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

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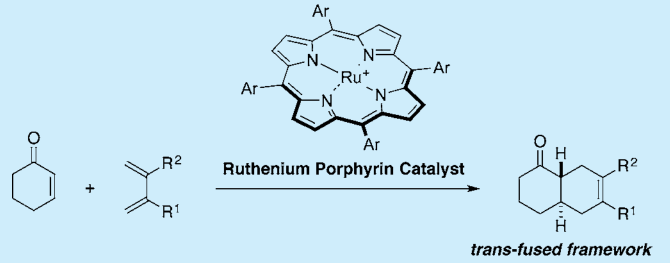
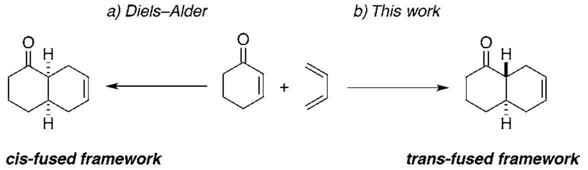
Supporting Information

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.

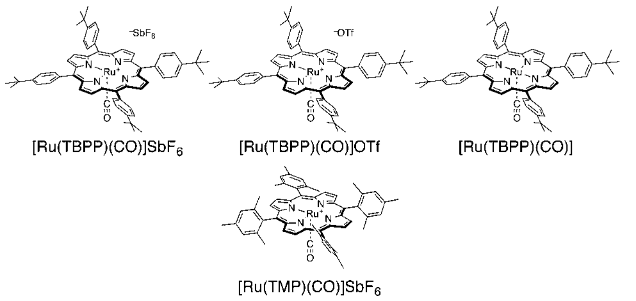


Octalones are among the most versatile building blocks for the synthesis of various natural products such as polycyclic sesquiterpenes and triterpenes. The [4 + 2] cycloaddition of cyclohexenones with butadienes, namely, the Diels−Alder reaction, would be one of the most straightforward synthetic routes 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]

Scheme 1. Cycloaddition To Afford Octalone



Porphyrins have emerged as useful ligands for transition-metal catalysts in organic synthesis in cases where the use of other ligands is infeasible.[8,9] Recently, we developed the iron-porphyrin-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 compounds[12] and found that ruthenium porphyrin complex [Ru(TBPP)-(CO)]SbF_6 (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]



[Ru(TBPP)(CO)]SbF_6
[Ru(TBPP)(CO)]OTf
[Ru(TBPP)(CO)]
[Ru(TMP)(CO)]SbF_6

Figure 1. Ruthenium porphyrin complexes.

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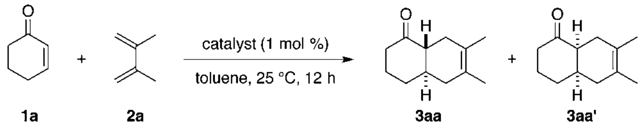
Table 1. [4 + 2] Cycloaddition of Cyclohexenone **1a** and 1,3-Butadiene **2a** To Afford *Trans*-Fused Octalone **3aa**[a]



