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A Facile Diels−Alder Reaction with Benzene: Synthesis of the Bicyclo[2.2.2]octene Skeleton Promoted by Rhenium

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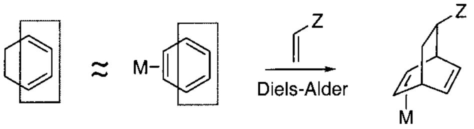
The Diels−Alder reaction, in which a diene is combined with an alkene to form a cyclohexene, is one of the most synthetically useful of all cyclization reactions.[1,2] Since the reaction is both concerted and stereoselective, two new C−C bonds and up to four new stereocenters may be generated in a single step with a high degree of stereocontrol.

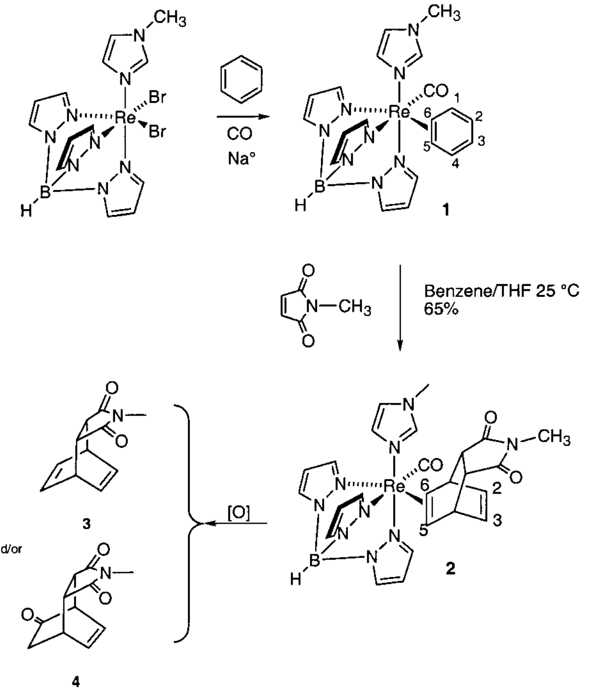
Although ubiquitous in nature, simple aromatic molecules are rarely employed as dienes in Diels−Alder reactions due to their inherent aromatic stability. A thermodynamic barrier of 20−40 kcal/mol must be overcome in order to induce such reactivity from benzene, the benchmark of aromatic systems.[3,4] In the proper coordination environment, both osmium[5] and rhenium[6,7] can form stable complexes with arenes in which only two of the six carbons are coordinated. Once complexed in a dihapto fashion, the uncoordinated portion of the arene more closely resembles a conjugated diene. We therefore hypothesized that the complexation should increase the propensity of arenes to undergo cycloaddition reactions.



Only a small number of Diels−Alder reactions with aromatic compounds have been reported.[8,9] These examples fall roughly into two categories based on the approach employed in overcoming the resonance energy of the starting materials. One technique exploits the reactivity of highly strained aromatic compounds so that the relief of this strain compensates for the loss in aromaticity. Alternatively, employing harsh conditions such as high temperatures and pressures or the use of strong Lewis acids has been moderately successful. Usually, however, side reactions dominate: the adducts are isolated in low yields (typically less than 10%) and are prone to retrocycloaddition.

Over the past decade, one of the primary goals of our research has been to develop metal fragments that bind aromatic compounds in an η^2-fashion in order to activate them toward reactions with electrophiles. Recently, we have developed an electron-rich metal fragment, {TpRe(CO)(MeIm)},[10] that binds benzene to form complex **1**. The crystal structure of this complex shows dearomatization of the π-system to such an extent that the uncoordinated portion of the ring closely resembles cyclohexadiene.[7]

Scheme 1. Rhenium-Promoted Diels−Alder Cycloaddition Reaction with Benzene and a Maleimide



