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Click Chemistry with Cyclopentadiene

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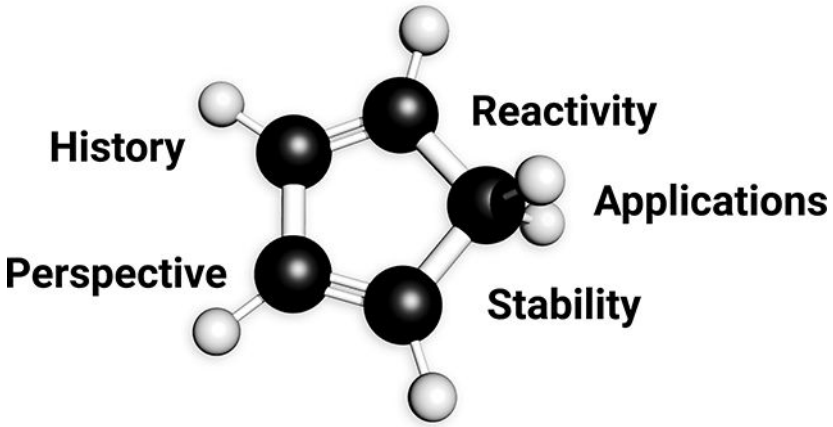
Abstract

Cyclopentadiene is one of the most reactive dienes in normal electron-demand Diels–Alder reactions. The high reactivities and yields of cyclopentadiene cycloadditions make them ideal as click reactions. In this review, we discuss the history of the cyclopentadiene cycloaddition as well as applications of cyclopentadiene click reactions. Our emphasis is on experimental and theoretical studies on the reactivity and stability of cyclopentadiene and cyclopentadiene derivatives.

Graphical Abstract



1. Introduction

In 2001, Sharpless and co-workers introduced the term “click reaction” to describe chemical transformations that are high-yielding under mild conditions.[1] The Diels–Alder reaction is a chemical transformation between a conjugated diene and dienophile that results in the formation of a 6-membered cycloadduct. The most reactive Diels–Alder dienes are 5- or 6-

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ASSOCIATED CONTENT

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membered cyclic dienes such as 1,2,4,5-tetrazine, *ortho*-quinone, thiophene dioxide, cyclopentadienone, and cyclopentadiene. Without electron-withdrawing heteroatoms, cyclopentadiene differs from the other Diels–Alder dienes used as click reagents in being able to react rapidly via normal electron-demand Diels–Alder reaction mechanism with electron-deficient dienophiles.

Despite cyclopentadiene being among the first and most widely used Diels–Alder dienes, the cyclopentadiene cycloaddition has yet to be the subject of a review. Here, we cover the history as well as modern applications of cyclopentadiene click reactions with emphasis on experimental and theoretical studies on the reactivities and stabilities of cyclopentadiene and cyclopentadiene derivatives.

2. History of Cyclopentadiene

In 1886, Roscoe observed a $C_{10}H_{12}$ hydrocarbon from the pyrolysis of phenol and correctly surmised that this compound formed from the spontaneous dimerization of a C_5H_6 hydrocarbon.[2] The structures of these two hydrocarbons were elucidated as cyclopentadiene and its dimer, dicyclopentadiene, by Etard and Lambert in 1891 and by Kraemer and Spilker in 1896.[3,4]

Albrecht reported the formation of 1:1 and 2:1 adducts[3,4] from the reaction of cyclopentadiene with 1,4-benzoquinone in 1906, but the structures of these adducts were incorrectly characterized as if the cyclopentadiene underwent a Michael addition to the α,β-unsaturated ketone, as shown in Scheme 1.[5] Diels and Alder correctly characterized the products and recognized the significance of the chemical transformation for the synthesis of 6-membered rings in their seminal 1928 publication (Scheme 2).[6] The *endo* stereochemistry of the Diels–Alder reaction was established by Alder and Stein in 1937.[7] Alder's observation that the diene and dienophile orient to maximize the accumulation of double bonds became known as the Alder *endo* rule. For this work Diels and Alder would go on to win the 1950 Nobel prize in chemistry, and the Diels–Alder reaction would go on to become one of the most widely used reactions in synthetic organic chemistry.[8]

3. Diels–Alder Reactivity and π-Facial Selectivity of Cyclopentadiene Cycloadditions

3.1. Diels–Alder Reactivity

Cyclopentadiene is unique in having high reactivity as a Diels–Alder diene without the presence of any activating electron-withdrawing or electron-donating groups.[9] The rate constants for the Diels–Alder reactions of cyclopentadiene, 1,3-cyclohexadiene, 1,3-cycloheptadiene, and butadiene with tetracyanoethylene (TCNE) at 20 °C are listed in Table 1.[10] Cyclopentadiene reacts 2,600-fold faster than 1,3-cyclohexadiene, 820,000-fold faster than 1,3-cycloheptadiene, and 2,100,000-fold faster than the acyclic diene, butadiene. The highest-occupied molecular orbital (HOMO) energies measured from the experimental ionization potentials of the dienes shown in Table 1 do not correlate with their Diels–Alder reactivities.[11–14] Saur, Susstman, and others related the Diels–Alder reactivity trend of cisoid fused dienes to the distance between the C1 and C4 diene carbons, wherein shorter

C1–C4 distances correlated with a faster cycloaddition.[10,15,16] Levandowski and Houk expanded upon this analysis by showing that a shorter C1–C4 distance increases the Diels–Alder reactivity by decreasing the out-of-plane distortion required of the conjugated diene double bonds to reach the transition state geometry.[17]

Sauer and co-workers studied the Diels–Alder reactivity of cyclopentadiene toward the acyclic and cyclic electron-deficient dienophiles shown in Scheme 3.[18] Cyclic electron-deficient dienophiles, such as *N*-phenyl maleimide, maleic anhydride, and *p*-benzoquinone, react significantly faster with cyclopentadiene than do acyclic electron-deficient dienophiles. Consequently, maleimides, maleic anhydride, and *p*-benzoquinones are choice reaction partners of cyclopentadiene in click chemistry applications.

Solvent can have a significant influence on the rate of Diels–Alder reactions.[19–23] The rate of the Diels–Alder reaction of methyl vinyl ketone with cyclopentadiene was measured in various solvents by Breslow and co-workers (Scheme 4).[24,25] The reaction in water is nearly 10^3-fold faster than in isooctane. QM/MM calculations by the Jorgenson group[26–29] and others[30] suggested that the rate-enhancement in water is the result of hydrophobic aggregation and enhanced hydrogen bonding in the transition state caused by the increased polarization of the carbonyl moiety in the transition state.

The ambiphilicity of cyclopentadiene allows cyclopentadiene to partake in both normal and inverse electron-demand Diels–Alder reactions, depending on the electronic nature of the dienophile.[31] The Diels–Alder reaction of 1,2,3,4-tetrachlorocyclopentadiene ethylene ketal (TCK) with styrene at 80 °C in dioxane occurs with a rate constant of 3.3×10^{-3} $M^{-1}s^{-1}$. The electronic nature of the styrene can be tuned through substitution at the *para* position. As shown in Scheme 5, both electron-withdrawing and electron-donating substituents increase the reactivity of styrene toward TCK. This increase is because of a change in reaction mechanism from a normal electron-demand Diels–Alder reaction when there is an electron-withdrawing group to an inverse electron-demand Diels–Alder reaction when there is an electron-donating group at the *para* position of styrene. The ambiphilic properties of the cyclopentadiene scaffold allow cyclopentadiene to react with both electron-rich and electron-deficient dienophiles.

3.2. Hyperconjugative Aromaticity and Antiaromaticity

In 1939, Mulliken observed that cyclopentadiene and 1,3-cyclohexadiene have considerably longer ultraviolet absorption wavelengths than do open-chain dienes.[32] The redshift results from the hyperconjugation of the diene π-electrons with the saturated CH_2 groups. The heats of hydrogenation for cyclopentadiene, 1,3-cyclohexadiene, and butadiene had previously been reported as −50.9, −55.4, and −57.1 kcal/mol, respectively.[33] From these values, Mulliken estimated the strengths of the hyperconjugative interactions to be 6.2 kcal/mol in cyclopentadiene and 1.7 kcal/mol in 1,3-cyclohexadiene. The increased strength of the hyperconjugative interactions in cyclopentadiene led Mulliken to consider if cyclopentadiene is aromatic. Sixty years later, computational studies of cyclopentadiene and 5,5-disubstituted cyclopentadienes by the Schleyer group provided energetic, geometric, and magnetic evidence of aromatic electron delocalization in cyclopentadiene and 5,5-disilylcyclopentadiene, and antiaromatic electron delocalization in 5,5-

difluorocyclopentadiene.[34,35] Schleyer introduced the terms “hyperconjugative aromaticity” and “hyperconjugative antiaromaticity” to describe, respectively, the aromatic (4N + 2) and antiaromaticity (4N) π-electron delocalization that arise from hyperconjugative interactions of the saturated linkages with the formal π-electrons of cyclopentadiene.

The Diels–Alder reactivity of cyclopentadienes can be tuned through the hyperconjugative aromaticity or antiaromaticity invoked by the substituents at the 5-position.[36,37] Frontier molecular orbital theory would predict that 1,2,3,4,5,5,-hexachlorocyclopentadiene with a semiempirically derived HOMO energy of −9.0 eV would react faster than 1,2,3,4-tetrachloro-5,5-difluorocyclopentadiene with a HOMO energy of −9.2 eV in normal electron-demand Diels–Alder reactions.[31] Despite the less favorable frontier molecular orbital interactions, the Diels–Alder reaction of 1,2,3,4-tetrachloro-5,5-difluorocyclopentadiene occurs ~100-fold faster than does the Diels–Alder reaction of 1,2,3,4,5,5,-hexachlorocyclopentadiene when the electron-deficient *p*-nitro-*N*-phenyl maleic anhydride is the dienophile (Scheme 6). Computations by the Houk group predicted that the hyperconjugative antiaromatic 5-fluorocyclopentadiene will react 4,600-fold faster than cyclopentadiene, whereas the hyperconjugative aromatic 5-silylcyclopentadiene will react 160-fold slower than cyclopentadiene with the electron-deficient dienophile, maleic anhydride.[36]

3.3. π-Facial Selectivity of 5-Substituted Cyclopentadienes

Facially asymmetric cyclopentadienes can undergo stereoselective Diels–Alder reactions. During their seminal studies of 7-norbornyl cations, Winstein, Woodward, and co-workers reported the surprising contrasteric (*syn*) Diels−Alder reaction of 5-acetoxycyclopentadiene with ethylene shown in Scheme 7.[38] Studies on the π-facial selectivity of 5-substituted cyclopentadienes by the Burnell and Fallis groups showed that the π-facial selectivity of the cycloaddition is controlled by the substituent at the 5-position.[39–41] For example, with dimethyl acetylenedicarboxylate (DMAD) as the dienophile, 5-fluorocyclopentadiene[42] provides exclusively the *syn* cycloadduct, 5-trimethylsilylcyclopentadiene[43] provides exclusively the *anti* cycloadduct, and 5-chlorocyclopentadiene[44] provides a mixture of the *syn* and *anti* cyclic adducts (Scheme 8).

The π-facial selectivity in 5-substituted cyclopentadienes arises from hyperconjugative interactions of the cyclopentadiene π-system with the σ-bond of the C5 substituent.[37] When the C5 substituent is a σ-acceptor, the cyclopentadiene puckers into an envelope geometry that minimizes the overlap of the diene π-system with the C5–X antibonding σ* orbital (Figure 1). This puckering minimizes the destabilizing effects of the negative hyperconjugation that lead to hyperconjugative antiaromaticity and predistorts the cyclopentadiene into the envelope-like geometry of the *syn* transition state. Conversely, when the C5–X substituent is a σ-donor, the cyclopentadiene puckers in the opposite direction to maximize the overlap of the cyclopentadiene π-system with the C5–X σ-bond. This puckering maximizes the stabilizing effects of hyperconjugative aromaticity and favors the *anti* cycloaddition because the ground state geometry is distorted to resemble the envelope-like transition-state geometry of the *anti* cycloaddition.

The synthesis of neofinaconitine by Gin and co-workers is an elegant application of π-facial selectivity.[45] The key step in the synthesis is the cycloaddition between the 5-methoxycyclopentadiene and cyclopropene shown in Scheme 9 that establishes the stereochemistry of the C14 methoxy group in the neofinaconitine product. The products from the *syn* cycloaddition were isolated as a 1:1.6 mixture of regioisomers in 85% yield, whereas the products from the *anti* cycloaddition were isolated as a 1:1.5 mixture of regioisomers in 15% yield. Overall, the desired regioisomer from the *syn* cycloaddition was isolated with a 54% yield.

4. Stability of Cyclopentadiene

4.1. Dimerization

Cyclopentadiene is a liquid with a neat concentration of 11.9 M at 25 °C. As both a diene and a dienophile, cyclopentadiene can react with itself to form dicyclopentadiene. The rate constant for the dimerization of cyclopentadiene to *endo*-dicyclopentadiene at 25 °C has been reported to be 8.3×10^{-7} $M^{-1}s^{-1}$.[46,47] Accordingly, the half-life of neat cyclopentadiene is ~28 h at 25 °C. The dimerization of cyclopentadiene is reversible; at 170 °C, the cyclopentadiene monomer can be distilled from dicyclopentadiene.[48–50] *Exo*-dicyclopentadiene is 0.7 kcal/mol more stable than *endo*-dicyclopentadiene, but at temperatures between 40 and 120 °C, the formation of *exo*-dicyclopentadiene occurs two to three orders of magnitude more slowly than does the formation of *endo*-dicyclopentadiene.[49,50] *Exo*-dicyclopentadiene and other cyclopentadiene oligomers, from the trimer to the hexamer of cyclopentadiene, are observed only when cyclopentadiene is heated at higher temperatures over long periods of time.[51–54]

Substitution affects the rate of cyclopentadiene dimerization, as shown in Scheme 10. Dialkyl substitution at the 5-positions of cyclopentadiene significantly diminishes dimerization. 5,5-Dimethylcyclopentadiene does not dimerize, even at temperatures as high as 200 °C.[55,56] Spiro[2.4]hepta-4,6-diene does not dimerize at room temperature and is commercially available as a monomer. Formation of the spiro[2.4]hepta-4,6-diene dimer requires 2 days of prolonged heating between 70 and 80 °C.[57] The computed activation energy for the dimerization of spiro[2.4]hepta-4,6-diene is 4.5 kcal/mol higher than that of cyclopentadiene.[58] Monoalkylation has little effect on the rate of cyclopentadiene dimerization. An isomeric mixture of 1-, 2-, and 5-methylcyclopentadiene dimerizes at a rate comparable to cyclopentadiene.[49] At 120 °C, the rate constants for the dimerization of cyclopentadiene and methyl cyclopentadiene are 1.13×10^{-3} $M^{-1}s^{-1}$ and 1.08×10^{-3} $M^{-1}s^{-1}$, respectively. Methyl and ethylene cyclopentadiene ketals dimerize 790- and 497,000-fold faster, respectively, than does cyclopentadiene.[59] The destabilizing effects of hyperconjugative antiaromaticity promote dimerization.

