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Contrasting Diastereofacial Selectivity Associated with *N*-Phenyltriazolinedione Cycloadditions to Oxaspirocycloheptatrienes

Leo A. Paquette,* Peter Webber, and Iain Simpson

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

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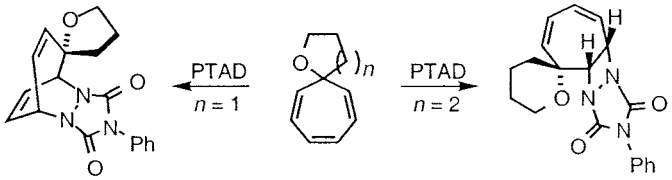
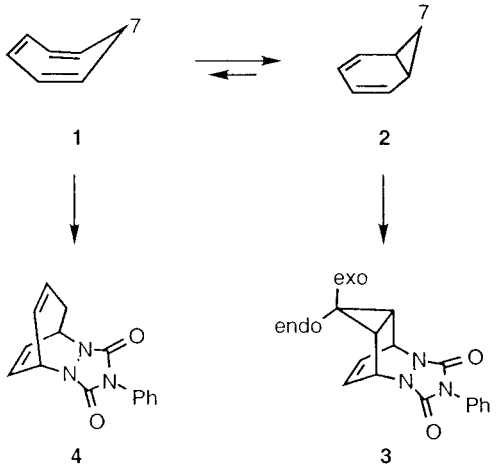
ABSTRACT



The cycloaddition of *N*-phenyltriazolinedione to a pair of spirocyclic cycloheptatrienes featuring a tetrahydrofuran or tetrahydropyran ring is shown to proceed with opposite π-facial stereoselectivity. In addition, the furan undergoes direct [4+2] cycloaddition to the cycloheptatriene whereas the pyran product is a diazetidine.

The symmetry-allowed interconversion of cycloheptatriene (**1**) with norcaradiene (**2**) forms the basis of one of the more exciting early chapters in the evolution of our appreciation for valence isomerization.[1] Substitution with a pair of powerful electron-withdrawing groups (CN, CF_3) at C-7 has the consequence of shifting this equilibrium to the right.[2] Although the situation is much less biased in 7-monosubstituted examples (CN, CO_2CH_3, CHO, OCH_3, C_6H_5), these systems enter into [4+2] cycloaddition with *N*-phenyltriazolinedione (PTAD) with formation of the exo adduct **3**. Only in the cyano example is the isomer having an endo substituent also produced.[3] The small size and linear nature of CN are considered responsible.

Although the kinetic preference for dienophile capture by **2** can be understood in terms of the heightened coplanarity of the conjugated double bonds in the bicyclic tautomer, important exceptions have been uncovered. For example, 7,7-difluorocycloheptatriene and the 1,3-dioxolane derivative of tropone react with PTAD to give **5** and **6**, respectively.[4] In



contrast, 7,7-dimethoxycycloheptatriene and the 1,3-dioxolane homologue cycloadd via their norcaradiene tautomer and lead to **8** and **9**.[4] The possible impact of constraining the external angle at C-7 has long been recognized. Thus,

(1) Maier, G. *Valenzisomerisierungen*; Verlag Chemie: Weinheim/Bergstr., Germany, 1972.

(2) (a) Ciganek, E. *J. Am. Chem. Soc*. **1965**, *87*, 652. 1149. (b) Ciganek, E. *J. Am. Chem. Soc*. **1967**, 1454. (c) Staley, S. W.; Fox, M. A.; Cairncross, A. *J. Am. Chem. Soc*. **1977**, *99*, 4524.

(3) (a) Adam, W.; Balci, M. *J. Org. Chem*. **1979**, *44*, 1189. (b) Adam, W.; Balci, M.; Pietrzak, B. *J. Am. Chem. Soc*. **1979**, *101*, 6285.

