+2.82° (c 10.87, benzene), optical purity 11% (lit.[7] mp 54–54.5 °C, $[\alpha]_D^{22}$ +25.9° (c 2.24, benzene)). The carbinol was both recrystallized from ether–pentane and sublimed under reduced pressure, but neither process resulted in a product of higher rotation. The structure of the product was confirmed by NMR spectra (four singlet signals). This preparation of *tert*-butylphenylcarbinol was repeated with levo 2-MeTHF ([α] −22.40, optical purity 81.5%) and using the same amounts of reactants indicated above. In this case, pure pivaldehyde was added to refluxing (85 °C) Grignard reagent mixture. A 78% yield of levo product distilled at 70–72 °C (1.4 mm). The specific rotation was $[\alpha]_D^{20}$ −1.52° (c 25, benzene). This corresponds to an optical purity of 5.87% and stereoselectivity of 7.2%.

b. In Ethyl Ether–2-MeTHF (1:1). Phenylmagnesium bromide was prepared from 0.510 g (0.021 mol) of magnesium and 3.14 g (0.02 mol) of bromobenzene in 3.75 g (0.05 mol) of ethyl ether. After the reaction was complete, 4.31 g (0.05 mol) of (+)2-MeTHF was added and the mixture was stirred for 30 min to equilibrate the solvated 2-MeTHF. Pivaldehyde (2.15 g, 0.025 mol) was added as in part a. After hydrolysis and isolation as above, 1.9 g (58%) of *tert*-butylphenylcarbinol was obtained. This product was racemic and provided an NMR spectrum identical with that of the authentic carbinol.

c. In Ethyl Ether–2-MeTHF with Excess 2-MeTHF (Solvent Exchange). Phenylmagnesium bromide was prepared as in part b except using 7 g (0.1 mol) of ethyl ether. When the Grignard reagent formation was complete, the solvent was removed at reflux with a stream of dry nitrogen. Finally the reagent was pumped at 1 mm to leave a viscous residue. After 7.0 g of 2-MeTHF was added, the mixture was stirred 30 min to attain solvent equilibration. Pivaldehyde (2.15 g, 0.025 mol) was added and the reaction and product isolation were completed as above. The *tert*-butylphenylcarbinol (2.1 g, 64%) was optically active: $[\alpha]_D^{19}$ +0.15°, optical purity 0.6%.

Asymmetric Reduction of Isobutyrophenone. Isobutylmagnesium chloride was prepared by the reaction of magnesium (0.0563 g, 0.024 mol) with isobutyl chloride (1.85 g, 0.02 mol) in 8.55 g (10 mL) of (+)2-MeTHF at reflux. The reaction was difficult to start and was assisted by the addition of a trace of bromobenzene. The isobutylmagnesium chloride solution was cooled to 20 °C and a solution of 2.52 g (0.017 mol) of isobutyrophenone in 10 mL of pentane was added during 2 h. The reaction mixture was hydrolyzed immediately and after the usual workup 2.20 g (86%) of 2-methyl-1-phenylpropanol was isolated by distillation: bp 57–62 °C (0.5 mm); $[\alpha]_D^{22}$ +1.59° (c 10.09, ether); optical purity 3.3%. Levene and Mikeska[8] report $[\alpha]_D^{20}$ +47.7° (c 6.997, ether) for a pure enantiomer. The reaction mixture was shown by GC to contain no unreacted ketone and the NMR spectra of the product was consistent with the indicated structure. The reaction was repeated with the temperature maintained at −10 °C during the addition of the isobutyrophenone. In this case the optical purity of the product was 2.1%.