Introducing substituents across the cyclopentadiene double bonds provides another means to slow the dimerization. 1,2,3,4-Tetrachlorocyclopentadiene dimerizes 3-fold slower than does cyclopentadiene.[31] 1,2,3,4-Tetraalkyl-substituted cyclopentadienes, such as 1,2,3,4-tetramethyl and 1,2,3,4,5-pentamethylcyclopentadiene (Cp*), do not dimerize and are commercially available as monomers. Collective substitution across the diene double bonds and at the 5-positions is an effective way to slow dimerization. For example, the

cyclopentadiene ethylene ketal dimerizes 497,000-fold faster than does cyclopentadiene, but upon chlorination it dimerizes 25-fold slower.[31,59] Methoxy groups at the 5-positions of cyclopentadiene accelerate the dimerization by 790-fold, however the tetrachloro derivative, 1,2,3,4-tetrachloro-5,5-dimethoxy cyclopentadiene, does not dimerize.[31,59]

Though often viewed as an undesirable side reaction, the dimerization of cyclopentadiene has found applications in synthetic organic chemistry. As a graduate student, Schleyer developed a synthesis of adamantane using the cyclopentadiene dimer, dicyclopentadiene, as the starting material (Scheme 11).[60] The dicyclopentadiene was hydrogenated with platinum oxide then transformed into adamantane using aluminum chloride as a Lewis acid. Olah and co-workers improved the yield of the second step to 98% through the use of sonication in the presence of the superacid, $CF_3SO_3H{\cdot}SbF_5$.[61] This simple two-step preparation provides an affordable route to adamantane that is still used today.

Cubane was thought to be too strained to exist until the ring system was synthesized and shown to be stable by Eaton and Cole in 1964.[62–64] The key synthetic step involved the dimerization of 2-bromocyclopentadienone. Chapman simplified the synthesis by switching the diene from 2-bromocyclopentadienone to 2-bromocyclopentadiene ethylene ketal, as shown in Scheme 12.[65]

Thiele's ester was first reported in 1901 from the acid-catalyzed esterification of the dicyclopentadiene dicarboxylic acid (Thiele's acid) prepared from the treatment of cyclopentadiene with potassium and carbon dioxide.[66] An "ester first" synthesis shown in Scheme 13 was later developed as a direct route to Thiele's ester from the dimerization of the esterified cyclopentadiene.[67] Despite the 72 theoretically possible products that could arise from the dimerization of the esterified cyclopentadiene, Thiele's ester is isolated as the major product in 40% yield along with 1:1 mixture of regioisomers in 22% yield.[68] The origin of the product distribution has been of great interest to experimental and theoretical chemists. Explanations for the selectivity enlisting frontier molecular orbital theory,[69,70] bent bond theory,[71,72] and paralocalization energies[73] have been put forth. Photochemical intramolecular [2 + 2] cycloaddition of Thiele's ester and other *endo*-dicyclopentadienes allows access to functionalized 1,3-bishomocubane polycyclic cages.[74–78]

Absinthin is a bitter-tasting naturally occurring triterpene lactone that is isolated from *Artemisia absinthium* (wormwood)[79] and is a key component of a renowned spirit, absinthe.[80] The biosynthesis of absinthin is postulated to occur through the dimerization of artabsin, as shown in Scheme 14. A similar dimerization has been shown to occur spontaneously and in good yield over the course of ten days.[81] It is not yet known if an enzyme catalyzes the biosynthesis of absinthin.

4.2. 1,5-Sigmatropic Shifts

In 1939, Drake and Adams reported the unexpected formation of 1,4-diphenylcyclopentadiene from the decarboxylation of 2,4-diphenylcyclopentadiene-1-carboxylate, as shown in Scheme 15.[82] The double bonds of the expected 1,3-diphenylcyclopentadiene product migrated to form 1,4-diphenylcyclopentadiene with a

continuous chain of conjugated double-bond linkages. Double-bond migration became a general characteristic of substituted cyclopentadienes as other reports followed.[83–87]

Csicsery showed that methylcyclopentadiene exists as a mixture of the 5-methyl, 1-methyl, and 2-methyl isomers in a 3:45:52 ratio at thermodynamic equilibrium, as shown in Scheme 16.[88] Mironov and Elizarova elucidated the mechanism of the isomerization as a 1,5-hydrogen shift through a series of communications in 1963.[89,90] The isomerization occurs via a rapid 1,5-hydrogen shift of 5-methylcyclopentadiene to 1-methylcyclopentadiene that is complete within 3–4 h, followed by a slower 1,5-hydrogen shift of 1-methylcyclopentadiene to 2-methylcyclopentadiene with equilibration occurring over 2–3 days. Kinetic studies by McLean showed that the rearrangement of 5-methylcyclopentadiene to 1-methylcyclopentadiene occurs with a rate constant of 1.8×10^{-4} s^{-1} at 25 °C.[91]

1,5-Sigmatropic hydrogen migrations occur more readily across the cyclopentadiene scaffold than across other cyclic and acyclic diene scaffolds. In 2-methly-1,3-cycloheptadiene, the 1,5-sigmatropic hydrogen migration proceeds with a rate constant of 3.27×10^{-4} s^{-1} at 160 °C.[92] The rate constant for the 1,5-sigmatropic hydrogen shift in the acyclic *cis*-1,1-dideutero-1,3-pentadiene at 185 °C is 1.38×10^{-6} s.[93] Alabugin and co-workers reported the calculated activation energies at the B3LYP/6–31G(d,p) level of theory for the 1,5-hydrogen migration in cyclopentadiene, 1,3-cycloheptadiene, and *cis*-1,3-pentadiene to be 27.0, 33.2, and 36.6 kcal/mol, respectively.[94]

1,5-Sigmatropic shifts are pericyclic reactions that occur through transition states with aromatic electron delocalization.[95] The transition-state structures for the 1,5-sigmatropic hydrogen migration in *cis*-1,3-pentadiene and cyclopentadiene calculated with a 3–21G split valence basis set are shown in Scheme 17.[96] The transition state for the 1,5-hydrogen migration in cyclopentadiene with nearly equivalent C–C bond lengths is geometrically more aromatic than in *cis*-1,3-pentadiene.[96,97] The distances across the migrating termini in *cis*-1,3-pentadiene and cyclopentadiene are 2.6 and 1.5 Å, respectively. The closer termini distance facilitates the transfer of the migrating hydrogen atoms by permitting better overlap between the orbitals of the migrating hydrogen and the carbon atoms.[98]

Mulliken charges show the migrating hydrogen atom bears a partial positive charge of 0.22 and 0.31 in the transition state of *cis*-1,3-pentadiene and cyclopentadiene, respectively.[99] Alabugin and co-workers reported natural bond orbital (NBO) charges on the hydrogen atom in the ground and transition state of *cis*-1,3-pentadiene and cyclopentadiene.[94] The partial charge on the hydrogen atom is 0.25 in both the *cis*-1,3-pentadiene ground and the transition state. In cyclopentadiene, the partial charge on the hydrogen atom increases from 0.27 in the ground state to 0.37 in the transition state. In the transition state, the cyclopentadiene carbon skeleton resembles that of the aromatic cyclopentadienyl anion and is better able to accommodate the charge transfer that results from the migrating “protonic” hydrogen atom. The increased contribution of the cyclopentadienyl anion structure is also reflected in the NICS(1) values of the transition state.[94] The cyclopentadiene transition state is more aromatic, having a NICS(1) value of −9.6 compared to −8.8 in the *cis*-1,3-pentadiene transition state. The rapid 1,5-sigmatropic hydrogen migration in cyclopentadiene arises from a combination of the conformational rigidity of the five-membered ring that enforces

the favorable proximity of the reacting termini and the amplified aromatic cyclopentadienyl anion character of the transition state.

The addition of alkyl groups across the cyclopentadiene double bonds appreciably lowers the rate of the 1,5-hydrogen shift, as shown in Scheme 18. Methyl substitution at the 1-position of a 5-methylcyclopentadiene slows the 1,5-hydrogen shift by an order of magnitude, from a rate constant of 6.2×10^{-4} s^{-1} in 5-methylcyclopentadiene to 5.5×10^{-5} s^{-1} in 1,5-dimethylcyclopentadiene at 30 °C.[100] The 1,5-hydride shift of a Cp* containing a deuterated methyl group at 30 °C is 3 orders of magnitude slower, having a rate constant of 2.4×10^{-7} s^{-1}.[101]

Electropositive silyl groups migrate faster than does hydrogen in 1,5-sigmatropic shifts. In 1970, Ashe showed that the trimethylsilyl group in 5-trimethylsilylcyclopentadiene migrates a million-fold faster than does the hydrogen atom.[102] A year later, Ustynyuk and co-workers reported a rate constant of 50 s^{-1} for the 1,5-sigmatropic shift of the trimethylsilyl group in 5-trimethylsilylcyclopentadiene at 25 °C.[103] 1,5-Alkyl migrations are significantly slower than 1,5-hydrogen migrations. 5,5-Dimethylcyclopentadiene isomerizes at temperatures >200 °C.[56] At 225 °C, the 1,5-methyl shift in 1,2,3,4,5,5-hexamethylcyclopentadiene occurs with a rate constant of 5.1×10^{-7} s^{-1}.[104] This alkyl shift is over a million-fold slower than the 1,5-hydride shift in 1,2,3,4,5-pentamethylcyclopentadiene, which occurs with a rate constant of 1.8 s^{-1} at a slightly lower temperature of 200 °C.[101]

Fowler and co-workers calculated the migratory aptitudes of different functionalities across cyclopentadiene.[105] The computed activation enthalpies for the migration of a trimethylsilyl group, hydrogen atom, methyl group, and fluorine atom are 13.5, 25.8, 42.6, and 48.0 kcal/mol, respectively. The reactivity parallels the charge of the migratory group in the transition state, which were calculated to be 0.504, 0.387, 0.170, and −0.379 for the trimethylsilyl group, hydrogen atom, methyl group, and fluorine atom, respectively. The **π** current–density maps of cyclopentadiene and 5-fluorocyclopentadiene supported that the 1,5-hydrogen migration proceeds through a diatropic (aromatic) transition state and the 1,5-fluoro migration proceeds through a paratropic (antiaromatic) transition state. The migratory aptitude is related to the ability of the group to draw positive charge. Groups that migrate with a partial positive charge rapidly migrate through an aromatic transition state that resembles the cyclopentadienyl anion, whereas groups that migrate with a partial negative charge do so slowly through a high-energy antiaromatic transition state that resembles the cyclopentadienyl cation.

In 5-formyl-1,2,3,4,5-pentamethylcyclopenta-1,3-diene, the formyl group migrates with a rate constant of 90 s^{-1} at 25 °C.[106] This rapid migration is a result of secondary orbital interactions. The mixing of the cyclopentadiene HOMO with the low lying lowest-unoccupied molecular orbital (LUMO) of the migrating formyl group to stabilize the transition state is depicted in Scheme 19.[107]

The tricyclo[$4.4.0^{1,6}.0^{2,8}$]decane and tricyclo[$5.4.0^{1,7}.0^{2,9}$]undecane scaffolds present in bridged sesquiterpene natural products such as sativene,[108] longifolene,[109] and sinularene[110] were initially challenging to access synthetically. Early attempts to synthesize these

scaffolds through intramolecular Diels–Alder reactions were unsuccessful because 1,5-hydrogen shifts preceded the intramolecular cycloaddition. From these failed attempts emerged imaginative solutions.

In 1963, Breiger attempted the synthesis of longifolene through an intramolecular cycloaddition of a cyclopentadiene tethered to a dienophile at the 5-position.[111] It was, however, the 1-substituted cyclopentadiene isomer that reacted to form the undesired product (Scheme 20). In an effort to shift the equilibrium toward the desired 5-isomer, Glass synthesized a 5-tethered-1,2,3,4-tetrachlorocyclopentadiene.[112] The chlorinated cyclopentadiene equilibrated to a mixture containing 30% of the 5-isomer and 70% of the 1- and 2-isomers, but the resulting intramolecular cycloadduct was still that of the 1-substituted cyclopentadiene isomer. It has since been established that the selectivity of the intramolecular cycloadditions involving isomeric mixtures of cyclopentadienes is dependent on the length of the tether between the diene and dienophile.[113]

Stille and Grubbs systematically studied the effect of the tether length on the selectivity of cyclopentadiene compounds tethered to α,β-unsaturated ester dienophiles (Scheme 21).[113] They observed that two-carbon tethers exclusively form the cycloadduct of the 5-substituted cyclopentadiene with a 53% yield after 18 h of refluxing in toluene. A three-carbon tether forms the 1-substituted cyclopentadiene cycloadduct as the major product in 68% yield and the 2-substituted cyclopentadiene cycloadduct as the minor product in 6% yield after 2 h of refluxing in benzene. After refluxing in benzene for 4 h, the four-carbon tether forms the *endo* and *exo* cycloadducts from the 1-substituted cyclopentadiene cycloaddition in 40% and 17% yields, respectively. The intrinsic preference of the 1-isomer to undergo the intramolecular cycloaddition in systems where the length of the tether is three or four carbon atoms makes the synthesis of the tricyclo[$4.4.0^{1,6}.0^{2,8}$]decane and tricyclo[$5.4.0^{1,7}.0^{2,9}$]undecane scaffolds via an intramolecular Diels–Alder reaction a distinct challenge.

Instead of trying to prevent the 1,5-hydrogen shift, Fallis considered ways to favor the intramolecular cycloaddition of the 5-substituted cyclopentadiene isomer over the 1- and 2-substituted cyclopentadiene isomers.[114] Molecular mechanics calculations showed that encompassing the dienophile in a 6-membered ring increased the strain of the 1- and 2-substituted cyclopentadiene cycloadducts making their formation unfavorable relative to the 5-substituted cyclopentadiene cycloadduct. By encompassing the dienophile in a 6-membered ring as shown in Scheme 22, Fallis and co-workers were able to establish the tricyclic core of (+)-longifolene via intramolecular cyclopentadiene 5,6-dihydro-2*H*-pyran-2-one Diels–Alder reaction with 97% yield to complete the total synthesis of (+)-longifolene.

An alternative synthetic approach developed by Fallis and co-workers involved blocking the 1,5-hydrogen shift by linking the tether to the cyclopropane moiety in spiro[2.4]heptadiene.[115,116] Following the intramolecular cycloaddition, the selective cleavage of the cyclopropane ring shown in Scheme 23 allows access to the tricyclo[$4.4.0^{1,6}.0^{2,8}$]decane or tricyclo[$5.4.0^{1,7}.0^{2,9}$]undecane scaffolds.[117] This approach enabled the synthesis of sinularene in 14 steps and 9% overall yield starting from a spiro[2.4]heptadiene.[118]

The Diels–Alder reaction of methylcyclopentadiene with methyl acrylate results in the formation of a complex mixture of *endo* and *exo* cycloadducts from the Diels–Alder reactions of the 1- and 2-substituted cyclopentadiene isomers after reacting for 16 h at 18 °C in benzene, as shown in Scheme 24.[119] Corey keenly realized that Lewis acids accelerate the Diels–Alder reaction without affecting the rate of the 1,5-sigmatropic shift. The $AlCl_3$-catalyzed Diels–Alder reaction of 5-(benzyloxymethyl)cyclopentadiene with an acrylate ester at −55 °C shown in Scheme 25 results in the formation of only the *endo* and *exo* cycloadducts of the 5-substituted cyclopentadiene isomer in 89% and 7% yield, respectively.[120] The use of a Lewis acid to obtain Diels–Alder adducts of 5-substituted cyclopentadienes was crucial in Corey's landmark synthesis of prostaglandin $F_{2\alpha}$ in 1969.[121]

Tsuji and co-workers observed that Diels–Alder reactions of 2-alkoxycyclopentadienes do not form a mixture of isomeric cycloadducts.[122–124] By incorporating an alkoxy functional group at the 2-position, Tsuji and co-workers were able to trap the cycloadducts of 5-substituted cyclopentadienes via intramolecular cycloaddition with a doubly activated dienophile to form the tricyclo[5.2.1.$0^{1,5}$]decane scaffold, as shown in Scheme 26.[125] Gleason showed that incorporating a silyl ether at the 2-position of a cyclopentadiene increased the half-life of a 5-substituted cyclopentadiene from ~1 h at 20 °C to ~37 h at 23 °C (Scheme 27).[126] Intramolecular Diels–Alder reactions of 2-silyloxycyclopentadienes have since been applied in the synthesis of the antifungal agent Sordarin.[127,128]

4.3. *In Situ* Sources of Cyclopentadiene

Bench-stable sources of cyclopentadienes eliminate the need to distill cyclopentadiene from the dimer prior to use. The Richert group developed a crystalline ready-to-use form of cyclopentadiene.[129] They showed that cyclopentadiene can be encapsulated as a guest molecule in the crystalline matrix of 1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane (TDA), which is shown in Scheme 28. The crystallization occurs in a stoichiometric ratio of 5 cyclopentadienes for every 4 TDAs. After storing for 4 weeks at 22 °C, more than 85% of the cyclopentadiene remained in monomeric form. Dissolving the crystals in organic solvents results in the release of the encapsulated cyclopentadienes. The Diels–Alder reactions of cyclopentadiene generated from the crystalline form occurred in yields similar to that from freshly distilled dicyclopentadiene.