When **1** is combined with NMM in a cosolvent mixture of benzene/THF and allowed to stir at 20 °C for 2 days, a Diels−Alder cycloaddition occurs to form product **2**, recovered as a single diastereomer in 65% yield (Scheme 1). This complex is stable in air and water and may be purified by column chromatography on silica gel. The ^{1}H NMR spectrum of **2** features a set of doublet-of-doublets assigned to the bound olefin protons at 2.84 ppm for H(6) and 2.25 ppm for H(5), a sharp singlet assigned to the imidazole methyl at 3.81 ppm, and a second sharp singlet assigned to the succinamide *N*-methyl group at 2.74 ppm. The ^{13}C NMR spectrum shows the metal-bound carbons at 69.1 and 61.2 ppm, assigned to C(6) and C(5), respectively. Additionally, the infrared spectrum displays prominent carbonyl absorptions at 1785 (CO) and 1688 cm^{-1} (amide). The cyclic voltammagram of **2** features a reversible oxidation wave with $E_{1/2} = 160$ mV, indicative of a Re(I)−olefin complex.[7] The stereochemistry of the cycloaddition was first elucidated through NOESY spectral data that suggested that the reaction occurred to the arene face opposite metal coordination with exclusively endo selectivity. This assignment was later confirmed by an X-ray crystal structure analysis (Figure 1).

Liberation of the organic cycloadduct **3** from the metal complex was achieved through oxidation of the rhenium center under a variety of conditions in up to 90% yield (Supporting Information). Convenient oxidants were CuBr$_2$, AgOTf, [FeCp$_2$]PF$_6$, or O$_2$/TFA. No attempt was made to recover the metal from these reactions. We were surprised to discover that under certain conditions, the bound olefin underwent further oxidation, yielding the enone cycloadduct **4** (55% isolated yield). Although the exact mechanism of this oxidation is yet to be fully understood, it is apparent that the rhenium in a higher oxidation state inserts an oxygen atom, presumably originating from adventitious water, into the C−H bond of the bound olefin. The putative enol resulting would tautomerize to the enone after decomplexation. The spectroscopic

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(10) Abbreviations used throughout the text: MeIm, 1-methylimidazole; Tp, hydrido(tris)pyrazolyl borate; NMM, *N*-methylmaleimide; DMAD, dimethylacetylene dicarboxylate; pz, pyrazole.

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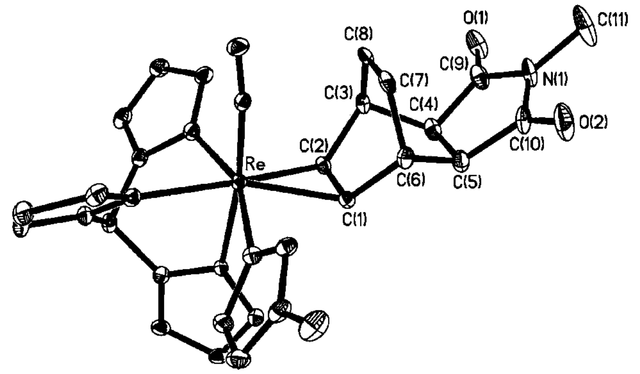


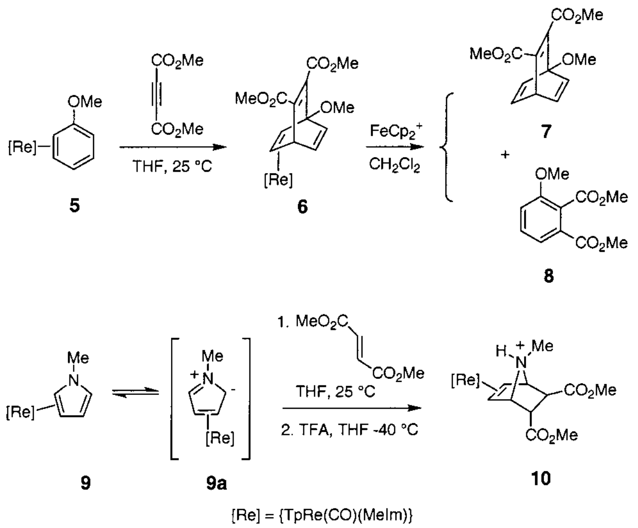
Figure 1. ORTEP diagram (30% ellipsoids) of the benzene/NMM cycloadduct complex **2**. For clarity, atom labels are displayed only for the metal center and the cycloadduct ligand.