Kinetic Resolution of 2-Bromo-1-phenylpropane. Magnesium (0.365 g, 0.015 mol) and 2-bromo-1-phenylpropane (5.97 g, 0.03 mol) were reacted in 5.4 g of (+)2-MeTHF and 5 mL of pentane. After the reaction started the reaction flask was cooled in an ice–water bath. During 2 h most of the magnesium dissolved. The reaction mixture was hydrolyzed and the unreacted 2-bromo-1-phenylpropane was isolated and purified by preparative GC and finally vacuum distilled: bp 47–50 °C (0.3 mm); $[\alpha]_D^{20}$ −0.5 °C (c 8.01, ethanol), optical purity 2.1% (lit.[9] $[\alpha]_D^{20}$ −22.96° (c 4.964, ethanol)).

Discussion and Results

Each type of reaction examined produced optically active products when active 2-MeTHF was used as solvent (2.1 to 11% optical purity). Each example was chosen so that steric factors would be as significant as possible in the developing diasteromeric reaction transition states leading to chiral products. Nevertheless, the extent of enantiomeric enrichment was not superior to that reported earlier with Grignard reagents in chiral ethers. For example, the reaction of phenylmagnesium bromide with pivaldehyde in (+)2-MeTHF provided *tert*-butylphenylcarbinol in 11% optical purity. For a comparison, the reaction of the same Grignard with 2-butanone (which has a carbonyl group with less difference in steric requirement for it's attached groups than that in pivaldehyde) in (+)-2,3-dimethoxybutane gave methylethylphenylcarbinol in about 18% optical purity.[10]

Optically active *tert*-butylphenylcarbinol was prepared by addition of pivaldehyde to phenylmagnesium bromide at −10 and 85 °C with the greater stereoselectivity at the lower temperature. At the concentration used with this Grignard reagent a viscous unstirrable mixture developed at −30 °C and precluded lower temperature experiments.

The attempts to achieve asymmetric synthesis from the Grignard reagent first prepared in ethyl ether and followed by an equal molar amount of (+)-2-methyltetrahydrofuran added before reaction with pivaldehyde or solvent exchange with (+)2-MeTHF effected before reaction with the aldehyde, resulted in lower enantiomeric enrichment in the carbinol product. This suggests that the 2-methyltetrahydrofuran may be less competitive in solvating the Grignard reagent than expected. A thermodynamic measure of the basicity of 2-methyltetrahydrofuran compared to tetrahydrofuran relative to an acid having steric requirements comparable to the magnesium atom site in the Grignard reagent would be desirable.

Other reactions in 2-MeTHF including Grignard reduction and kinetic resolution also gave products having observable but low enantiomeric enrichment.

Registry No.—(+)2-MeTHF, 63798-12-9; (−)2-MeTHF, 63798-13-0; acetaldehyde, 75-07-0; (+)-1-phenylethanol, 15157-69-7; phenyl bromide, 108-86-1; (+)-*tert*-butylphenylcarbinol, 23439-91-0; pivaldehyde, 630-19-3; (−)-*tert*-butylphenylcarbinol, 24867-90-1; (±)-*tert*-butylphenylcarbinol, 57377-60-3; isobutyl chloride, 513-36-0; isobutyophenone, 611-70-1; (+)-2-methyl-1-phenylpropanol, 14898-86-3; (±)-2-bromo-1-phenylpropane, 14367-52-3; (−)-2-bromo-1-phenylpropane, 63798-14-1.

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Cycloadditions of 2,5-Dimethyl-3,4-diphenylcyclopentadienone to Cyclooctene, Cyclooctadienes, and the 76 °C Melting Dimer of Cyclooctatetraene

K. N. Houk* and L. J. Luskus

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

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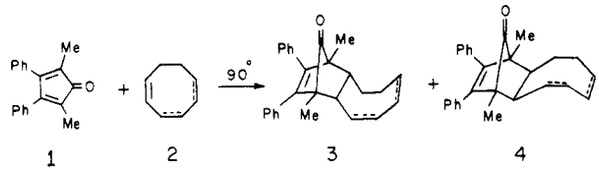
The cycloaddition reactions of the potent electron-deficient diene, 2,5-dimethyl-3,4-diphenycyclopentadienone (1) to a remarkable variety of alkenes have been reported. These adducts have been used in the synthesis of novel substances,[2] and the structures of the Diels–Alder adducts have given some insight into the origins of cycloaddition stereoselectivity.[3,4] We wish to report facile and remarkably stereoselective cycloadditions of 1 to cyclooctenes and cyclooctadienes and to show that attempted cycloadditions to cyclooctatetraene give mainly cycloadducts of 1 to a cyclooctatetraene dimer.