Norbornadiene can function as a masked cyclopentadiene that is released upon reacting with a 1,2,4,5-tetrazine. This unmasking was first demonstrated by Sauer and co-workers in 1966 when they generated cyclopentadiene as a side product from the Diels–Alder reaction of norbornadiene with 3,6-diphenyl 1,2,4,5-tetrazine *en route* to the 1,2-diazine (Scheme 29).[130] The approach has since been applied to the synthesis of substituted cyclopentadienes. An example of a substituted cyclopentadiene generated from norbornadiene and its subsequent trapping with dimethyl acetylenedicarboxylate is shown in Scheme 30.[131,132] If, however, the substituted cyclopentadiene is not trapped with a highly reactive dienophile it will isomerize and dimerize as expected.

5. Polymer Chemistry with Cyclopentadiene

5.1. Synthesis of Cyclopentadiene-Functionalized Polymers

Click chemistry, with its high yields, rapidity, and facility of product-purification, has enriched the field of polymer synthesis. Click reactions involving cyclopentadiene are attractive to polymer chemists because the cyclopentadiene scaffold can be introduced into polymer systems readily via multiple methods. Kennedy and Castner used dimethylcyclopentadienylaluminum as an initiator for the cationic polymerization of *tert*-butylchloride toward isobutylene monomers, as shown in Scheme 31.[133,134] Termination of the isobutylene polymerization occurred by the reaction of the isobutylene cation with the cyclopentadienyl anion, providing polyisobutene polymers containing a terminal cyclopentadiene unit. Termination of 72% of the propagating polymer chains occurred via cyclopentadienylation. The remaining chains were terminated via methylation. When the polymerization was performed at −40 °C, the number of polymer chains terminated by cyclopentadienylation increased to 90%. Heating at 80 °C for 2 h did not result in any dimerization of the terminal cyclopentadiene-terminated polyisobutene polymers. The lack of dimer formation was attributed to the low concentration of cyclopentadiene (0.31% by weight) in the polymer. Whereas the terminal cyclopentadiene polymers were not prone to dimerize, they readily underwent Diels–Alder reactions with maleic anhydride.

Grubbs and co-workers prepared cyclopentadiene-functionalized styrene divinylbenzene copolymers by the two routes shown in Scheme 32.[135,136] Cyclopentadienes can be prepared from the reaction of cyclopentenones with organolithium or Grignard reagents followed by an acid catalyzed dehydration.[137,138] Grubbs and co-workers used this to synthesize a cyclopentadiene-functionalized styrene–divinylbenzene copolymer.[136] Bromination followed by lithium–halogen exchange led to the lithiation of the styrene rings in the copolymer. The reaction of the lithiated styrene rings with cyclopentenone and successive acid-catalyzed dehydration provided the cyclopentadiene-functionalized polymer.

Nucleophilic substitution of alkyl halides or tosylated alcohols with a cyclopentadienyl anion source is the predominant method for the preparation of cyclopentadiene-functionalized polymers.[139] The use of this approach for the synthesis of cyclopentadiene-functionalized styrene divinylbenzene copolymers is apparent in Scheme 32.[135,136] Treatment of the copolymer with chloromethyl ethyl ether led to the chloromethylation of 14% of the styrene rings. The chloromethylated groups then react with sodium cyclopentadienide to provide cyclopentadiene-functionalized styrene divinylbenzene copolymer linked through a methylene group. Nickelocene can be substituted for sodium cyclopentadienide as a milder source of the nucleophilic cyclopentadienyl anion when potentially reactive electrophilic functionalities are present in the polymer.[140,141]

5.2. Synthesis of Homopolymers

Homopolymers are polymers with identical repeating units. In 1961, Stille and Plummer prepared high molecular weight homopolymers from the intermolecular Diels–Alder reaction of biscyclopentadienes linked via alkyl tethers.[142] The biscyclopentadienes 1,6-bis(cyclopentadienyl)hexane, bis(cyclopentadienyl)nonane, and α,α′-bis(cyclopentadienyl)-

p-xylene shown in Scheme 33 were prepared from the reaction of the corresponding dibromo species with 2 equiv of sodium cyclopentadienide. The intermolecular cycloaddition was favored over the intramolecular cycloaddition, resulting in the polymerization of the biscyclopentadiene monomers to form dicyclopentadiene homopolymers under nitrogen gas. Cross-linking trimers from a subsequent Diels–Alder reaction across the strained dicyclopentadiene double bond were observed when the reaction was performed under air. This type of cross-linking has also been observed with dicyclopentadiene diester (Thiele's ester) cycloadducts formed from the polymerization of a biscyclopentadiene linked via 1,4-butanediyl ester tether.[143] The biscyclopentadienes can also copolymerize with highly reactive bis-dienophiles to form homopolymers.[142] The 1:1 copolymerization of biscyclopentadienes with *p*-benzoquinone is shown in Scheme 34.

5.3. Synthesis of Cyclic Polymers

Cyclic polymers can exhibit unique properties compared to their corresponding acyclic analogues.[144] An efficient route to cyclic polymers proceeds through an intramolecular Diels–Alder reaction of a cyclopentadiene tethered to a highly reactive dienophile.[145] Barner-Kowollik and co-workers tethered cyclopentadiene to a protected maleimide dienophile through a low-molecular weight poly(methyl methacrylate) polymer, as shown in Scheme 35. Refluxing in toluene for 6 h resulted in the deprotection of the maleimide dienophile, allowing the linear polymer to then cyclize via an intramolecular Diels–Alder reaction of the cyclopentadiene and maleimide termini to generate a cyclic polymer.

5.4. Synthesis of Diblock Copolymers

Block copolymers consist of two polymers held together through a covalent linkage. The coupling of cyclopentadiene-terminated polymers with dienophile-terminated polymers is an effective method for the preparation of diblock copolymers. The synthesis of a diblock copolymer from the Diels–Alder reaction of a cyclopentadiene-terminated poly(2-ethyl-2-oxazoline) polymer with a maleimide-terminated poly(ethylene glycol) (PEG) polymer is shown in Scheme 36.[146] The reaction results in the formation of a mixture of block copolymers from the reaction of the 1- and 2-isomers of the cyclopentadiene polymer. The Hawker and Read de Alaniz groups were able to generate pure diblock copolymers from cyclopentadiene maleimide Diels–Alder reactions in which the desired cyclopentadiene polymer was released from the inverse electron-demand Diels–Alder reaction of a norbornadiene with tetrazine.[147,148] This strategy, which is depicted in Scheme 37, takes advantage of the orthogonality of the tetrazine–norbornadiene and cyclopentadiene–maleimide cycloadditions.

The Read de Alaniz group demonstrated the reversible formation of diblock copolymers through the hetero-Diels–Alder reaction of a cyclopentadiene-terminated polystyrene polymer with a nitroso-terminated PEG (Scheme 38).[149] The nitroso group can be generated *in situ* from the copper-catalyzed oxidation of a hydroxyamino group or the retro-Diels–Alder reaction of a 9,10-dimethyl anthracene adduct. The homopolymers were regenerated from the diblock copolymers upon heating. At 95 °C, the nitroso-functionalized PEG was liberated through the retro-Diels–Alder reaction and trapped with benzyl amine. Retro-Diels–Alder reactions of the cycloadducts from peralkylcyclopentadiene and nitroso–

carbonyl species have been studied by Yakelis and the Boydston group as thermal triggers for the self-immolation of block copolymers.[150]

Thiocarbonyl compounds have been described as “superdienophiles” because of their rapid reactivity as dienophiles in Diels–Alder reactions.[151] The Diels–Alder reaction of thiofluorenone with cyclopentadiene occurs rapidly with a rate constant of 5.1 $M^{-1}s^{-1}$ in methylene chloride at 20 °C. Barner-Kowollik and co-workers applied the hetero-Diels–Alder reaction of dithioester species with cyclopentadiene to polymer chemistry for the rapid synthesis of diblock copolmyers.[152,153] Scheme 39 shows the hetero-Diels–Alder reaction of a cyclopentadiene-functionalized PEG polymer reacting with the diethoxy phosphoryl dithioester-functionalized polymer to form a diblock copolymer under aqueous conditions after 15 min. With the open-chain diene, *trans*,*trans*-2,4-hexadien-1-ol, the reaction occurred significantly slower with a required reaction time of 4 h for the quantitative formation of the block copolymer. Cycloadducts from the Diels–Alder reactions of open-chain dienes are less strained and thus more stable than cyclopentadiene cycloadducts.[154] The formation of the cyclopentadiene diethoxy phosphoryl dithioester cycloadduct is reversible at temperatures above 90 °C.[155,156] Cycloreversion of the diethoxy phosphoryl dithioester cycloadducts of open-chain dienes required temperatures above 160 °C.[157,158]

Triazoline diones are considered to be the most reactive bench-stable dienophiles.[159] The Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with cyclopentadiene has been reported to occur instantaneously at temperatures as low as −78 °C.[160] At 25 °C in toluene, the rate constant for the Diels–Alder reaction 4-phenyl-1,2,4-triazoline-3,5-dione with cyclopentadiene is 1.6×10^5 $M^{-1}s^{-1}$.[161] The Winne and Prez groups prepared a diblock copolymer from the Diels–Alder reaction of a cyclopentadiene-functionalized polyisobornylacralate polymer with 4-butyl-1,2,4-triazoline-3,5-dione bearing a butyl chain (Scheme 40).[162] The reaction in THF was complete within 5 s at 20 °C. Triazolines undergo a range of reactions with a wide variety of functional groups. For example, triazoline-3,5-diones undergo ene reactions with polyisoprene polymers.[163,164] This reactivity limits the polymers that can be conjugated to the triazoline-3,5-dione to those lacking functionalization.

5.5. Reversible Cross-Linking of Polymers

Cross-linked polymers are polymers held together through one or more chemical bonds. Kennedy and Castner reported the reversible cross-linking of chlorinated butyl rubber (isobutylene-isoprene) polymers containing randomly distributed pendant cyclopentadienes (Scheme 41).[133] After 72 h, the cyclopentadienylated polymers cross-linked to form a gel. Heating to 215 °C led to the thermal dissociation of the dicyclopentadiene cross-linked networks and regeneration of the cyclopentadienylated monomers. Ruckstein and Chen studied the thermal reversibility of chlorinated polymers cross-linked through dicyclopentadiene carboxylates (Thiele’s acid).[165–167] Thermally reversible dicyclopentadiene cross-linked networks have potential application as self-healing materials.[168,169] The Miura group showed that treating cyclopentadienylated polymers with sodium metal prevented cross-linking by converting the cyclopentadienes to the inert sodium cyclopentadienide species.[170]

6. Surface Functionalization of Carbon-Based Materials with Cyclopentadiene

6.1. Fullerene Functionalization

Curl, Kroto, and Smalley shared the 1996 Nobel prize in chemistry for the discovery and synthesis of the C_{60} fullerene carbon allotrope from soot.[171] The size, hydrophobicity, three-dimensionality, electronic configuration, and photophysical properties of fullerenes have led to applications as electron-acceptors in bulk-heterojunction solar cells and as therapeutic agents in medicinal chemistry.[172] In 1992, Wudl discovered that C_{60} reacts with a variety of nucleophiles, dipoles, and dienes.[173] This work inspired more detailed studies into the reactivity of C_{60} toward cyclopentadiene. The Rotello group added cyclopentadiene to a solution of C_{60} in benzene at 20 °C and observed an immediate color change from a deep purple to golden brown (Scheme 42).[174,175] The resulting C_{60}–cyclopentadiene monoadduct was isolated in 74% yield. Nagami and co-workers reacted C_{60} with cyclopentadiene in a 1:1.5 molar ratio and isolated a mono- and diadduct in 68% and 28% yield, respectively.[176] Kroto and co-workers reported that six cyclopentadienes react with C_{60} in the presence of 10 equiv of cyclopentadiene.[177] The ensuing cycloadditions propagate on the norbornene adduct of the previous cycloadduct to form the “ball and chain”[178] system shown in Scheme 43.

The cycloaddition of cyclopentadiene selectively occurs across the [6,6] double bond between two 6-membered rings and not the [5,6] double bond between a 5- and 6-membered ring (Scheme 44).[174,177] Computational methods have provided insight into this regioselectivity. With the M06–2X[179] functional, the cycloaddition of cyclopentadiene across the [5,6] double bond is predicted to be 15–16 kcal/mol less favorable than across the [6,6] double bond.[180–182] This regioselectivity has been attributed to increased orbital overlap between the cyclopentadiene HOMO and the 3-fold degenerate LUMOs of fullerene when the reaction occurs across the [6,6]-double bond.[183]

The cycloaddition of cyclopentadiene across the [6,6] double bond of fullerene is rapid, having a rate constant of 0.6 $M^{-1}s^{-1}$ at 25 °C.[184] This high reactivity is a result of the low-lying 3-fold degenerate LUMOs in C_{60}. At the AM1[185] level of theory, the energy of the C_{60} LUMO is −2.95 eV, which can be compared to 1.44 eV for ethylene.[186] The electron-deficient nature of the alkene bonds in C_{60} leads to poor reactivity with electron-deficient dienes such as 1,2,4,5-tetrazines.[187,188]

The Diels–Alder reaction of the cyclopentadiene to C_{60} is thermally reversible at temperatures >75 °C.[175] For comparison, the retro-Diels–Alder reaction of norbornene requires temperatures >300 °C.[189] The increased lability of the C_{60}–cyclopentadiene adduct relative to norbornene has been attributed to the destabilization that results from the loss of aromaticity in C_{60}.[175] At 80 °C, the rate constant of the retro-Diels–Alder reaction is 1.2×10^{-4} s^{-1} and that of the forward reaction is 3.63 $M^{-1}s^{-1}$.[175,184] The reversible reaction of fullerenes to cyclopentadiene-functionalized silica gels allows for nonchromatic purification of fullerenes.[190] Rotello and Nie used a cyclopentadiene-functionalized silica gel to extract C_{60} selectively from soot at room temperature (Scheme 45). Heating the C_{60}-functionalized

silica gel to 100 °C in toluene for 5 h resulted in the release of 93.7% of the bound C_{60}. The increased thermal stability of the cycloadduct with the functionalized cyclopentadiene is the result of stabilizing van der Waals interactions between the alkyl tether that links cyclopentadiene to the silica gel and the C_{60} surface. This methodology enabled the cost-effective large-scale purification of C_{60}.

