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[3+2] versus [4+3] cycloaddition of conjugated dienes to TMM diradicals

Wade A. Russu, Veronica P. Villalon, Vivian R. Wang, James A. Miranda and R. Daniel Little*

Department of Chemistry and Biochemistry, University of California Santa Barbara, Santa Barbara, CA 93106, USA

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Abstract—Conjugated dienes preferentially undergo intramolecular [3+2] cycloaddition to TMM diradicals. Subsequent sigmatropic rearrangement of affords products corresponding to those expected from a direct [4+3] path.

2-Alkylidenecyclopentane-1,3-diyls **1**, first explored in Berson's laboratory, are well established as partners in [3+2] cycloadditions.[1] In 1970, Dowd et al. reported that the parent diyl, trimethylenemethane (**2**, TMM), reacts with 1,3-butadiene to form a [3+2] cycloadduct via a 1,2-addition to the diene;[2] a [4+3] adduct was not reported. While [4+3] cycloaddition to TMM diyls is a rarity, the Trost organopalladium analog of the parent system, **3**, undergoes [4+3] cycloaddition to electron deficient *s-cis* constrained 1,3-dienes in good to excellent yields (Fig. 1).[3]

In 1978, Berson and co-workers showed that diyl **4** reacts with the *s-cis*-constrained diene, cyclopentadiene, to afford *both* the [3+2] adduct **5** as well as the bridged product **6** resulting from 1,4- rather than 1,2-addition to the diene (Scheme 1).[4] These results are in accord with a frontier molecular orbital (FMO) analysis for a symmetry allowed suprafacial–suprafacial cycloaddition between the diene and a closed shell singlet diyl whose HOMO is represented by the symmetric orbital Ψ_S. Reversal of that ordering leads to the opposite prediction. That is, if Ψ_A is the HOMO, then one would anticipate the formation of the 1,2-bridged and the 1,4-fused adducts as illustrated in Scheme 1.

For some time we have been interested in the phorbol esters and structurally related biomaterials that possess a 5-7-6 fused ring system (cf **19**, $n=2$, Scheme 5).[5] Realizing that an intramolecular [4+3] cycloaddition to a TMM diyl **7** (Fig. 2) could provide direct access to the framework, we initiated the studies described

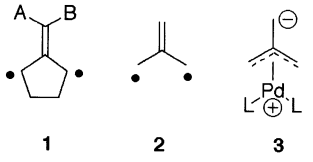
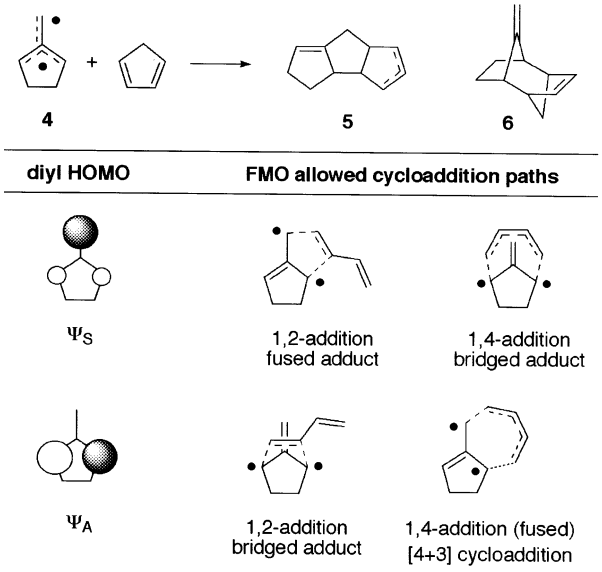


Figure 1.



Scheme 1.

Keywords: [3+2] and [4+3] cycloaddition reactions; TMM diradicals; sigmatropic rearrangement.

* Corresponding author. Tel.: 805-893-3693; fax: 805-893-4120; e-mail: little@chem.ucsb.edu

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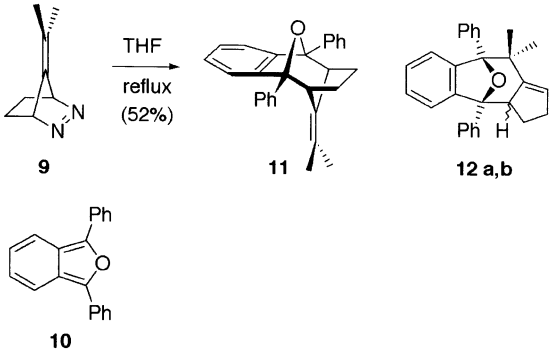
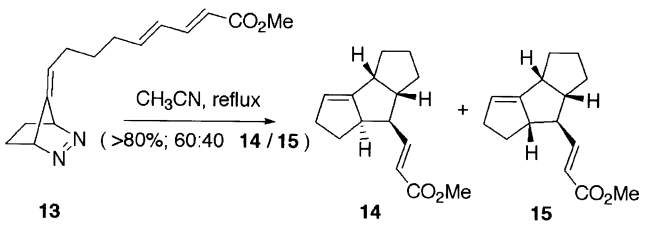
herein. We report the results of an investigation of the intermolecular cycloaddition of TMM-diyl precursor **9** with an *s-cis* constrained diene, 1,3-diphenylisobenzofuran (**10**) and the *intra*molecular cycloaddition chemistry of the diyl derived from diazene **13** with an unconstrained 1,3-dienes (Schemes 2 and 3). Two points emerge: (1) the [3+2] pathway illustrated by **8** (Fig. 2), dominates when an unconstrained 1,3-diene is used as the diylophile; (2) transformation of the [3+2] adduct to that expected from a direct [4+3] cycloaddition can be achieved via sigmatropic rearrangement (Scheme 4).