Heating the dimer of 1 with cyclooctene at 90 °C for 1 day gave a product which appeared, by NMR, to be a 96:4 mixture of 1:1 adducts. The bridged carbonyl at 5.69 μm established the Diels–Alder nature of the adduct. Recrystallization from methanol gave a pure adduct **3a**, mp 171–172 °C, which had a methyl singlet at 1.25 ppm in the NMR spectrum ($CDCl_3$).



1 2 3 4

a: cyclooctene
b: 1,5-cyclooctadiene
c: 1,3-cyclooctadiene

The crude product mixture displayed, in addition to the intense methyl resonance due to **3a**, a small singlet at 1.14 ppm whose area was about 4% that of the 1.25-ppm resonance. The endo stereochemistry, **3a**, is tentatively assigned to the major adduct on the basis of the similarity of the chemical shift of the methyl resonances in **3a** (1.25 ppm) to those of the endo adducts of cyclohexene and **1** (1.25 ppm),[4c] or of cyclopentene and **1** (1.32 ppm).[4b] The minor adduct from cyclooctene has a methyl resonance (1.14 ppm), similar in location to those in the exo adducts of cyclohexene and **1** (1.10 ppm)[4c] or of cyclopentene and **1** (1.15 ppm).[4b] The minor adduct is, therefore, assigned the exo structure, **4a**.

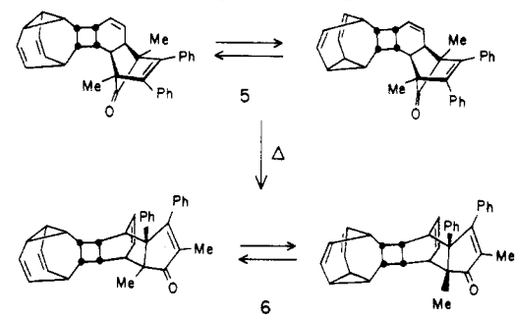
A solution of **1** in 1,5-cyclooctadiene was heated at 97 °C for 1 day. After evaporation of excess 1,5-cyclooctadiene, the NMR spectrum of the crude product had an intense singlet at 1.24 ppm and a singlet at 1.10 ppm whose area was less than 5% of the 1.24-ppm singlet. Recrystallization gave the major adduct, mp 124–126 °C, **3b**, with a bridged carbonyl at 5.69 μm in the IR. The chemical shifts of the methyl resonances indicate that the major adduct is the endo adduct. Catalytic hydrogenation of **3b** (5% Pd/C, EtOAc) resulted in the uptake of 1 mol of hydrogen to give a product identical in all respects to **3a**.

The reaction of **1** with 1,3-cyclooctadiene gave a single adduct, **3c**, mp 144 °C, in 84% yield, with methyl resonances at 1.08 and 1.27 ppm. Catalytic hydrogenation again resulted in the formation of a dihydro adduct identical to **3a**. A rigorous proof of the endo *nature* of adducts **3a, 3b,** and **3c** could not be accomplished, since **3c** did not undergo photochemical cyclization (decarbonylation is observed), and no Cope rearrangement occurs upon heating. The endo adducts of **1** with cyclopentadiene and with 1,3-cyclohexadiene undergo Cope rearrangements at 90 °C with half-lives of 30 min and 159 h, respectively.[4b,c] Thus, the failure of **3c** to undergo Cope rearrangement after heating at 120–125 °C for 5 days is not unlikely even if the adduct has the endo structure.