The Rotello group reported the reaction of a cyclopentadiene-functionalized Merrifield resin[191] with C_{60} (Scheme 46).[192,193] The resulting cycloadduct exhibited increased stability relative to the free C_{60}–cyclopentadiene adduct. Heating the polymer-functionalized C_{60} in decalin at 180 °C in the presence of maleic anhydride as a trapping agent resulted in a 48% recovery of fullerene. The increased stability of the fullerene cyclopentadiene resin cycloadduct is the result of stabilizing noncovalent interactions (**π**-stacking and dispersion) between the aryl groups in the styrene–divinylbenzene copolymer of the resin and the C_{60} surface. The use of cyclopentadiene-capped styrene–divinylbenzene copolymer resins was implemented by the Dorn group for the purification of endohedral lanthanide trimetallic nitride metallofullerenes.[194]

Biological applications of C_{60} are limited by their sparse solubility in polar solvents.[195–199] Derivatives of C_{60} have been developed to increase the solubility across different solvents.[200] Barner-Kowollik and Nebhani reacted a cyclopentadiene having a pendant PEG polymer with C_{60} to prepare a water soluble PEG-functionalized C_{60} derivative.[201] A C_{60} soluble in fluorous solvents was synthesized by Wilson and Cowers (Scheme 47). They functionalized C_{60} with a cyclopentadiene having a pendant perfluoroalkyl group.[202] The fluorinated cyclopentadiene was less reactive toward C_{60} than was cyclopentadiene itself and formed a 1.5:1 isomeric mixture of cycloadducts from the reaction of the 1- and 2-cyclopentadiene, respectively. The isomeric cycloadducts were soluble in perfluorohexane. The electron-withdrawing effects of the perfluoroalkyl group decreased the stability of the cycloadduct. At temperatures as low as 60 °C the isomeric cycloadducts began to revert back into starting materials.

Since the discovery of C_{60}, a number of fullerene allotropes and endohedral derivatives have been synthesized and treated with cyclopentadiene. The reactivity of cyclopentadiene toward C_{70}, $Li^+@C_{60}$, and $La@C_{82}$, in particular, has been studied in detail. C_{70} is an order of magnitude less reactive than C_{60} toward cyclopentadiene, having a rate constant of 8.8×10^{-2} $M^{-1}s^{-1}$ at 19 °C.[184] In the same study, the rate constant for the reaction of cyclopentadiene with C_{60} was reported to be 6.4×10^{-1} at 20 °C. The lithium ion encapsulated fullerene, $Li^+@C_{60}$, was more reactive than C_{60} itself toward cyclopentadiene.[203] The reaction of $[Li^+@C_{60}]PF_6^-$ with 1.1 equiv of cyclopentadiene resulted in the formation of the monoadduct in 56% yield along with a regioisomeric mixture of bis cycloadducts. The second cycloaddition occurs on the fullerene cage, suggesting that the double bonds in $Li^+@C_{60}$ monoadduct are more reactive than norbornene double bonds from the initial cycloadduct. Matsuo and co-workers reported that the reaction of $Li^+@C_{60}$ reached equilibrium in 15 s and was too fast for the determination of a rate constant.[203] The computationally predicted Gibbs free activation energies for the Diels–Alder reaction of cyclopentadiene with C_{60} and $Li^+@C_{60}$ are 21.3 and 12.7 kcal/mol, respectively, corresponding to a 3.3 million-fold rate enhancement.[182] With the less reactive diene,

cyclohexadiene, the experimental rate constant with $Li^+@C_{60}$ was measurable and a 2,400-fold rate enhancement was reported over C_{60}.[204] The encapsulated Li^+ ion promotes the cycloaddition by lowering the LUMO of C_{60}. The monoadduct of $La@C_{82}$ and cyclopentadiene readily decomposes at room temperature with a half-life of ~1.8 h.[205] 1,2,3,4,5-Pentamethylcyclopentadiene fullerene adducts are significantly more stable than the cyclopentadiene fullerene adducts.[206] After 12 h at 298 K, 36% of $La@C_{82}$ Cp* adducts decomposed to $La@C_{82}$ and Cp*.[207] The increased stability of the Cp* cycloadduct is the result of dispersion interactions between the fullerene cage and the methyl substituents of Cp*.[208]

6.2. Carbon Nanotube Functionalization

The Barner-Kowollik group studied the functionalization of carbon nanotubes with cyclopentadiene-capped poly(methyl methacrylate) polymers via the direct functionalization and prefunctionalization routes shown in Scheme 48. The grafting ratios for direct functionalization of the carbon nanotube with cyclopentadienyl–capped poly(methyl methacrylate) polymers were measured using thermogravimetric analysis, elemental analysis, and x-ray photoelectric spectroscopy.[209] Depending on the method of analysis, the grafting ratio was 18–60% higher when the reaction was carried out at 80 °C. This approach has been used to bioconjugate single stranded DNA to carbon nanotubes.[210] The alternative route involves prefunctionalizing the carbon nanotube surface with pyridine-based dithioesters that then undergo Diels–Alder reactions with the cyclopentadienyl-functionalized polymers.[211] Although this approach leads to higher polymer grafting densities, the prefunctionalization process involves refluxing the carbon nanotubes for 8 h in 8 M nitric acid. The harsh acid treatment results in the oxidation of the carbon nanotube to the detriment of its mechanical and electrical properties.[212,213]

6.3. Graphene Functionalization

Graphene is a two-dimensional material consisting only of sp^2-hybridized carbon atoms.[214] Diels–Alder reactions have been demonstrated on its surface with graphene acting as either a diene or dienophile.[215] The curvature of fullerene and carbon nanotubes introduces a strain that promotes Diels–Alder reactivity.[216–218] Graphene lacks any curvature and is less reactive as a dienophile. In 2012, the functionalization of a graphene surface with cyclopentadiene-capped PEG monomethyl ether polymers was carried out to improve the solubility of the material.[219] At ambient temperature and 80 °C, grafting ratios of 16.7% and 21.8%, respectively, were observed after 24 h. The functionalized graphene displayed solubility in tetrahydrofuran, ethylene glycol, ethanol, water, acetone, and chloroform.

Houk and co-workers studied computationally the reaction enthalpies for the Diels–Alder reactions of cyclopentadiene across a representative 5 × 5 graphene surface shown in Scheme 49.[220] The reaction enthalpies are favorable for the cycloaddition across the double bonds on the edges of the graphene surface and unfavorable across the interior graphene double bonds. Peripheral double bonds *a* and *b* have reaction energies of −11.4 and −1.4 kcal/mol, respectively, whereas the cycloaddition across the internal double bond *c* is unfavorable with a reaction energy of 36.6 kcal/mol. The cycloaddition of a second

cyclopentadiene across the norbornene adduct has a reaction enthalpy of −25.8 kcal/mol and is favored over the multisite-functionalization of the graphene surface.

7. Bioconjugation with Cyclopentadiene

7.1. Biomolecule Surface Immobilization

Cyclopentadiene Diels–Alder reactions are recognized as an effective method to immobilize biomolecules onto a surface.[221–227] In 1999, Yousaf and Mrksich pioneered the use of the Diels–Alder reaction for this purpose.[228] They prepared a gold self-assembled monolayer containing unreactive hydroquinone groups. The hydroquinones were oxidized into 1,4-benzoquinones that are reactive toward cyclopentadiene (Scheme 50). The immobilization of biomolecules via the Diels–Alder reaction of bioconjugated cyclopentadienes with the oxidized hydroquinone groups of a self-assembled monolayer allowed the Mrksich group to develop peptide chips for the quantitative evaluation of protein kinase activity and carbohydrate chips for the quantitative evaluation of carbohydrate protein interactions.[229–231] These chips are amenable for high-throughput screening applications.

In 2005, the Waldmann group immobilized a cyclopentadiene streptavidin conjugate onto a maleimide-functionalized glass surface.[232] Maleimides react an order of magnitude faster than does 1,4-benzoquinone toward cyclopentadiene (see: Scheme 3).[18] Ravoo and co-workers made use of the cyclopentadiene maleimide reaction in carbohydrate microarrays.[233] The immobilization of the cyclopentadiene-functionalized carbohydrates occurred rapidly on the maleimide surface with reaction times between 5 and 15 min at room temperature.

7.2. Noncanonical Cyclopentadienyl Amino Acids

The Christie and Read de Alaniz groups introduced the cyclopentadiene (CpHK) and spiro[2.4]hepta-4,6-diene (SCpHK) noncanonical amino acids shown in Scheme 51 into antibodies.[234–236] Dimerization was observed between antibody side chains bearing CpHK amino acids in close proximity, whereas antibody side chains bearing the less reactive SCpHK amino acids in close proximity did not dimerize. The incorporated CpHK and SCpHK amino acid side chains react toward maleimide-linked drugs with respective rate constant of 77 $M^{-1}s^{-1}$ and 3 $M^{-1}s^{-1}$ to form antibody drug conjugates.

7.3. Bioorthogonal Chemistry

Click reactions that can be carried out in biological environments without perturbing any native biological processes are also known as “bioorthogonal” reactions.[237] Bioorthogonal reactions enable biological targets functionalized with a chemical handle to be labeled with a chemical probe. Tetrazines,[238] cyclopentadiones,[239,240] thiophene dioxides,[241] and *ortho*-quinones[242,243] have been been explored widely and applied as bioorthogonal dienes. These electron-deficient dienes are generally paired with a *trans*-cyclooctene (TCO), cyclooctyne, cyclopropene, or norbornene reaction partner. Cyclopentadiene also reacts readily with these strained dienophiles under mild conditions.[244,245]

Sauers early kinetic studies on the Diels–Alder reactions of tetrazines toward cyclopropene, norbornene, and *trans*-cyclooctene inspired their use as bioorthogonal reagents.[246] Like other bioorthogonal reagents, a cyclopentadiene, 1,2,3,4-tetrachlorocyclopentadiene ethylene ketal (TCK), was revived from the literature and adapted for modern application as a bioorthogonal reagent (Scheme 52).[31,247] TCK was the most reactive cyclopentadiene that resisted dimerization from Sauer's 1997 studies on the Diels–Alder reactivity and dimerization of substituted cyclopentadienes. Houk refers to cyclopentadienes that do not dimerize as being "self-orthogonal" cyclopentadienes.[248] The rate constant of the Diels–Alder reaction of TCK with 4-phenyl-1,2,4-triazoline-3,5-dione is 6.0 $M^{-1}s^{-1}$ in methylene chloride at 20 °C. Although this reaction rate is fast enough for applications in bioorthogonal chemistry, 4-phenyl-1,2,4-triazoline-3,5-dione is a strong Michael acceptor and unstable in physiological contexts.[159] Swapping 4-phenyl-1,2,4-triazoline-3,5-dione for the biologically stable dienophile, BCN, resulted in a rate constant of 0.26 $M^{-1}s^{-1}$ in methanol at 23 °C.[248] This rate constant is of the same order of magnitude as the fastest strain promoted azide–alkyne cycloadditions, which are widely used in bioorthogonal chemistry.[249] The biocompatibility of the reaction was demonstrated through a labeling study performed in vitro between a TCK–neuropeptide and TCO–fluorophore conjugate. The field of bioorthogonal chemistry is expanding rapidly, driven by active efforts to optimize the stability and reactivity of known bioorthogonal reagents and to develop new bioorthogonal reactions.[250] The emergence of cyclopentadiene as a potential bioorthogonal reagent is exciting, as new applications often arise from new reagents.[251]

8. Heterocyclopentadienes

8.1. 1- and 2-Azacyclopentadienes

The Wong and Jung groups explored the potential of 2,3,4,5,5-pentachloro-1-azacyclopentadiene as a Diels–Alder diene.[252–254] Heating 2,3,4,5,5-pentachloro-1-azacyclopentadiene in the presence of styrene or vinyl acetate as the dienophile did not afford the expected l-azabicyclo[2.2.1]hept-2-ene cycloadduct but rather the unexpected 2-azabicyclo[2.2.1]hept-2-ene cycloadduct (Scheme 53). The Diels–Alder cycloaddition proceeds through the 2-azacyclopentadiene isomer, which is in equilibrium with the 1-azacyclopentadiene isomer at elevated temperatures. The Houk group computationally studied the reluctance of the 1-azacyclopentadiene isomer to undergo Diels–Alder cycloadditions.[255] With ethylene as the dienophile, the computed activation energy for the Diels–Alder reaction with 1-azacyclopentadiene is 11 kcal/mol less favorable than with the 2-azacyclopentadiene isomer. The decreased reactivity of the 1-azacyclopentadiene is related to the decreased overlap of the nitrogen p-orbital, which is contracted relative to a carbon p-orbital, with the p-orbital of ethylene during bond formation.

8.2. 2,3-Diazacyclopentadienes

Diels–Alder reactions of 2,3-diazacyclopentadienes have been extensively explored by Hünig, Adam, and others.[256–260] 5,5-Dimethyl-2,3-diazacyclopentadienes do not readily undergo Diels–Alder reactions, even with strained dienophiles, unless promoted with an acid catalyst (Scheme 54). Fluorination of 2,3-diazacyclopentadienes at the 5-position increases the diene character by lowering the LUMO energy of the pyrazole and inducing

hyperconjugative antiaromativity.[261,262] The rate constants for the Diels–Alder reactions of 4-fluoro-4-methyl-3,5-diphenyl-4*H*-pyrazole (MFP) and 4,4-difluoro-3,5-diphenyl-4*H*-pyrazole (DFP) toward BCN were 0.76 $M^{-1}s^{-1}$ and 5.2 $M^{-1}s^{-1}$, respectively. Though more reactive than the tetrazine scaffold toward BCN, the DFP scaffold is unstable in biological settings.

9. Summary and Perspectives

This review has covered the development and applications of cyclopentadiene as a reagent in click chemistry. The use of monoalkylated cyclopentadiene as a click reagent has been challenging because of the intrinsic propensity of cyclopentadienes to dimerize and isomerize. This challenge can be overcome by generating the cyclopentadiene *in situ*. Click reactions of cyclopentadiene with electron-deficient dienophiles as reaction partners have limited biological applications because of the instability of electron-deficient dienophiles in biological systems. Finding highly reactive dienophile partners such as BCN that are biologically stable would expand the utility of cyclopentadiene click reactions to biological systems.

Despite the rich structural diversity of the cyclopentadiene scaffold that can be generated through substitution at one of six positions, monoalkyl-substituted cyclopentadienes currently dominate the landscape of cyclopentadiene click chemistry reactions. A number of complex cyclopentadiene scaffolds have been generated as precursors in the synthesis of cyclopentadienyl transition metal complexes. Exploring the Diels–Alder reactivities of these highly substituted cyclopentadienes could reveal new cyclopentadienes with ideal reactivity and stability for applications in click chemistry. We hope this review inspires readers to explore the field of cyclopentadiene click chemistry and to expand upon its scope.