When a THF solution of the dimethyl diazene **9** is added dropwise to a ten-fold excess of 1,3-diphenylisobenzofuran (**10**) in refluxing THF, cycloaddition occurs to afford nearly equivalent quantities of 1,4-addition products. Three products, isolated in a combined yield of 46–52%,[6] were determined to have the structures **11** and **12a**,**b**.[7] Structures **12a**,**b** constitute our first observation of [4+3] cycloaddition.[2,4] The formation of **11** is consistent with a diyl-HOMO controlled cycloaddition (see Scheme 1), while the production of **12a**,**b** is not. That the FMO-allowed 1,2-addition pathway (Scheme 1) was not observed is not surprising. Thus unlike the 1,4-path, it would fail to establish a 6π electron aromatic unit in the anticipated product.

In contrast to **10**, the *use of an unconstrained 1,3-diene* could afford either the [3+2] or [4+3] cycloaddition pathways, or both.[8] When heated in refluxing acetonitrile, diazene **13** was transformed to a 60:40 mixture of diastereomeric [3+2] cycloadducts **14** and **15** in a combined yield of >80%.[9] Less than 2% of the [4+3] pathway leading directly to **16a** (see Scheme 4) was observed. Nevertheless, the desired framework did prove to be readily accessible (vide supra).



Scheme 2.



Scheme 3.

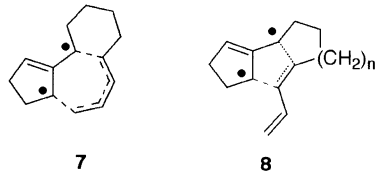
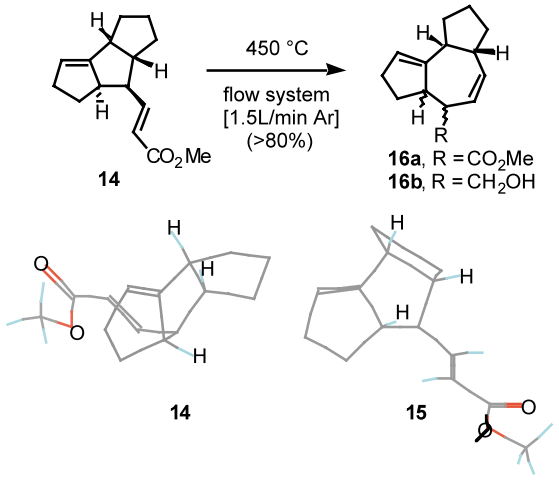


Figure 2.

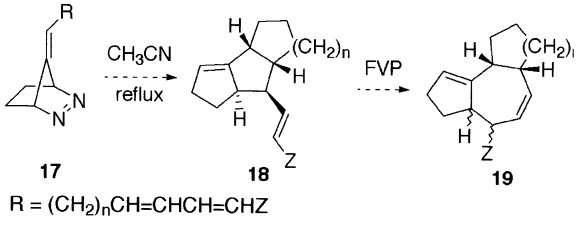


Scheme 4.

When **14** and **15** were passed through a heated tube (Ar carrier gas, 450°C), the *cis-anti* isomer **14** rearranged to afford **16a** (Scheme 4), a substance that was characterized as the alcohol **16b** formed by treating **16a** with LAH.[10] Formally, **16a** corresponds to the result of either a [1,3], or a [3,3] sigmatropic rearrangement of **14**, and is the substance one would have expected from a direct [4+3] cycloaddition to the diyl generated from **13**.

In contrast to **14**, the *cis-syn* isomer **15** was recovered unchanged from the flow pyrolysis (FVP). This difference in behavior is reasonable when one takes into account the differing geometries of the two systems. As illustrated in Scheme 4 by the energy-minimized structures,[11] the terminal carbons of the 1,5-diene of the *cis-anti* form, **14**, but not the *cis-syn* isomer, **15**, are well positioned for a concerted [3,3] sigmatropic rearrangement.