features of **4** include a ^{13}C NMR resonance at 205.7 ppm and an infrared absorption of 1701 cm^{-1} indicative of a keto-carbonyl carbon. Mass analysis of **4** using GC/MS shows the parent ion (M^+) of 205 amu, corresponding to a molecular formula of $C_{11}H_{11}NO_3$. Analysis of the spectral data along with a comparison of related compounds found in the literature led us to the assigned regioselectivity of the oxygen insertion.[11] Oxobicyclooctenes similar to **4** have been shown to be useful precursors to cyclopentanoid terpenes and prostacyclin analogues.[12] By comparison, reaction of phenol and *N*-phenylmaleimide at 170 °C for 3 days gives 36% of the enone cycloadduct as a 4:1 mixture of diastereomers.[11] In another useful comparison, the cycloaddition reaction between *N*-methylmaleimide and 1,3-cyclohexadiene was investigated under reaction conditions identical to those used for the formation of **2** (THF/benzene solvent; psuedo-first-order conditions; 25 °C). Here we find that the reaction with the organic diene has a specific rate [$k = (1.5 \pm 0.3) \times 10^{-2}$ M^{-1} s^{-1}] that is considerably lower than the rhenium−benzene complex rate [$k = (2.4 \pm 0.4) \times 10^{-2}$ M^{-1} s^{-1}].

The complex [Os(NH$_3$)$_5$(η^2-benzene)]$^{2+}$ prepared by Harman and Taube[13] is more thermally robust than **1**; however, this complex failed to undergo a Diels−Alder reaction with *N*-methylmaleimide. This difference in reactivity is attributed to the decreased ability of Os(II) to act as a π-donor in comparison to its Group 7 counterpart.[14] Cyclic voltammetric data also point to a greater π-donating ability of the Re(I) fragment compared to that of the osmium system. Compound **1** shows an irreversible oxidation wave that is ~300 mV more reducing than that of the Os(NH$_3$)$_5$(η^2-benzene) complex ($E_{p,a} = -150$ mV for **1** versus $E_{p,a} = +140$ mV for the latter; DMF, 100 mV/s). Although these values are not formal reduction potentials, the rates of arene displacement for these E_rC_i reactions are likely to be similar so that a qualitative comparison of peak potentials ($E_{p,a}$) is justified.

Initial studies suggest that a broad and useful scope of cycloaddition reactions may be accessed by this new methodology (Scheme 2). For example, the anisole complex **5** undergoes

Scheme 2. Rhenium-Promoted Cycloaddition Reactions That Generate a Barrelene and an Azanorbornene from Common Aromatic Precursors



cycloaddition with DMAD to form the complexed barrelene **6** which, upon demetalation, yields the functionalized barrelene **7** as well as the trisubstituted arene **8**, a product of a complementary retrocycloaddition in which acetylene is eliminated. Additionally, the 1-methylpyrrole complex **9** undergoes a 1,3-dipolar cycloaddition reaction with dimethylfumarate to form the 7-azabicyclo[2.2.1]heptene **10** via the transient azomethine ylide linkage isomer **9a**.[15] Current studies are underway to determine the extent of this reactivity and its applicability to the synthesis of more complex carbocyclic and heterocyclic compounds.

In conclusion, the dihapto coordination of benzene by the π-basic metal fragment {[TpRe(CO)(MeIm)} effectively dearomatizes benzene. The electron-donating metal activates the arene to such an extent that the unbound portion of the ligand acts as an electron-rich diene undergoing a Diels−Alder cycloaddition with NMM with a specific rate that is 60% greater than that observed for cyclohexadiene. Furthermore, the metal controls the stereochemistry of the cycloaddition and protects the resulting cycloadduct from undergoing a retrocycloaddition by blocking one of the π bonds. Oxidation of the rhenium metal center promotes decomplexation, providing access to the bicyclo[2.2.2]octadiene. Optionally, decomplexation accompanied by oxygen insertion yields bicyclo[2.2.2]octenone products. The strategy of using a transition metal to “switch off” resonance stabilization in arenes and aromatic heterocycles could prove to be a powerful new tool for synthetic chemists.

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Supporting Information Available: Synthetic procedures and detailed characterization data for compounds **1**−**6**, along with X-ray diffraction data for **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Although the analogous reaction of the complex [Os(NH$_3$)$_5$(η^2-benzene)]$^{2+}$ with NMM does not occur, the anisole complex, [Os(NH$_3$)$_5$(η^2-anisole)]$^{2+}$, does react with NMM in the presence of BF$_3$ at −50 °C to yield a para-substituted anisolium resulting from a Michael addition. The cycloadduct complex forms through nucleophilic ring closure of the BF$_3$-enolate, resulting in a formal [4 + 2] cycloadduct (ref 16).

(15) Pentaammineosmium(II) complexes of pyrrole and substituted pyrroles demonstrate similar cycloaddition reactivity although the rate of reaction appears to be significantly slower under similar conditions (ref 17).

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