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Abbreviations

BCN	*endo*-bicyclo[6.1.0]non-4-yn-9-ylmethanol
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CpHK	N^{ε}-((2-(cyclopenta-1,3-dien-1-yl)ethoxy)carbonyl)-L-lysine
DFP	4,4-difluoro-3,5-diphenyl-4*H*-pyrazole
DMAD	dimethyl acetylenedicarboxylate
DMP	4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole
HOMO	highest-occupied molecular orbital
LUMO	lowest-unoccupied molecular orbital
MFP	4-fluoro-4-methyl-3,5-diphenyl-4*H*-pyrazole
μw	microwave
NICS	nucleus independent chemical shift
PEG	poly(ethylene glycol)
NR	no reaction
rt	room temperature
SCpHK	N^{ε}-((spiro[2.4]hepta-4,6-dien-1-ylmethoxy)carbonyl)-L-lysine
TCK	1,2,3,4-tetrachlorocyclopentadiene ethylene ketal
TCNE	tetracyanoethylene
TDA	1,3,5,7-tetrakis(2,4-dimethoxyphenyl)adamantane
TCO	*trans*-cyclooctene

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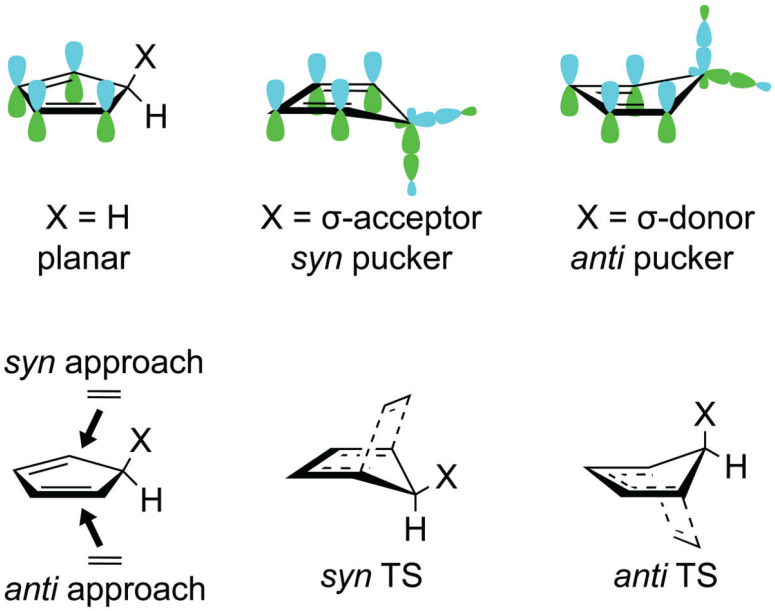
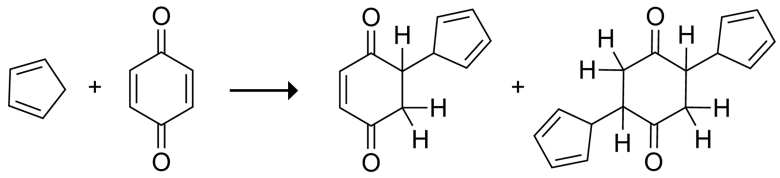


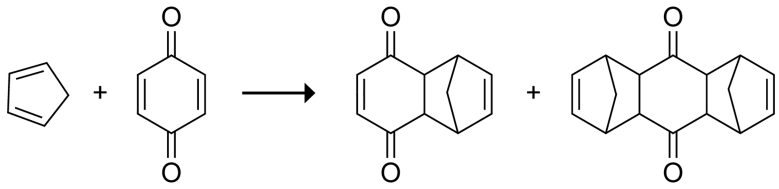
Figure 1.

Syn and *anti* puckering of the ground and transition state geometries of 5-substituted cyclopentadienes.[37]



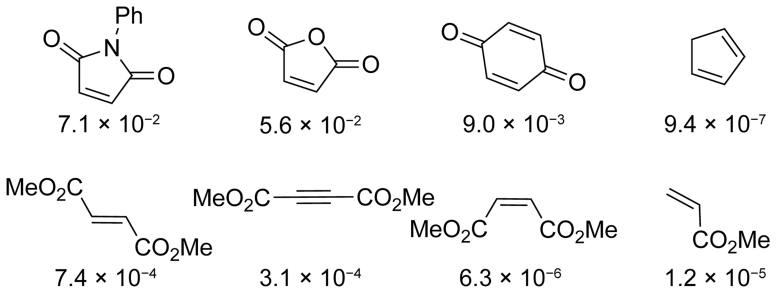
Scheme 1.

Mischaracterized 1:1 and 2:1 Adducts from the Reaction of Cyclopentadiene with 1,4-Benzoquinone as Reported by Albrecht in 1906.[5]



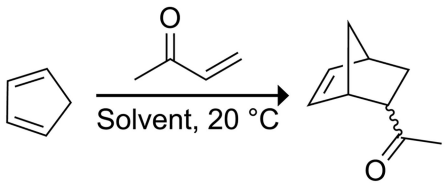
Scheme 2.

Correctly Characterized 1:1 and 2:1 Cycloadducts from the Reaction of Cyclopentadiene with 1,4-Benzoquinone by Diels and Alder in 1928.[6]



Scheme 3.

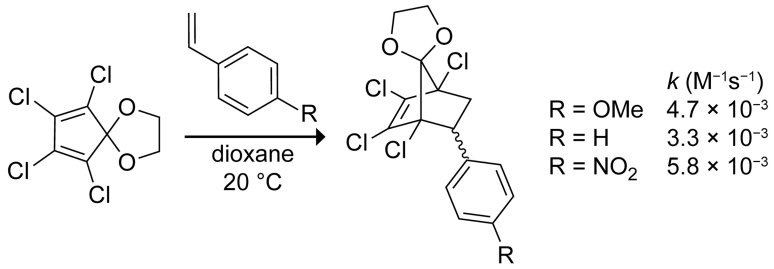
Rate Constants ($M^{-1}s^{-1}$) for the Diels–Alder Reactions of Various Dienophiles with Cyclopentadiene in Dioxane at 20 °C.[18]



Solvent	Isooctane	Methanol	Formamide	Water
k ($M^{-1}s^{-1}$)	5.9×10^{-5}	7.6×10^{-4}	3.2×10^{-3}	4.4×10^{-2}
k_{rel}	1	17	69	960

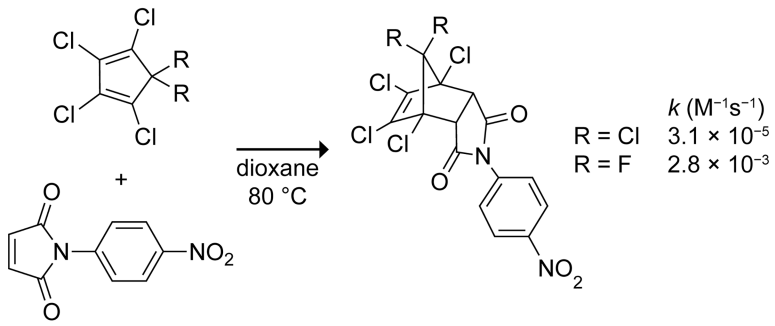
Scheme 4.

Reaction Rates for the Diels–Alder Reactions of Cyclopentadiene with Methyl Vinyl Ketone at 20 °C Across Different Solvents.[24,25]



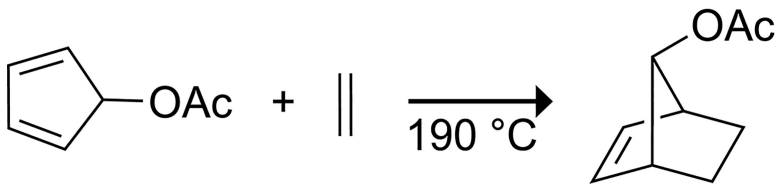
Scheme 5.

Rate Constants for the Diels–Alder Reactions of 1,2,3,4-Tetrachlorocyclopentadiene Ethylene Ketal (TCK) with Styrene, *p*-Methoxystyrene, and *p*-Nitrostyrene.[31]



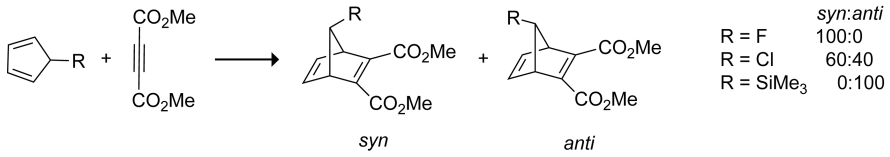
Scheme 6.

Rate Constants for the Diels–Alder Reactions of 1,2,3,4,5,5-Hexachlorocyclopentadiene and 1,2,3,4-Tetrachloro-5,5-Difluorocyclopentadiene with *p*-Nitro-*N*-Phenyl Maleic Anhydride.[31]



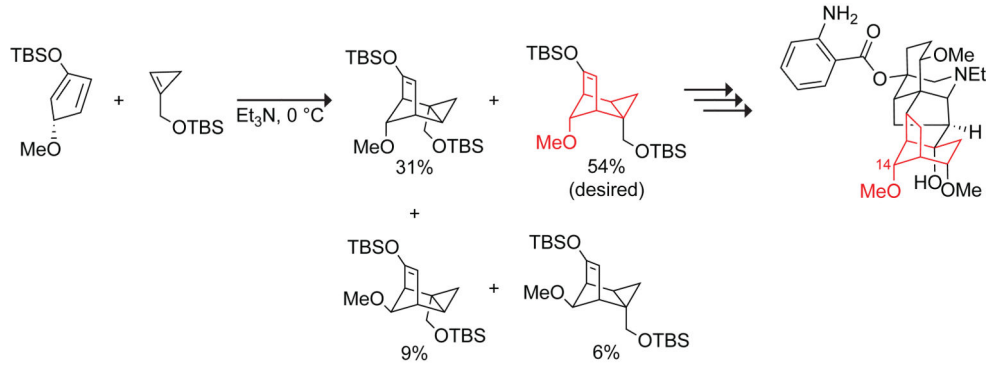
Scheme 7.

Contrasteric (*syn*) π-facial Selectivity in the Diels–Alder Reaction of 5-Acetoxy Cyclopentadiene with Ethylene.[38]



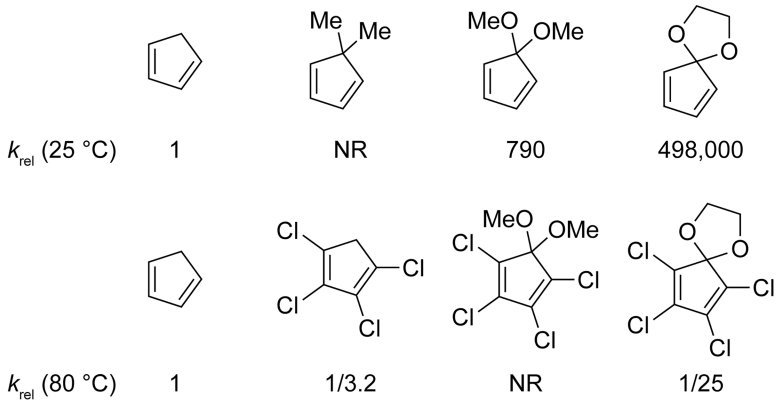
Scheme 8.

Syn and *anti* π-Facial Selectivities in Diels–Alder Reactions of Dimethyl Acetylenedicarboxylate (DMAD) with 5-Fluorocyclopentadiene, 5-Chlorocyclopentadiene, and 5-Trimethylsilylcyclopentadiene.[42–44]



Scheme 9.

Control of π-Facial Selectivity in the Synthesis of Neofinaconitine.[45]

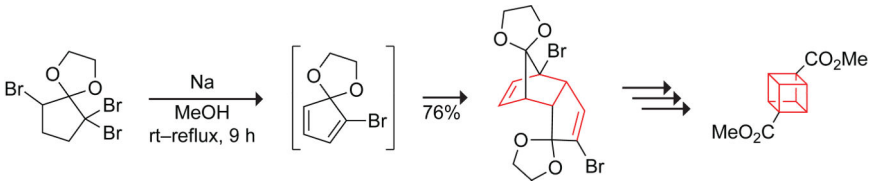


Scheme 10.

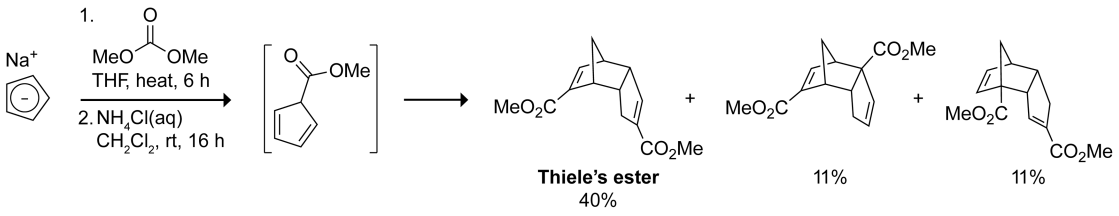
Relative Rates for the Dimerization of Cyclopentadiene and Substituted Cyclopentadienes at 25 and 80 °C.[31,55,56,59]

Scheme 11.

Two-step Synthesis of Adamantane from the Cyclopentadiene Dimer, Dicyclopentadiene.[60]

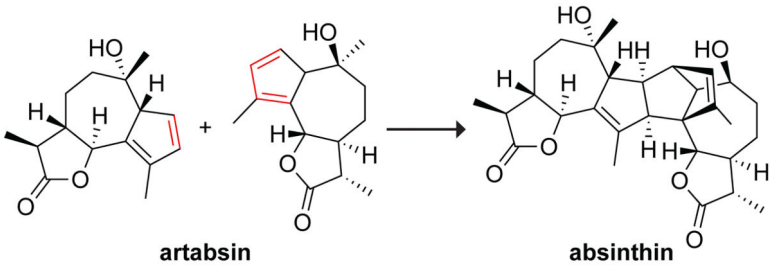


Scheme 12.
Dimerization of a Cyclopentadiene Ketal in the Synthesis of Cubane.[65]

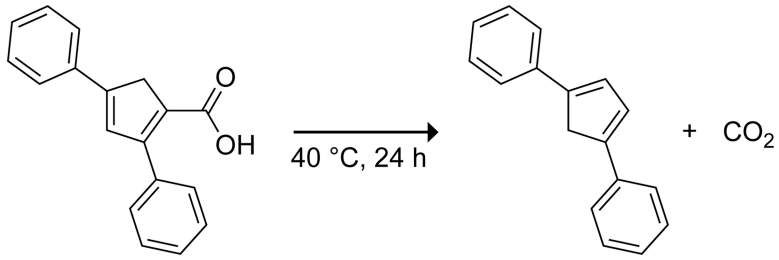


Scheme 13.

Synthesis of Thiele's Ester from the Dimerization of a Cyclopentadiene Methyl Ester.[67]

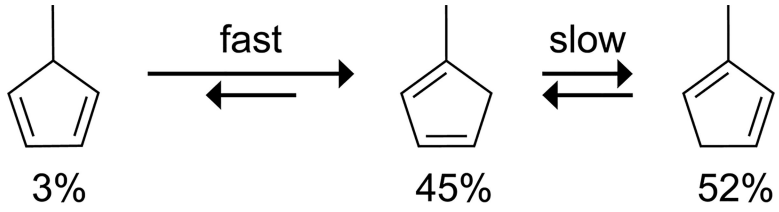


Scheme 14.
Dimerization of Artabsin to Absinthin.[79]

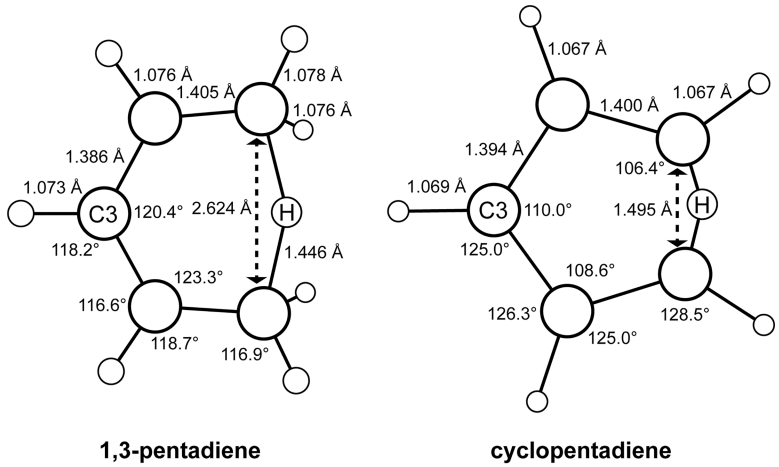


Scheme 15.