The difficulty of the Cope rearrangement in the eight-membered adduct is undoubtedly the result of the difficulty with which the requisite boat-like transition state can be attained. The similarity (but not identity) of a secondary orbital interaction-stabilized transition state for the Diels–Alder reaction leading to **3c** and the hypothetical Cope rearrangement transition state of **3c** indicates that secondary orbital interactions cannot be of much importance in the transition state leading to **3c**. The similar adduct mixtures from **2a,b,c,** only the last of which can have attractive secondary orbital interactions in the endo transition state, also suggests that the origin of the endo preference in the reactions of cyclooctene, 1,5-cyclooctadiene, and 1,3-cyclooctadiene with **1** probably arises from minimization of steric effects in the endo transition states.[4]

Whereas we found that **1** gives approximately equal amounts of endo and exo adducts with cyclopentadiene,[4b] and a 2:1 mixture of endo and exo adducts with 1,3-cyclohexadiene,[4c] Jones found that the analogous cyclopentadienone having a phenanthrene moiety in the place of the stilbene unit in **1** gives mainly the endo adduct with cyclopentene.[4d] This was attributed to the absence of repulsion between the out-of-plane phenyls in **1** and the cyclopentene hydrogens. Why then do the cyclooctenes appear to give mainly the endo adducts with **1**? We speculate that this could well be due to the preferred tub conformations of cyclooctenes, which may place most of the bulk of the cyclooctane rings away from the out-of-plane phenyl hydrogens. We are then left with the difficulty of explaining predominant endo addition. Perhaps Furukawa et al.'s attractive interactions between saturated and unsaturated centers,[5] a hypothesis we have heretofore argued against,[1a] must be invoked.

Cyclooctatetraene dimerizes more rapidly than it undergoes cycloaddition to **1**. Thus, heating **1** in freshly distilled cyclooctatetraene at 40 °C for 2 weeks gave a 2:1 adduct, **5**, mp 168–169 °C, of cyclooctatetraene and **1**.[6] The 2:1 nature was shown by mass spectrometry and elemental analysis, while the bridged carbonyl at 5.70 μm ($CHCl_3$) in the IR indicated that a Diels–Alder adduct had been formed. Confirmation of the adduct structure was achieved by independent reaction of the cyclooctatetraene 76 °C melting dimer,[7] with **1**. Reaction of equimolar amounts of the 76 °C dimer of COT and **1** at 60 °C in acetone for 12 h gave a 79% yield of **5**. Both **5** and **6** (see below) show temperature-dependent NMR spectra



similar to the 76 °C dimer and to other adducts of the dimer retaining the dihydrobullvalene moiety.[8-10] Thus, at −80 °C coalescence occurred in the spectra of both **5** and **6**, while sharpening of the resonances occurred at −100 °C.

When the reaction of **1** and cyclooctatetraene was carried out at higher temperatures, or upon heating of **5** at 120 °C for 2 h, a rearranged 2:1 adduct, **6**, mp 233–234 °C, IR 5.99 μm (C=O, $CHCl_3$), was formed. The relatively rapid Cope rearrangement is most likely due to the increased rigidity of the cyclohexene ring compared to that in the 1,3-cyclohexadiene adduct.[4c] This rigidity facilitates achievement of the Cope rearrangement transition state.