Based upon the results reported herein, we suggest that the simple two-step protocol outlined in Scheme 5 will



Scheme 5.

be generalizable and that it will provide reasonably direct access to wide array of tricyclic substances. Further studies employing more elaborately functionalized diyl precursors are in progress. Our application of the chemistry to the synthesis of bioactive materials will be reported in due course.

Acknowledgements

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6. As the ratio of diylophile to diazene decreases from 10:1 to 3:1 to 1:1, the amount of diyl dimerization increases.
7. Bridged isomer **11**: ^{1}H NMR (400 MHz) δ 1.20 (m, CH_2), 1.53 (s, $C(CH_3)_2$), 3.62 (m, bridgehead), 6.95 (m, Ar), 7.04 (m, Ar), 7.35 (t, Ar), 7.47 (t, Ar), 7.73 (dd, Ar); ^{13}C NMR (100 MHz) δ 20.0, 28.2, 50.3, 88.9, 118.9, 121.8, 125.3, 125.8, 126.9, 128.2, 137.1, 143.4, 148.9. HETCOR confirms the structural assignment. Fused isomers **12a**,**b**. The fused isomers proved inseparable; the data, therefore, refers to the mixture of diastereomers. ^{1}H NMR (400 MHz) δ 1.10 (s, CH_3), 1.17 (s, CH_3), 1.27 (m, CH_2), 1.56 (s, CH_3), 2.07 (m, allylic), 3.38 (m, bridgehead), 5.62 (m, vinyl), 7.09 (m, Ar), 7.28 (m, Ar), 7.44 (m, Ar), 7.76, (d, Ar), 7.90 (d, Ar); ^{13}C NMR (100 MHz) δ 28.2, 29.2, 29.4, 33.4, 51.3, 119.7, 123.5, 124.7, 125.5, 125.7, 125.2, 126.6, 126.7, 127.3, 127.8, 127.9.
8. For an overview of the route used to synthesize diazenes like **13**, see: Little, R. D. *Chem. Rev.* **1996**, *96*, 93–114.
9. Diazene **13**: ^{1}H NMR ($CDCl_3$) δ 7.26 (dd, 1H, J=12, 16 Hz), 6.19–6.03 (m, 2H), 5.82 (d, 1H, J=16 Hz), 5.36 (s, 1H), 5.13 (s, 1H), 5.09 (t, 1H, J=8 Hz), 3.75 (s, 3H), 2.12 (dd, 2H, J=8, 12 Hz), 2.05–1.94 (m, 2H), 1.66–1.63 (m, 2H), 1.48 (tt, 2H, J=6, 8 Hz), 1.12 (d, 2H, J=8); ^{13}C NMR ($CDCl_3$) δ 167.6, 145.4, 145.1, 143.7, 128.9, 119.2, 116.8, 76.9, 72.7, 51.5, 32.1, 28.4, 28.3, 21.5, 21.1; FTIR (neat, NaCl) 3053, 2990, 1708, 1427, 1268, 911 cm^{-1}.
cis-anti and *cis-syn* Isomers, **14** and **15**: ^{1}H NMR ($CDCl_3$). For **14**: δ 7.00 (dd, 1H, J=8, 16 Hz), 6.73 (dd, 1H, J=8, 16), 5.74 (d, 1H, J=16 Hz), 5.28 (br m, 1H), 3.72 (s, methyl), 3.32 (m, 1H); alkane region 2.87 (m, 2H), 2.54 (m, 4H), 1.92 (m, 2H), 1.64 (m, 2H), 1.39 (m, 2H). For **15**: δ 7.06 (dd, 1H, J=8, 16 Hz), 6.98 (dd, 1H, J=8, 16 Hz), 5.80 (d, 1H, J=16 Hz), 5.21 (m, 1H), 3.74 (s, methyl), 3.53 (m, 1H), alkane region 3.05 (m, 2H), 2.74 (m, 4H), 2.27 (m, 2H), 2.08 (m, 2H), 1.82 (m, 2H).
10. Ring expanded adduct, **16b**: ^{1}H NMR ($CDCl_3$) δ 5.56 (m, 1H), 5.43 (m, $1H_a$), 5.32 (ddd, 1H, J=2.5, 5, 10 Hz) 3.72 (d, 2H, J=7.7 Hz), 2.94 (m, 1H), 2.90 (m, 1H), 2.83 (br s, OH), 2.70 (m, 1H), 2.19 (m, 2H), 1.98 (m, 1H), 1.86, (m, 2H), 1.77–1.65 (m, 2H), 1.50–1.20 (m, 4H). FTIR (neat, NaCl) 3433, 3054, 2987, 1265 cm^{-1}.
11. Minimization was achieved using Chem 3D Pro (illustrations shown) as well as Spartan 2002 software.