**, 52, 3957. (b) Lee, J. H.; Zhang, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, 132, 14330. (c) Kim, W. H.; Lee, J. H.; Aussedat, B.; Danishefsky, S. J. *Tetrahedron* **2010**, 66, 6391. (d) Kim, W. H.; Lee, J. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, 131, 12576.

(6) For some examples of a photochemical reaction that provides trans-fused Diels-Alder products, see (a) Nikolai, J.; Loe, Ø.; Dominiak, P. M.; Gerlitz, O. O.; Autschbach, J.; Davies, H. M. L. J. Am. Chem. Soc. 2007, 129, 10763. (b) Ghosh, S.; Roy, S. S.; Saha, G. Tetrahedron 1988, 44, 6235. (c) Ghosh, S.; Saha, S. Tetrahedron Lett. 1985, 26, 5325. (d) Eaton, P. E.; Lin, K. J. Am. Chem. Soc. 1965, 87, 2052. (e) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. J. Am. Chem. Soc. 1965, 87, 2051.

(7) For the epimerization of *cis*-fused Diels–Alder products to *trans* Diels–Alder products, see: Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. J. Org. Chem. **1982**, 47, 5056.

(8) For some representative examples, see: (a) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Grove, J. T. Science **2012**, 337, 1322. (b) Morandi, B.; Carreira, E. M. Science **2012**, 335, 1471. (c) Breslow, R.; Huang, Y.; Zhang, X.; Yang, J. Proc. Natl. Acad. Sci. U.S.A. **1997**, *94*, 11156.

(9) For some examples of the use of metalloporphyrins in nonoxidative bond formation, see: (a) Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Chem. Commun.* **2002**, 2570. (b) Suda, K.; Kikkawa, T.; Nakajima, S.-I.; Takanami, T. *J. Am. Chem. Soc.* **2004**, 126, 9554. (c) Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Tetrahedron Lett.* **1999**, 40, 7243. (d) Chen, J.; Che, C.-M. *Angew. Chem., Int. Ed.* **2004**, 43, 4950. (e) Li, Y.; Chan, P. W. H.; Zhu, N.-Y.; Che, C.-M.; Kwong, H.-L. *Organometallics* **2004**, 23, 54. (f) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. J. Am. Chem. Soc. **2005**, 127, 11426. (g) Zhou, C.-Y.; Chan, P. W. H.; Che, C.-M.; Guo, Z.; Siu, F.-M.; Lok, C.-N.; Liu, F.; Yeung, K.-C.; Zhou, C.-Y.; Che, C.-M. *Org. Biomol. Chem.* **2012**, 10, 9165.

(10) Fujiwara, K.; Kurahashi, T.; Matsubara, S. J. Am. Chem. Soc. 2012, 134, 5512.

(11) (a) Wakabayashi, R.; Kurahashi, T.; Matsubara, S. Org. Lett. 2012, 14, 4794. (b) Ozawa, T.; Kurahashi, T.; Matsubara, S. Org. Lett. 2012, 14, 3008.

(12) The attempted cycloaddition of aldehyde and a diene with the ruthenium porphyrin $[Ru(TBPP)(CO)]SbF_6$ catalyst afforded a cycloadduct in 62% yield, which is lower than that obtained with the iron porphyrin $[Fe(TPP)]SbF_6$ catalyst.

(13) (a) Young, R. C.; Nagle, J. K.; Meyer, T. J.; Whitten, D. G. J. Am. Chem. Soc. 1978, 100, 4773. (b) Higuchi, T.; Satake, C.; Hirobe, M. J. Am. Chem. Soc. 1995, 117, 8879. (c) Jiang, G.; Chen, J.; Thu, H.-Y.; Huang, J.-S.; Zhu, N.; Che, C.-M. Angew. Chem., Int. Ed. 2008, 47, 6638. (d) Ke, M.; Sishta, C.; James, B. R.; Dolphin, D.; Sparapany, J. W.; Ibers, J. A. Inorg. Chem. 1991, 30, 4766. (e) Hu, W.-X.; Li, P.-R.; Jiang, G.; Che, C.-M.; Chen, J. Adv. Synth. Catal. 2010, 352, 3190. (f) Huang, Y.; Vanover, E.; Zhang, R. Chem. Commun. 2010, 46, 3776. (g) Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Masciocchi, N.; Sironi, A.; Cenini, S. Inorg. Chem. 2005, 44, 2039. (h) Lai, T.-S.; Kwong, H.-L.; Zhang, R.; Che, C.-M. J. Chem. Soc., Dalton Trans. 1998, 3559. (i) Ito, R.; Umezawa, N.; Higuchi, T. J. Am. Chem. Soc. 2005, 127, 834. (j) Ohtake, H.; Higuchi, T.; Hirobe, M. J. Am. Chem. Soc. 1992, 114, 10660.

(14) The cationic ruthenium complex $[Ru(TBPP)(CO)]SbF_6$ was prepared following the reported procedure: [Ru(TBPP)(CO)] (290 mg, 0.30 mmol) and AgSbF_6 (98 mg, 0.29 mmol) was dissolved in dry CH₂Cl₂ (10 mL) and stirred for 6 h in a dry box. The reaction mixture was filtered to remove Ag(0) and concentrated to dryness. The complex was used without further purification. ESI-MS and IR spectroscopy revealed that CO still remains coordinated to the Ru atom upon oxidation by AgSbF₆.

(15) The high regioselectivity can be explained in terms of the reaction mechanism; the ruthenium-catalyzed cycloaddition of cyclohexenone with dienes proceeds to afford initial *cis*-fused octalone through an asynchronous stepwise mechanism, which consists of the formation of a cationic intermediate.

(16) Even though $[Ru(TBPP)(CO)]SbF_6$ could be reduced to [Ru(TBPP)(CO)] under certain conditions, we observed that [Ru(TBPP)(CO)] is inactive for the catalyst. Furthermore, the results of the time course experiment with the $[Ru(TBPP)(CO)]SbF_6$ catalyst indicate that there is no induction period for the reaction (Supporting Information, Figure S1). Based on these results, we proposed that $[Ru(TBPP)(CO)]SbF_6$ is not reduced to [Ru(TBPP)(CO)] under the catalytic reaction conditions and [Ru(TBPP)(CO)]SbF_6 is the active catalyst for the reaction.

(17) The time-dependent changes in *cis-trans*-isomers also indicated that the ruthenium-porphyrin-catalyzed cycloaddition proceeded along with epimerization of the *cis*-fused octalone to *trans*-fused octalone (Supporting Information, Figure S1).