The reaction of the 1,3-cyclohexadiene moiety of the 76 °C dimer of cyclooctatetraene with the dienophile, vinylene carbonate, has been reported earlier.[9] Cyclopentadiene was believed to add the 76 °C dimer, in the same fashion,[10] but Fray and co-workers recently showed that the adduct actually has a structure analogous to the Cope rearrangement product **6**.[11] The 76 °C dimer itself dimerizes to a tetramer, in which the 1,3-cyclohexadiene moiety of dimer acts as both diene and dienophile.[12] By contrast to our results with **1**, 1,3-dipoles add readily to monomeric cyclooctatetraene.[13]

Cyclooctenes react faster than cyclopentenes, which, in turn, react faster than cyclohexenes with cyclopentadienones. Thus, the times and temperatures required for complete conversion to adducts using alkenes as solvents are 3 days at 115 °C, 1 day at 90 °C, and 8 days at 90 °C for cyclopentene,[4b] cyclooctene, and cyclohexene,[4c] respectively. This relatively high reactivity of the eight-membered ring has also been noted in hexachlorocyclopentadiene cycloadditions and diethylaluminum additions to cycloalkenes.[14] The sterically unencumbered nature of the cyclooctene double bond in additions seems to be verifed by these results.

Experimental Section

Preparation of 3a. A solution of 1.30 g (2.5 mmol) of the dimer of 1 in 10 mL of cyclooctene was heated under nitrogen at 90 °C for 17

h. Excess cyclooctene was removed in vacuo and the solid residue was recrystallized from methanol to give colorless **3a:** mp 171–172 °C; 1.70 g (92%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.24 (6 H), 1.2–2.2 (14 H), 6.9–7.3 (10 H). Anal. Calcd for $C_{27}H_{30}O$: C, 87.52; H, 8.16, O, 4.32. Found: C, 87.27; H, 8.24.

Preparation of 3b. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 10 mL of 1,5-cyclooctadiene containing 50 mg of hydroquinone was heated under nitrogen at 97 °C for 23 h. Excess diene was removed in vacuo and the residue was purified by TLC (silica gel, 5% ethyl acetate–petroleum ether), followed by three recrystallizations from methanol, to give colorless prisms, **3b:** mp 124–126 °C; 0.35 g (94%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.24 (6 H), 1.5–2.6 (10 H), 5.7–6.0 (2 H), 6.9–7.3 (10 H). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66; O, 4.34. Found: C, 88.20; H, 7.68.

Preparation of 3c. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 8 mL of 1,3-cyclooctadiene containing 50 mg of hydroquinone was heated under nitrogen at 100 °C for 72 h. Column chromatography (silica gel, benzene) and recrystallization from methanol gave colorless plates, **5:** mp 144 °C; 0.31 g (84%); IR 5.69 μm ($CHCl_3$); NMR ($CDCl_3$) δ 1.08 (3 H), 1.27 (3 H), 1.3–2.4 (9 H), 3.2 (br d, 1 H), 5.3 (dd, 1 H), 5.4–4.9 (1 H), 6.8–7.2 (10 H). Anal. Calcd for $C_{27}H_{28}O$: C, 88.00; H, 7.66; O, 4.34. Found: C, 87.71, H, 7.81.

Hydrogenation of 3b and 3c. Hydrogenations were carried out in ethyl acetate using 5% Pd/C as a catalyst. Quantitative yields of **3a** were obtained in both cases.

Preparation of 5. A solution of 0.26 g (0.5 mmol) of the dimer of 1 in 9 mL of cyclooctatetraene containing 50 mg of hydroquinone was heated under nitrogen at 40 °C for 2 weeks (similar results were obtained by heating at 65 °C for 3 days). Evaporation of excess tetraene in vacuo followed by preparative TLC (2% ethyl acetate–petroleum ether, three elution) and recrystallization from acetone–methanol gave **5:** mp 168–169 °C; 210 mg (45%); IR 5.69 μm ($CHCl_3$). The mass spectrum of **5** had intense peaks at 468 (parent), 338, and 260 (1) in the high-mass region. Anal. Calcd for $C_{35}H_{32}O$: C, 89.70; H, 6.88; O, 3.41. Found: C, 89.69; H, 7.10.

The same adduct was made from the 76 °C dimer[6] of cyclooctatetraene by heating 2.5-mmol amounts of **1** (as the dimer) and the 76 °C dimer in 10 mL of acetone under nitrogen at 61 °C for 18 h. Evaporation of solvent and recrystallization from acetone–methanol gave **5:** mp 168–169 °C; 0.92 g (79%).