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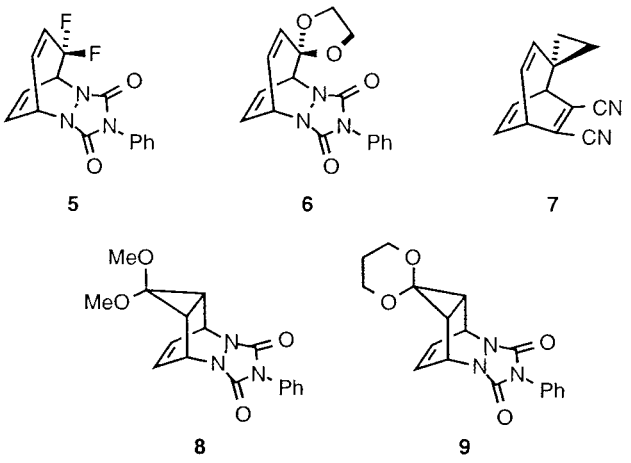
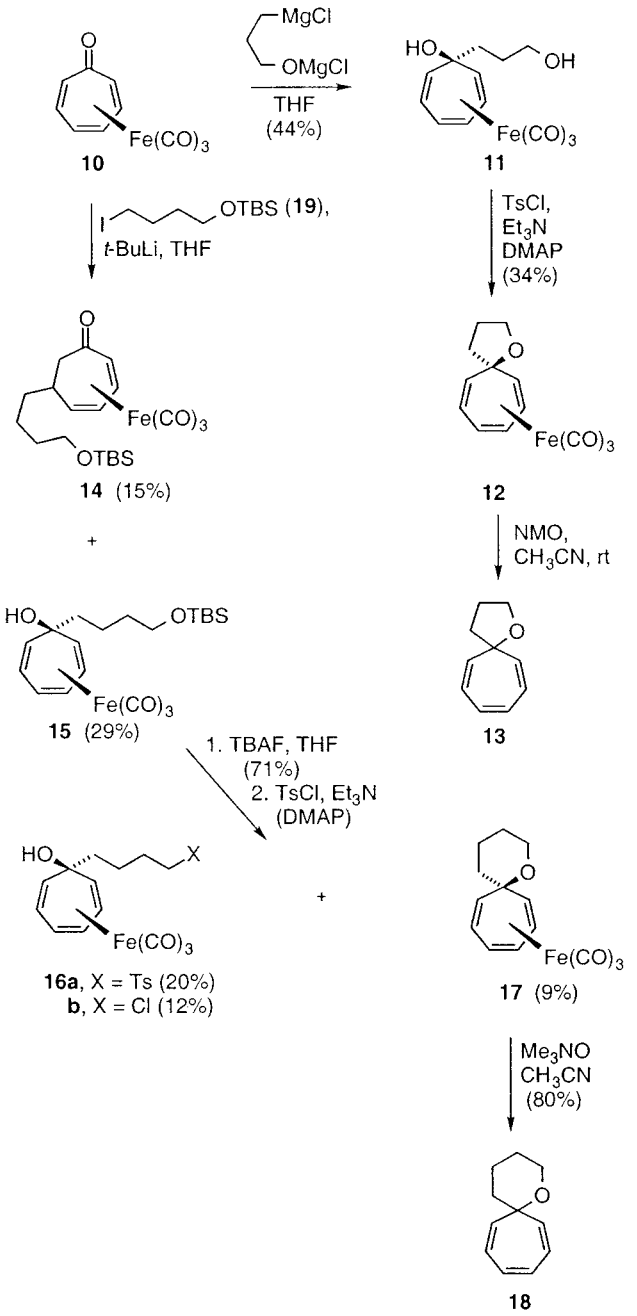
spiro(2,6)nona-4,6,8-triene enters into reaction with dicyanoacetylene to generate **7** in order to skirt the development of a spiropentane part structure.[5] Although stereoelectronic arguments have been offered in explanation of the differing pathways adopted along the routes to **6** and **9**,[4] the possibility that ring strain effects may be responsible remains unanswered. Additionally, the molecular symmetry associated with the precursors to **5**−**9** precludes simultaneous assessment of possible π-facial diastereoselectivity as the PTAD reagent approaches. If the cycloheptatriene is the more reactive partner in the equilibrium, the issue is one of the preferred dienophile approach to one or the other π-surface while ring inversion operates rapidly. The involvement of a norcaradiene tautomer is somewhat more complicated in that two bicyclic isomers now vie competitively for participation in the Diels−Alder reaction.



These defining mechanistic alternatives led us to develop synthetic routes to **13** and **18** as outlined in Scheme 1. The complementary reaction pathways take advantage of the fact that tricarbonyl(tropone)iron (**10**), unlike the uncomplexed ketone,[6] is amenable to 1,2-addition by various organometallic reagents.[7] In the first instance, diol **11** was obtained in 44% yield following the exposure of **10** to the Normant reagent[8] in THF solution. The chromatographically sensitive intermediate so obtained experienced direct cyclization to **12** when subjected to tosylation. This iron complex was in turn successfully converted to **13** by oxidation with NMO in acetonitrile at room temperature. To facilitate matters, the highly volatile spirocyclic tetrahydrofuran was handled as a concentrate in CH_3CN.