Unexpected Formation of the 1,4-Diphenylcyclopentadiene from the Decarboxylation of 2,4-Diphenylcyclopentadiene-1-Carboxylate.[82]

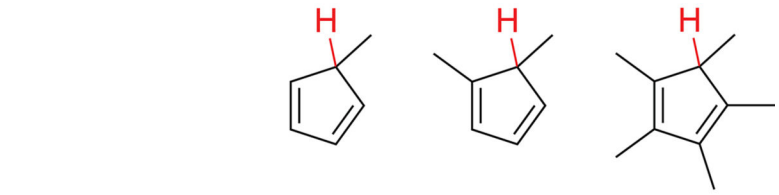


Scheme 16.
Isomerization of 5-Methylcyclopentadiene to 1-Methyl and 2-Methyl Cyclopentadiene.[88]



Scheme 17.

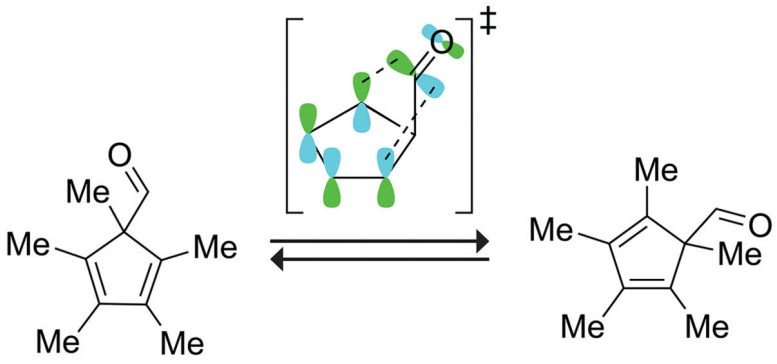
Optimized Transition-State Structures for the 1,5-Sigmatropic Hydrogen Migration in 1,3-Pentadiene and Cyclopentadiene.[96]



k (s^{-1}) (30 °C)	6.2×10^{-4}	5.5×10^{-5}	2.4×10^{-7}

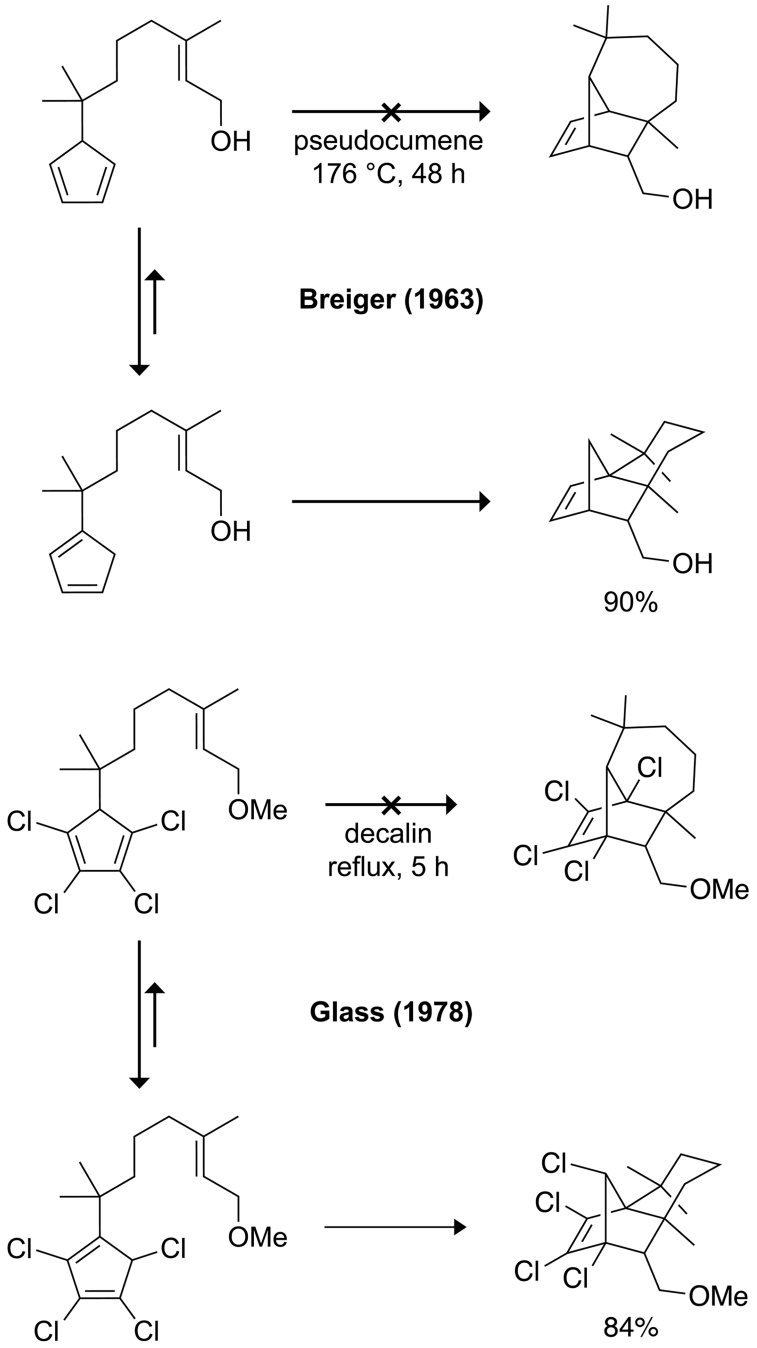
Scheme 18.

Rate Constants for 1,5-Hydrogen Migration in 5-Methylcyclopentadiene, 1,5-Dimethylcyclopentadiene, and Cp* at 30 °C.[100,101]



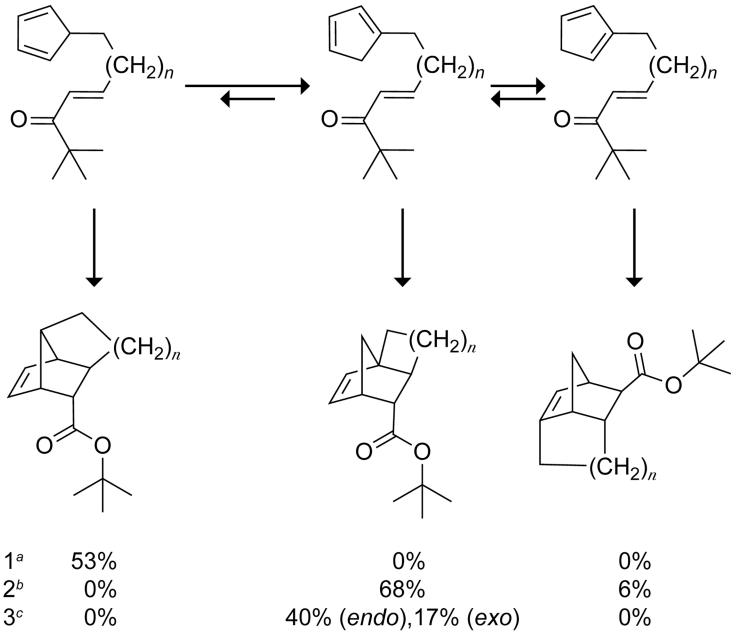
Scheme 19.

Secondary Orbital Interaction Involving the Overlap of the Cyclopentadiene HOMO with the LUMO of the Migrating Formyl Group in the Transition State for the 1,5-Sigmatropic Shift of the Formyl Group in 5-Formyl-1,2,3,4,5-Pentamethylcyclopenta-1,3-Diene.[107]



Scheme 20.

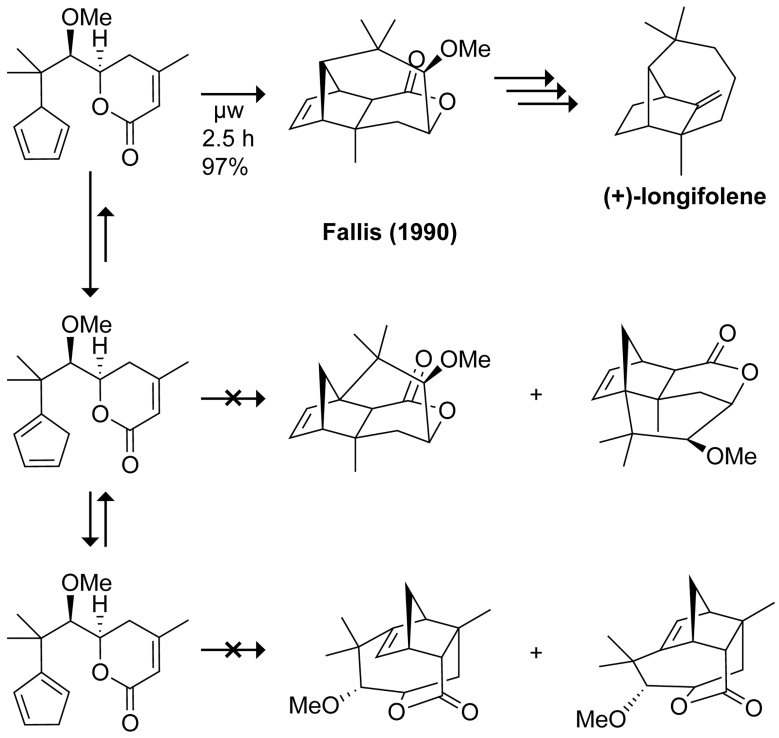
Early Synthetic Attempts to Access the Tricyclo[5.4.0^{1,7}.0^{2,9}]undecane Scaffold via Intramolecular Diels–Alder Reactions.[111,112]



n = 1[a]	53%	0%	0%
n = 2[b]	0%	68%	6%
n = 3[c]	0%	40% (*endo*),17% (*exo*)	0%

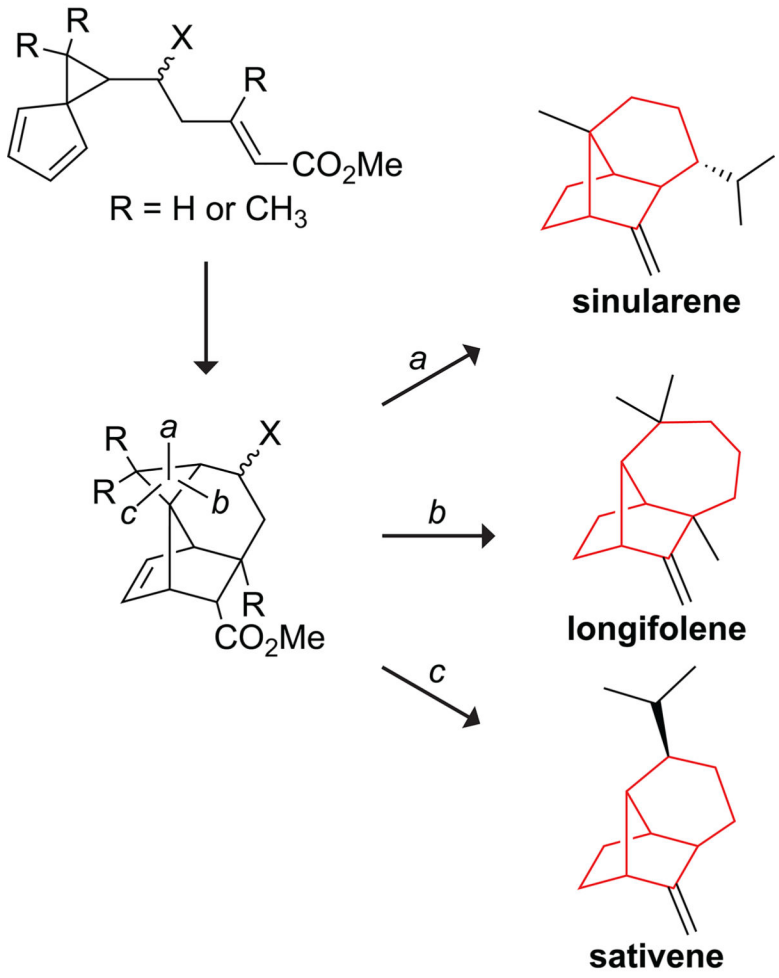
Scheme 21.

Selectivity of Tethered Cyclopentadiene Intramolecular Cycloadditions. [a]Reflux for 18 h in Toluene. [b]Reflux for 2 h in Benzene. [c]Reflux for 4 h in Benzene.[113]



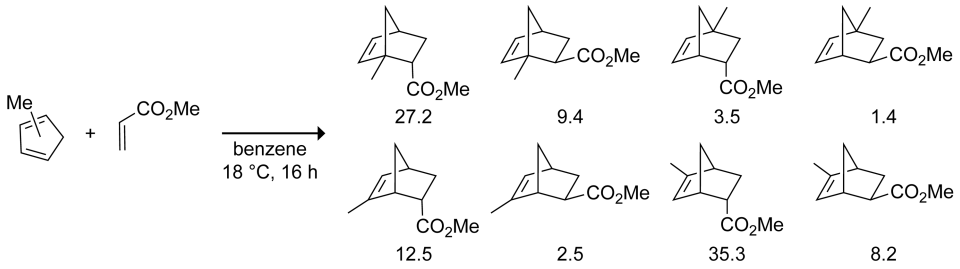
Scheme 22.

Successful Intramolecular Diels–Alder Reaction of a 5-Substituted Cyclopentadiene Containing a Four-Carbon Tether in the Synthesis of (+)-Longifolene.[114]



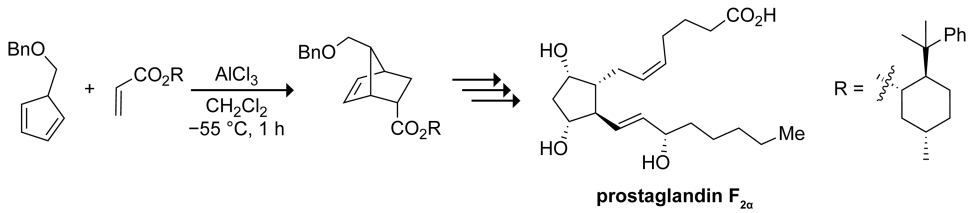
Scheme 23.

Use of a Tethered Spiro[2.4]heptadiene to Block the 1,5-Hydrogen Shift. Cleavage of the *b* Cyclopropane Bond Leads to the Tricyclo[5.4.0^{1,7}.0^{2,9}]undecane Skeleton of Longifolene; Cleavage of the *a* or *c* Bond Leads to the Tricyclo[4.4.0^{1,6}.0^{2,8}]decane Skeleton of Sinularene or Sativene.[117]



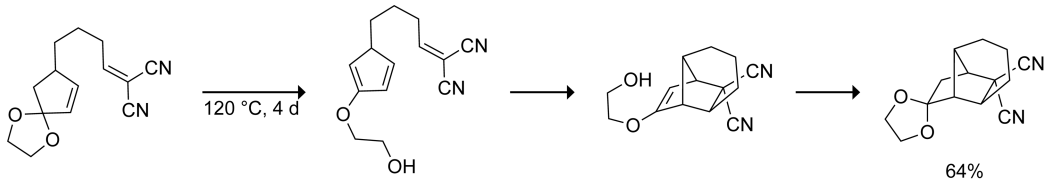
Scheme 24.