Cope Rearrangement of 5. A solution of 100 mg of **5** was heated in acetone under nitrogen for 2 h at 120 °C. Evaporation of solvent and recrystallization from acetone–methanol gave **6:** mp 233–234 °C; 85 mg (85%); IR 5.99 μm ($CHCl_3$). The mass spectrum had intense peaks at *m/e* 468 (parent), 338, and 260 (1), in the high-mass region. Anal. Calcd for $C_{35}H_{32}O$: C, 89.70; H, 6.88; O, 3.41. Found: C, 89.70; H, 7.01.

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Registry No.—1, 26307-17-5; 1 dimer, 38883-84-0; **2a,** 931-88-4; **2b,** 111-78-4; **2c,** 1700-10-3; **3a,** 63904-18-7; **3b,** 63904-19-8; **3c,** 63904-20-1; **5** isomer I, 63866-53-5; **5** isomer II, 63866-54-6; **6** isomer I, 63866-55-7; **6** isomer II, 63866-56-8; cyclooctatetraene, 629-20-9; cyclooctatetraene dimer, 14375-95-2.

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An Alternate Synthesis of 5,6-Dihydroxy-2,3-dihydroindole-2-carboxylates (Cyclodopa)

George Büchi* and Tadao Kamikawa

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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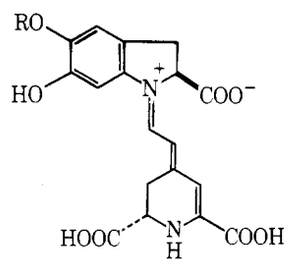
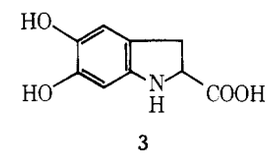
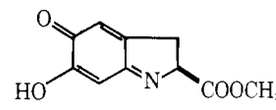
For the total synthesis of betanin (1),[1] the red-violet pigment of the beet (*Beta vulgaris*), and the corresponding aglycone betanidin (2)[1,2] an efficient synthesis of cyclodopa (3) (5,6-dihydroxy-2,3-dihydroindole-2-carboxylic acid) was required. The methyl ester of this acid was prepared previously by oxidation of dopa methyl ester (7) with potassium ferricyanide followed by reduction of the intermediate methyl 6-hydroxy-5-oxo-2,3-dihydroindole-2-carboxylate (dopachrome methyl ester) (4) with sodium dithionite.[3] This method serves poorly on a preparative scale because acceptable yields of product are obtained only when the oxidations are performed in less than 0.05 M solutions. The irreversible isomerization of dopachrome methyl ester (4) to methyl 5,6-dihydroxyindole-2-carboxylate in the basic oxidation medium creates further problems. In later work that led to a preparatively useful cyclodopa synthesis, the isomerization of dopachrome ester was avoided by performing the oxidation on dopa (6) itself rather than its esters.[4] A further improvement resulted when it was noticed that solutions of cyclodopa (3) could be stabilized by complexation with borate.[4]



1, R = glucose
2, R = H



3



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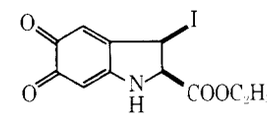
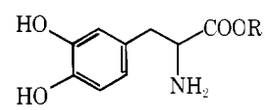
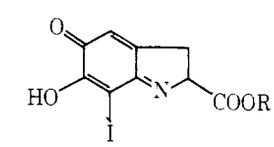


5



6, R = H
7, R = CH_3
8, R = C_2H_5



9, R = CH_3
10, R = C_2H_5

While the latter study was in progress we reinvestigated some older work of Bu'Lock and Harley-Mason.[5] They found that oxidation of dopa ethyl ester hydrochloride (8) with po-