To reach **18**, the tropone complex **10** was first treated with the lithiated form of iodide **19**.[9] This protocol gave rise to a separable 2:1 mixture of **14** and **15**. Following fluoride ion-induced cleavage of the silyl ether functionality to generate the homologue of **11**, the resulting diol proved to be less conducive to cyclization when tosylated as before. Thus, it now proved possible to isolate monotosylate **16a** and chloro alcohol **16b** in addition to **17**. All attempts to promote the independent conversion of **16a** and **16b** to the spiropyran were not encouraging. However, the decomplexation of **17** to give **18** proceeded readily.

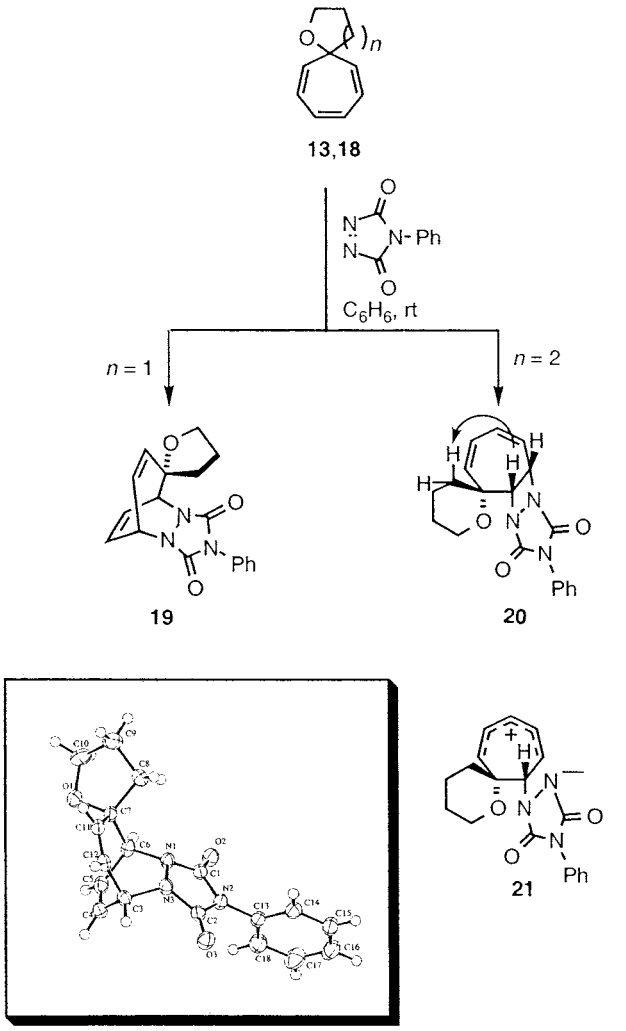
Scheme 1



The reactivity levels of **13** and **18** toward PTAD are sufficiently low that the cycloadditions were performed in benzene at room temperature. In both examples, a characterizable product was isolated in low (9−40%) yield[10] (Scheme 2). Proton and carbon NMR analysis revealed

(4) Welt, G.; Wolf, E.; Fischer, P.; Fohlisch, B. *Chem. Ber*. **1982**, *115*, 3427.
(5) (a) Jones, M., Jr.; Petrillo, E. W., Jr. *Tetrahedron Lett*. **1969**, 3953. (b) Rostek, C. J.; Jones, W. M. *Tetrahedron Lett*. **1969**, 3957.
(6) Rigby, J. H. *Studies in Natural Products Chemistry, Stereoselective Synthesis (Part A)*; ur-Rahman, A., Ed.; Elsevier: Amsterdam, The Netherlands, 1988; Vol. 1, pp 545−576.
(7) Rigby, J. H.; Ogbu, C. O. *Tetrahedron Lett*. **1990**, *31*, 3385.
(8) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett*. **1978**, 3013.
(9) Harusawa, S.; Tomii, S.; Takehisha, C.; Ohishi, H.; Yoneda, R.; Kurihara, T. *Chem. Pharm. Bull*. **1992**, *40*, 2279.