Product Distribution for the Diels–Alder Reaction of Methylcyclopentadiene with Methylacrylate.[119]



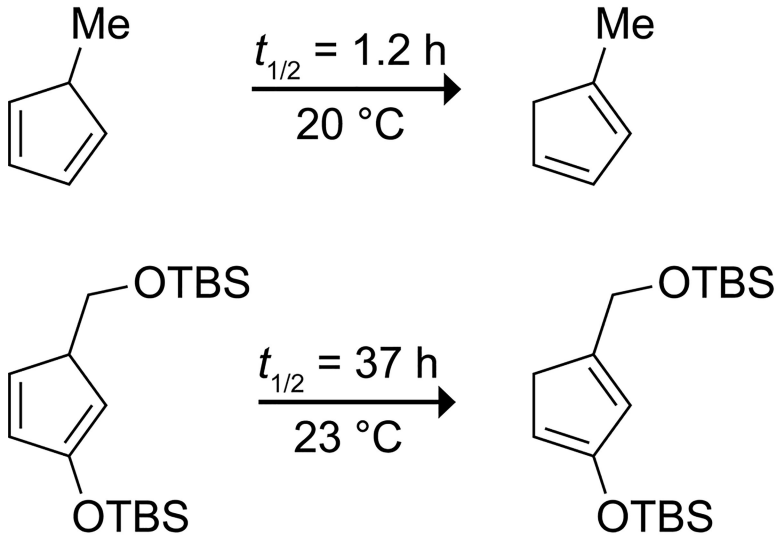
Scheme 25.

Lewis Acid-catalyzed Diels–Alder Reaction of 5-(Benzyloxymethyl)cyclopentadiene with an Acrylate Ester *en Route* to Prostaglandin $F_{2\alpha}$.[120,121]

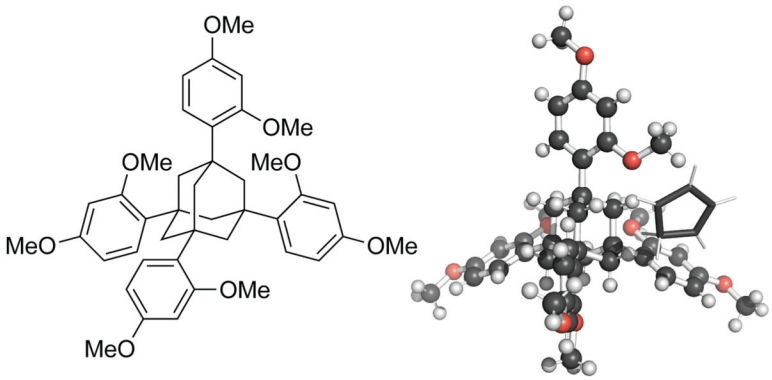


Scheme 26.

In situ Generation and Trapping of a 2-Alkoxy Cyclopentadiene Containing a Three-Carbon Tether at the 5-Position.[125]

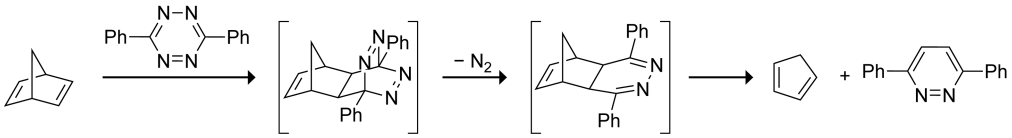


Scheme 27.
Half-lives of 5-Methyl Cyclopentadiene and a 2-Siloxycyclopentadiene Derivative.[126]



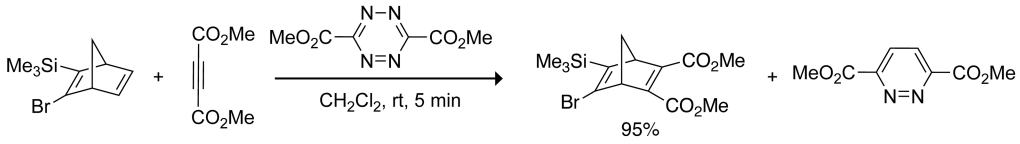
Scheme 28.

1,3,5,7-Tetrakis(2,4-dimethoxyphenyl)adamantane (TDA) and its Crystal Structure with Cyclopentadiene Encapsulated as a Guest Molecule.[129]



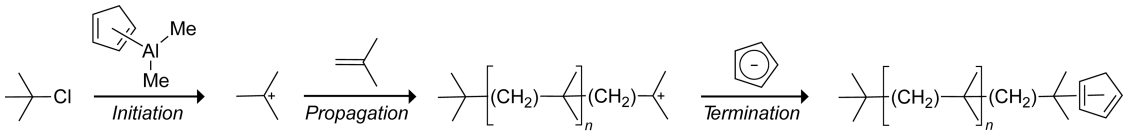
Scheme 29.

Mechanism for the Release of Cyclopentadiene from a Norbornadiene after Reacting with a Tetrazine.[130]



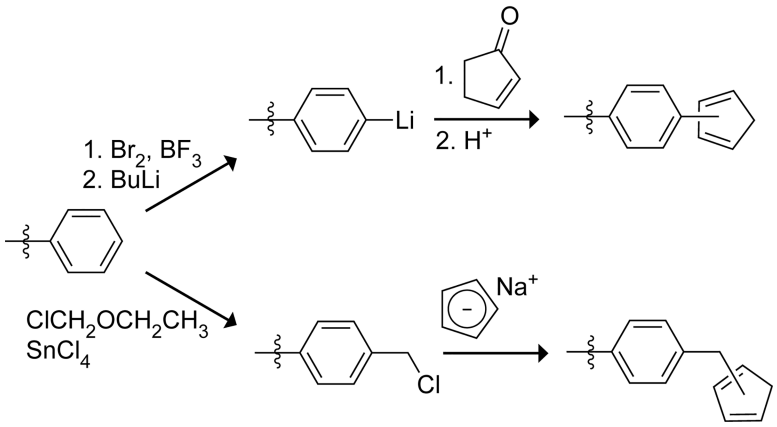
Scheme 30.

Trapping of a 2-Bromo-3-trimethylsilylcyclopentadiene Released from a Norbornadiene with Dimethyl Acetylenedicarboxylate.[131,132]



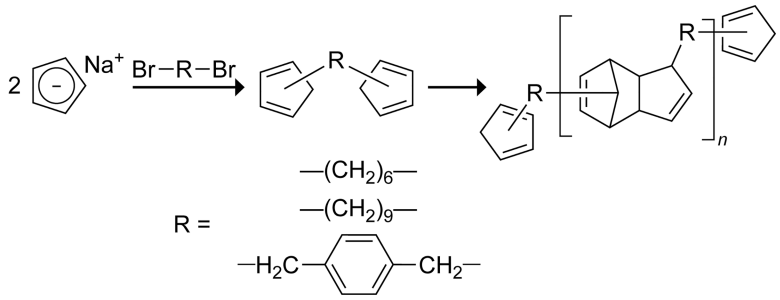
Scheme 31.

Initiation, Propagation, and Termination Steps in the Synthesis of a Cyclopentadiene-Capped Isobutylene Polymer.[133,134]



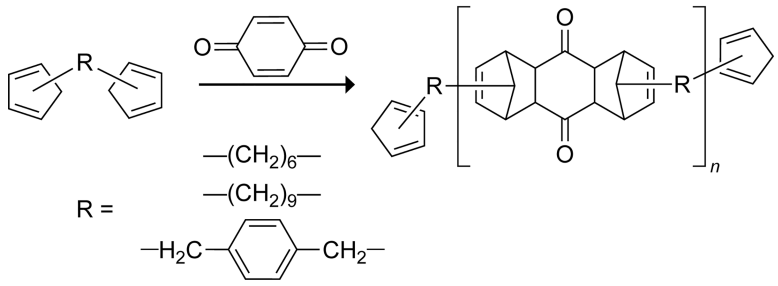
Scheme 32.

Cyclopentadienylation of a Styrene–Divinylbenzene Copolymer through the Reaction of the Organolithiated Styrene Motif with Cyclopentenone (top) and through the Reaction of Chloromethylated Styrene Motifs with the Cyclopentadienyl Anion (bottom).[135,136]

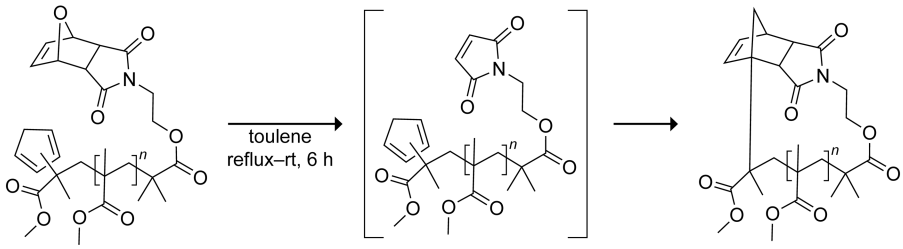


Scheme 33.

Synthesis of homopolymers via intermolecular Diels–Alder Reaction of Biscyclopentadienes.[142]

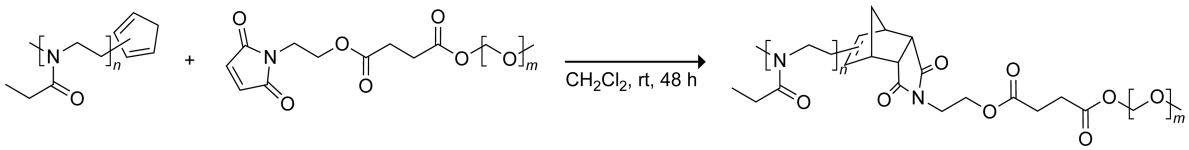


Scheme 34.
Copolymerization of Biscyclopentadienes with *p*-Benzoquinone.[142]



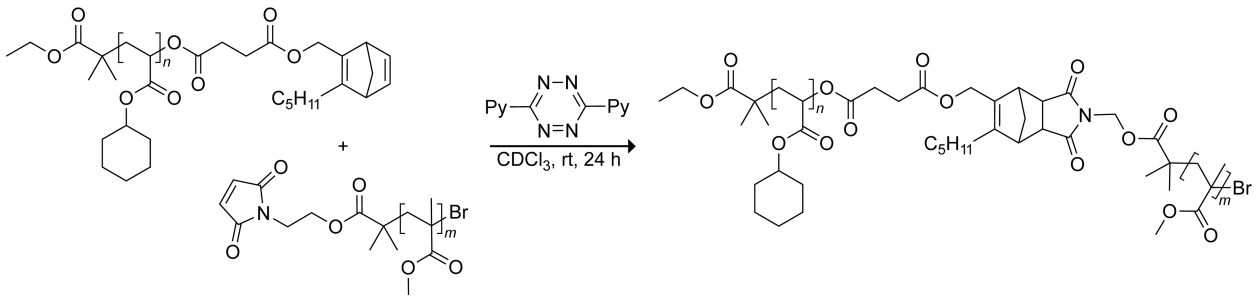
Scheme 35.

Formation of a Cyclic Polymer from the Intramolecular Diels–Alder Reaction of a Deprotected Maleimide with Cyclopentadiene.[145]



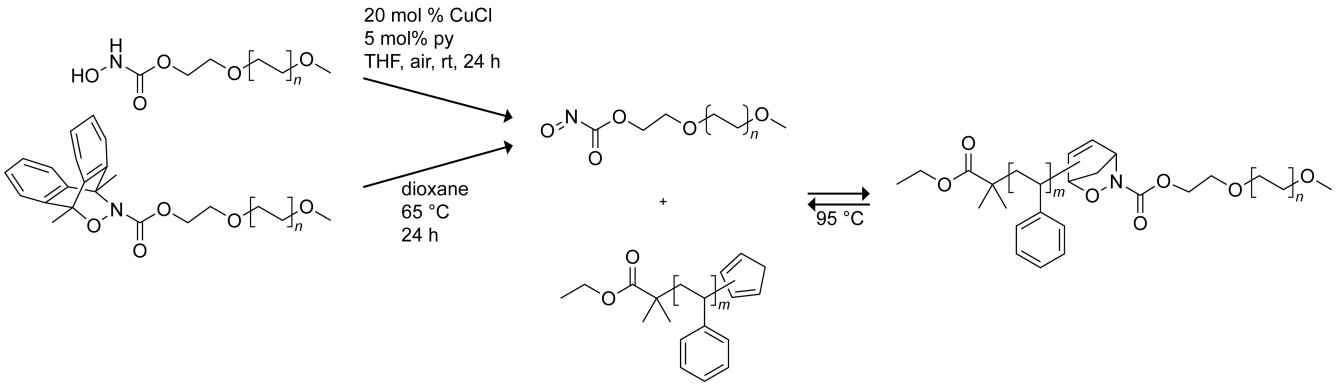
Scheme 36.

Synthesis of a Diblock Copolymer from the Diels–Alder Reaction of a Cyclopentadiene-Terminated Poly(2-Ethyl-2-Oxazoline) Polymer with a Maleimide-Terminated PEG Polymer.[146]



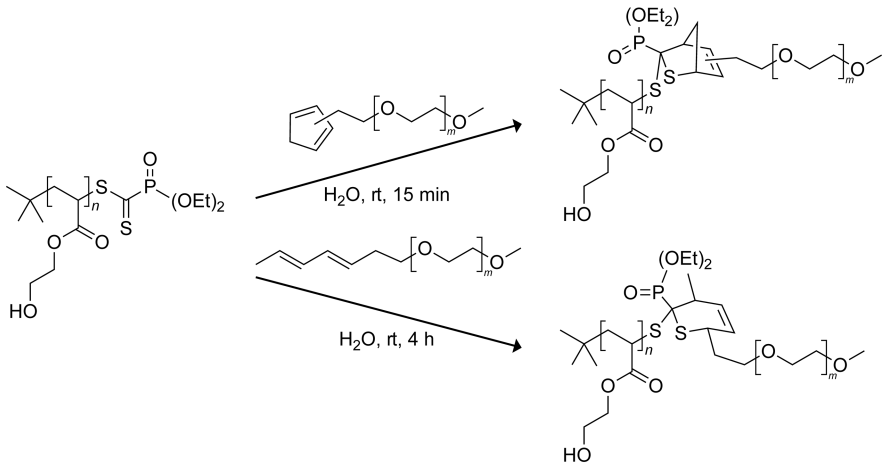
Scheme 37.

Diblock Copolymer Synthesis from the Diels–Alder Reaction of a Maleimide-Functionalized Polymer with a Cyclopentadiene-Functionalized Polymer Generated from the Reaction of a Tetrazine and a Norbornadiene.[148]



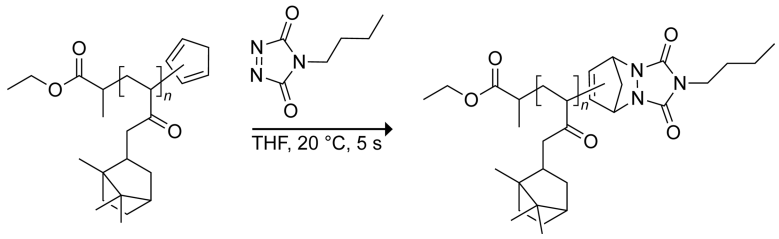
Scheme 38.

Synthesis and Thermal Reversibility of Diblock Copolymers Linked via a Cyclopentadiene Nitroso Cycloadduct.[149]



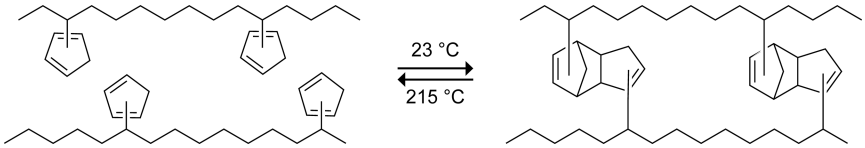
Scheme 39.