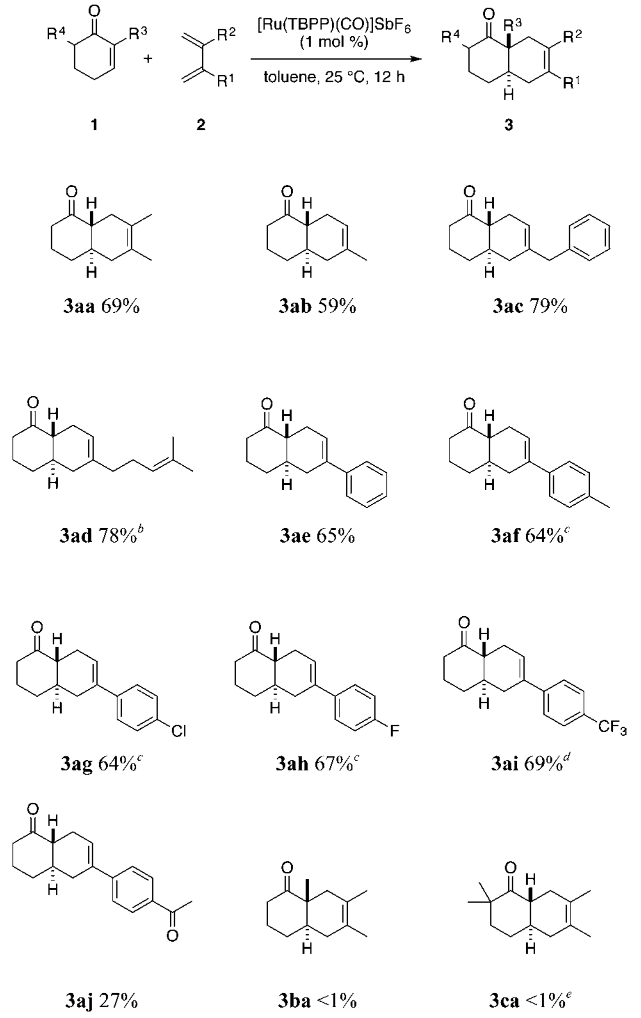
entry	catalyst	yield (%)[b,c]
1	$[Ru(TBPP)(CO)]SbF_6$[d]	74 (99/1)
2	[Ru(TBPP)(CO)]OTf[d]	35 (6/1)
3	[Ru(TBPP)(CO)][d]	<1 (−/−)
4	$[Ru(TMP)(CO)]SbF_6$[e]	60 (99/1)
5	$RuCl_3$	<1 (−/−)
6	$AlCl_3$	<1 (−/−)
7	$BF_3{\cdot}Et_2O$	<1 (−/−)
8	MAD[f]	<1 (−/−)
9	$AgSbF_6$	<5 (−/−)
10	TfOH	<1 (−/−)
11	$[Fe(TPP)]SbF_6$	<1 (−/−)
12	$[Co(TPP)]SbF_6$	<1 (−/−)

[a] Reaction conditions: catalyst (1 mol %), cyclohexenone **1a** (0.2 mmol), and butadiene **2a** (0.8 mmol) in 0.1 mL of toluene for 12 h. [b] GC yields are given. [c] Ratio of diastereomers (**3aa**/**3aa′**). [d] TBPP: *meso*-tetrakis(4-*tert*-butylphenyl)porphyrinate. [e] TMP: *meso*-tetrakis-(2,4,6-trimethylphenyl)porphyrinate. [f] MAD: methylaluminum bis-(2,6-di-*tert*-butyl-4-methylphenoxide).

desired product **3aa** was not obtained when using other Lewis acid catalysts such as $RuCl_3$, $AlCl_3$, $BF_3{\cdot}Et_2O$, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), and $AgSbF_6$ 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 1,3-butadiene **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 1,3-butadienes **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).

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



[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. [c] Butadiene (0.4 mmol). [d] Reaction temperature, 50 °C. [e] ***cis*-3ca′** was isolated in 55% yield.

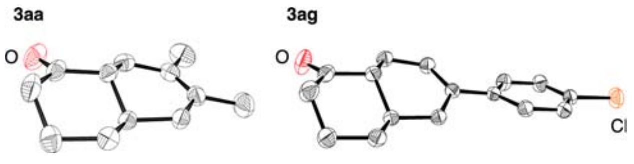
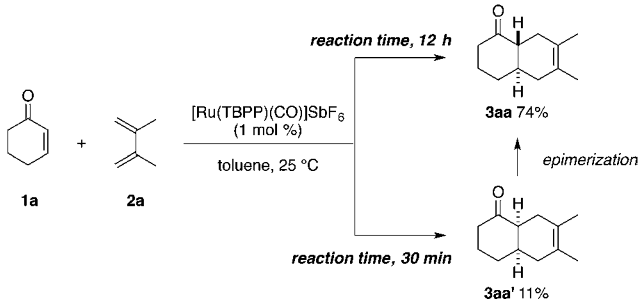


Figure 2. ORTEP drawings of **3aa** and **3ag**.

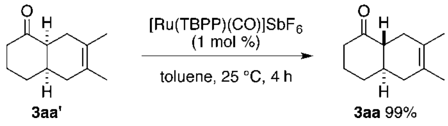
The cycloaddition of cyclohexenone **1a** with **2a** provided *trans*-fused octalone **3aa** in 74% yield after 12 h, while a shorter reaction time (30 min) afforded *cis*-fused octalone **3aa′** in 11% yield (Scheme 3). Furthermore, epimerization of *cis*-fused octalone **3aa′** to *trans*-fused octalone **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 ruthenium-porphyrin-catalyzed reaction of cyclohexenones with 1,3-butadienes 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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(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.

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(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 CH_2Cl_2 (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 $AgSbF_6$.

(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).