Reaction Times for the Formation of Diblock Copolymers from the Diel–Alder Reactions of a Diethoxy Phosphoryl Dithioester-Terminated Polymer with Cyclopentadiene and Butadiene-Terminated Polymers.[153]

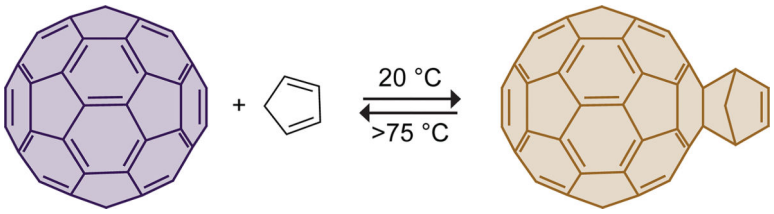


Scheme 40.

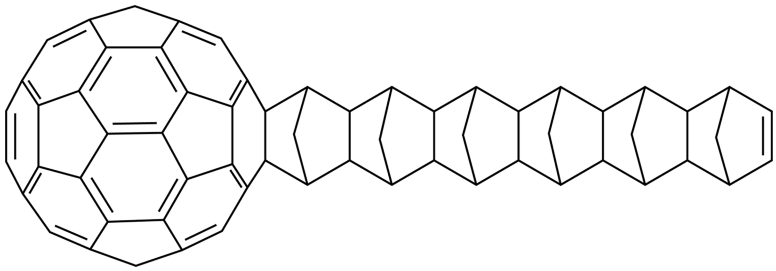
Formation of a Diblock Copolymer via the Diels–Alder Reaction of a Cyclopentadiene-Functionalized Polyisobornylacralate Polymer with 4-Butyl-1,2,4-Triazoline-3,5-Dione.[162]



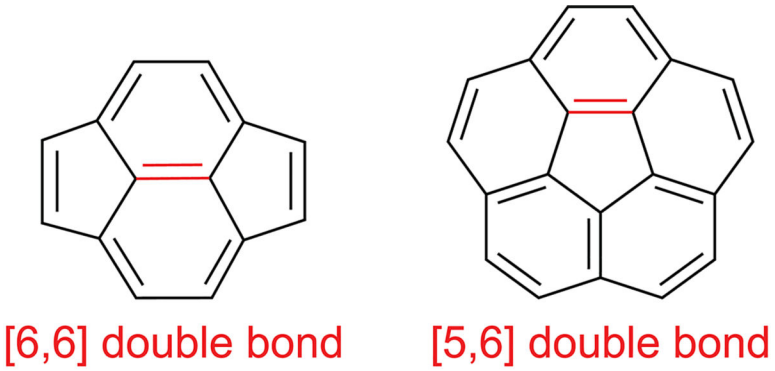
Scheme 41.
Thermally Reversible Cross-linking of Polymers Containing Pendant Cyclopentadienes.[133]



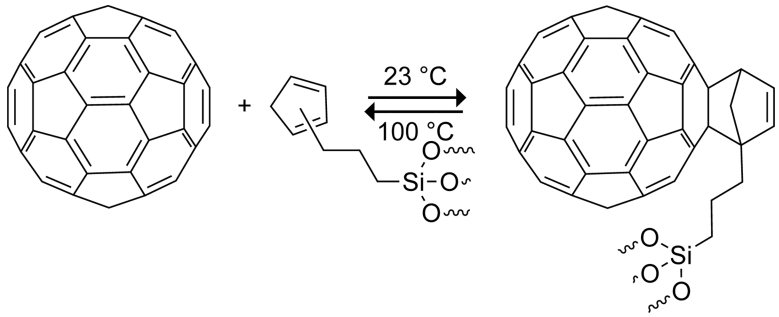
Scheme 42.
Thermally Reversible Cycloaddition of Cyclopentadiene with C_{60}.[174,175]



Scheme 43.
Product of the Diels–Alder Reaction of Fullerene with Six Cyclopentadienes.[177]

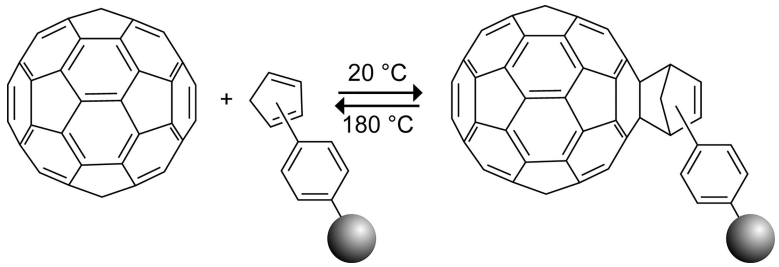


Scheme 44.
[6,6] and [5,6] Bonds in Fullerene.[174,177]



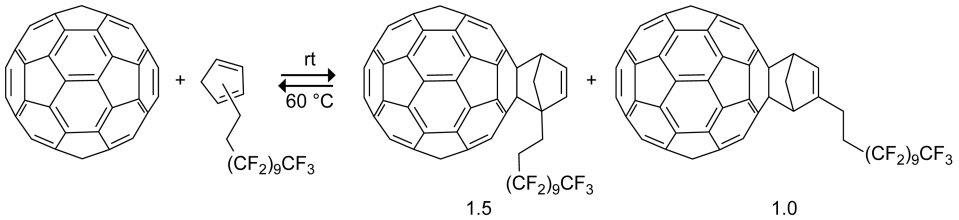
Scheme 45.

Thermally Reversible Diels–Alder Reaction of C_{60} to a Cyclopentadiene-Functionalized Silica Gel for Purification.[190]



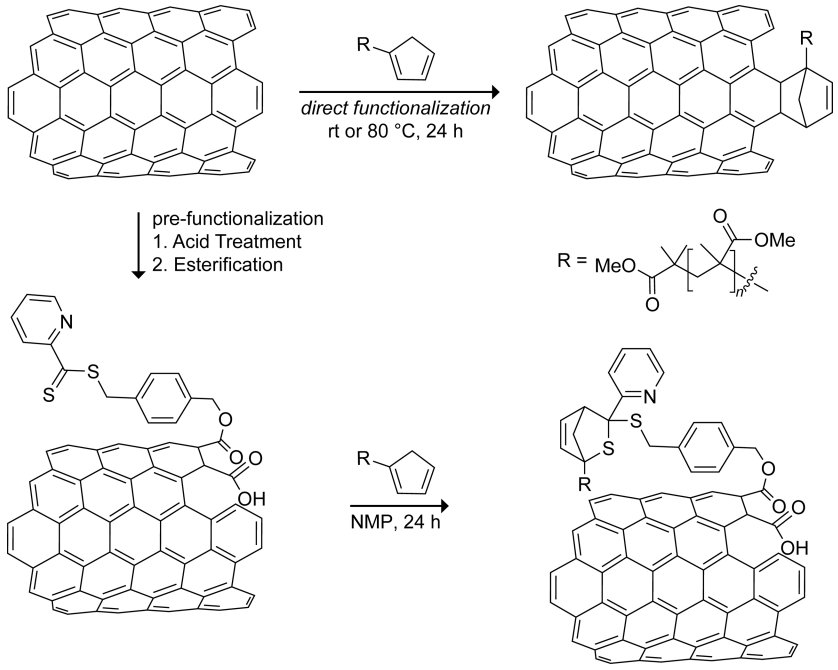
Scheme 46.

Reversible Diels–Alder reaction of a Cyclopentadiene-Functionalized Merrifield resin with C_{60}.[192,193]



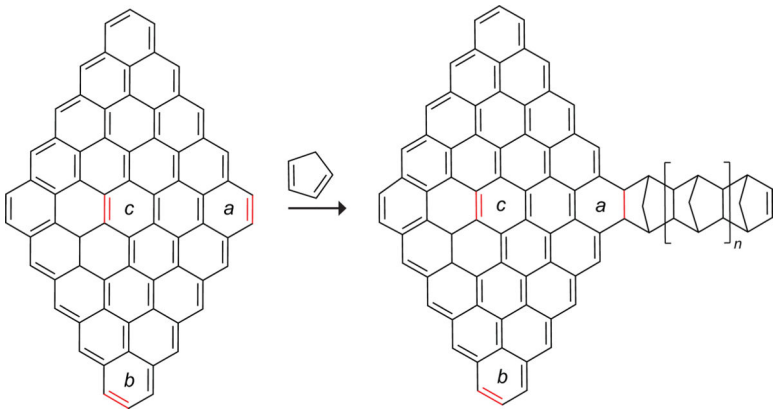
Scheme 47.

Functionalization of C_{60} with a Cyclopentadiene Bearing a Fluorinated Side Chain.[202]



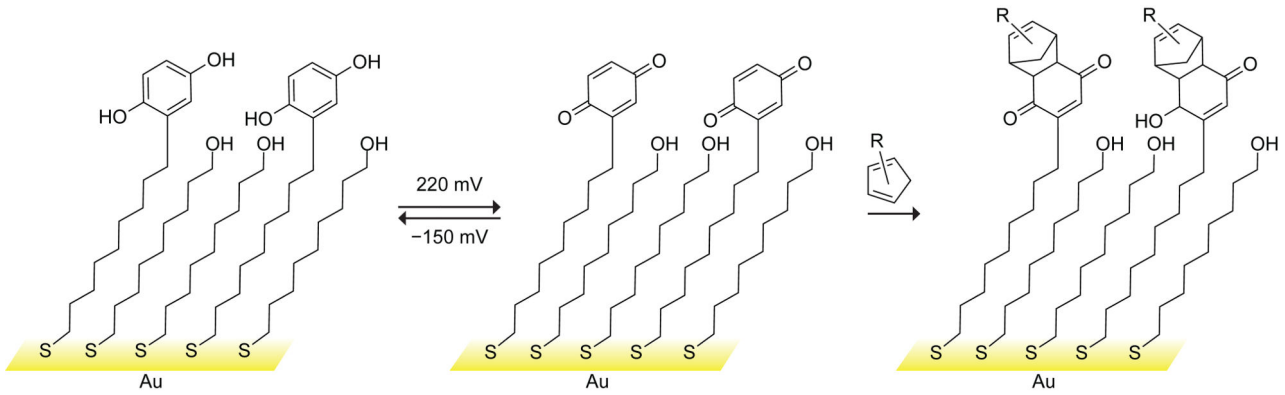
Scheme 48.

Direct Functionalization and Prefunctionalization of a Carbon Nanotube with Cyclopentadiene-Capped Polymers.[209,211]



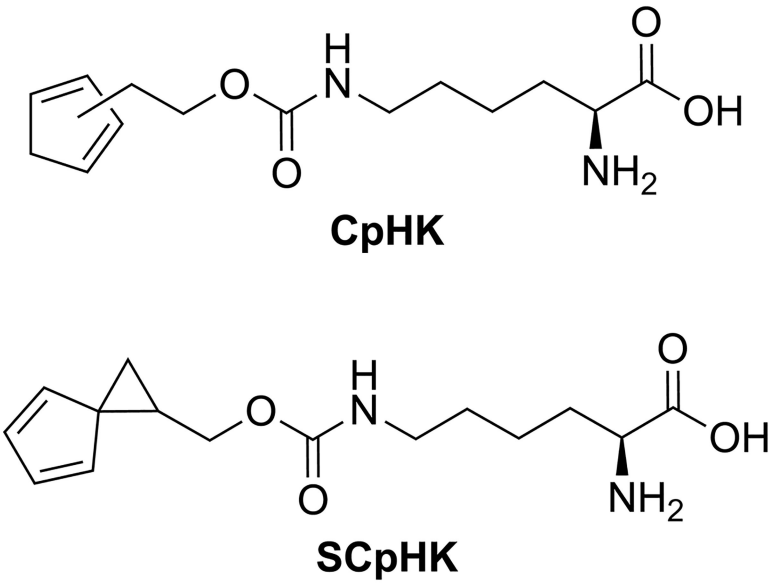
Scheme 49.

5 × 5 Graphene Model Showing the Selectivity of the Cyclopentadiene Diels–Alder Reaction across Bond ‘a’ on the Surface of Graphene.[220]

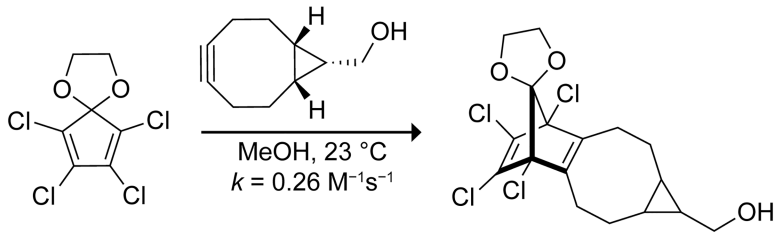


Scheme 50.

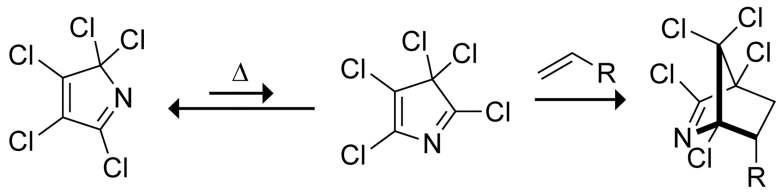
Reversible Electrochemical Oxidation of a Hydroquinone-Functionalized Surface to 1,4-Benzoquinone, Which Can Then React with Cyclopentadiene.[228]



Scheme 51.
Noncanonical Cyclopentadiene-Derived Amino Acids CpHK and SCpHK.[234–236]

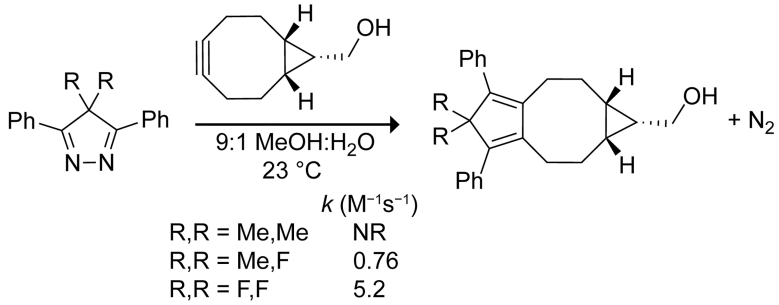


Scheme 52.
Rate Constant for the Diels–Alder Reaction of TCK with BCN.[248]



Scheme 53.

Diels–Alder Reaction of 1,3,4,5,5-Pentachloro-2-azacyclopentadiene Formed from the Thermal Isomerization of 2,3,4,5,5-Pentachloro-1-azacyclopentadiene.[252–254]



Scheme 54.

Rate Constants for the Diels–Alder Reactions of 4,4-Dimethyl-3,5-Diphenyl-4*H*-Pyrazole (DMP), MFP, and DFP with BCN.[261,262]

Table 1.

Rate Constants and Related Parameters for the Diels–Alder Reactions of Cyclopentadiene, 1,3-Cyclohexadiene, 1,3-Cycloheptadiene, and Butadiene with Tetracyanoethylene (TCNE) at 20 °C in CH_2Cl_2.[10]

				
k ($M^{-1}s^{-1}$)	3.6×10^{3}	1.4	4.3×10^{-3}	1.7×10^{-3}
k_{rel}	1	1/2600	1/820,000	1/2,100,000
HOMO (eV)	−8.52	−8.25	−8.09	−9.03
C1–C4 (Å)	2.36	2.82	3.15	—