Scheme 2

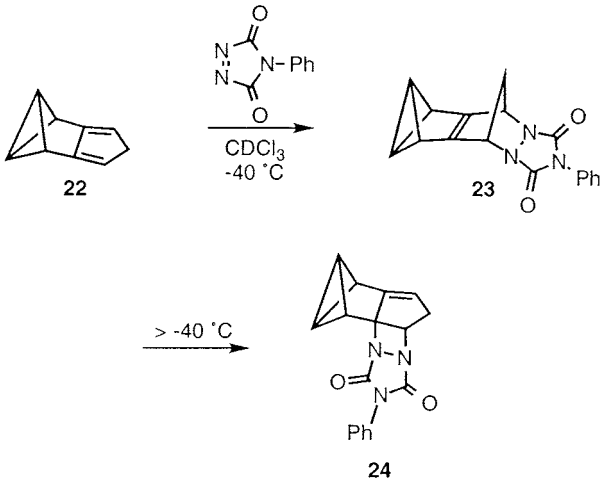


neither to be symmetrical, thereby ruling out the involvement of norcaradienes in these reactions. The similarity of the spectral features of **19** to those of **5** and **6** defined the structural framework. Corroboration of this conclusion and definition of the spirocyclic stereochemistry were arrived at by X-ray crystallography. As illustrated in the inset, **19** is the result of direct [4+2] cycloaddition syn to the methylene group and anti to the oxygen.

At temperatures of 0 °C or below, no reaction was observed in either case, thereby ruling out the possible execution of control experiments. Constant monitoring of the room temperature reactions showed that considerable baseline material was produced as the addition products **19** and **20** were being generated. No other products were detected by this means. This includes a [4+2] cycloadduct derived from **18**.

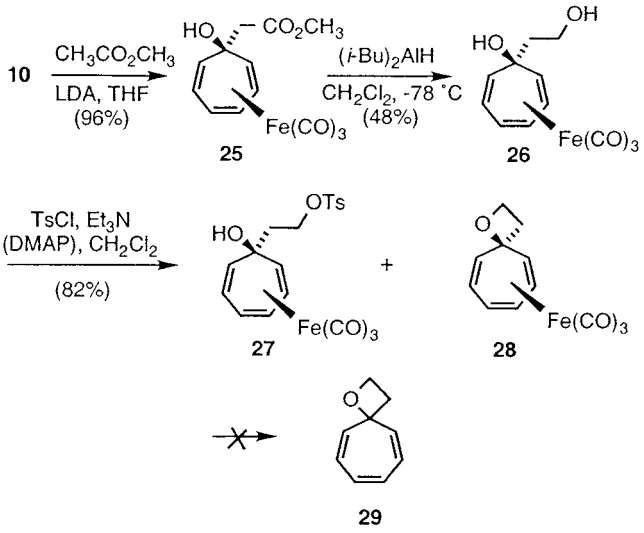
Assignment of the ^{1}H and ^{13}C NMR spectra of **20** was based on COSY and HMQC data. The strong NOE effect derived from its NOESY spectrum established the formation of a [2+2] cycloadduct, with bonding to the PTAD now occurring from the direction syn to oxygen. The formation of **20** may be mediated by initial generation of the zwitterionic intermediate **21**. The capacity of **21** for cyclization to the diazetidine gains support from the recent observation by the Christl group of the isomerization of **23** to **24** (Scheme 3).[11]

Scheme 3



The contrasting reaction pathways adopted by **13** and **18** prompted examination of a viable synthetic route to spiro oxetane **29**. In this connection, the addition of methyl lithioacetate to **10** was found to proceed very smoothly, giving rise to **25** in 96% yield (Scheme 4). Dibal-H reduction

Scheme 4



of **25** to diol **26** and formation of monotosylate **27** could be reduced to practice with minimal complications. From this point on, we were able to isolate the very labile **28** in low yield by the direct cyclization of **27**. However, target molecule **29** evaded isolation either by processing **28** or by prior decomplexation of **27** to the free ligand. This particular end-product gave evidence of high instability, a property that

may stem from strain-facilitated opening to a dipolar tropylium ion pair.

Rationalization of the sole production of diazetidine **20** is a bit too complex for a ready computational explanation. The involvement of a charged intermediate such as **21** is a reasonable assumption. However, to ascertain the feasibility of its generation and ultimate fate in the two systems under scrutiny would require a very substantial calculation involving a good solvent model to support the zwitterion. We leave the pursuit of these objectives to others.

Without doubt, a number of different factors are capable of influencing the facial selectivity of cycloaddition reactions in general. Secondary orbital interactions, orbital tilting, torsional effects, and steric factors are representative.[12] The present study reveals that molecules having higher levels of unsaturation and a more extensive array of mechanistic pathways available to them are capable of reflecting a wider range of intriguing alternatives.

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Supporting Information Available: Experimental procedures and spectral characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Comparably low yields have been observed for a number of cycloadditions involving PTAD. See, for example: Paquette, L. A.; Wells, G. J.; Wickham, G. *J. Org. Chem*. **1984**, *49*. 3618.

(11) Fischer, T.; Kunz, U.; Lackie, S. E.; Cohrs, C.; Palmer, D. D.; Christl, M. *Angew. Chem., Int. Ed*. **2002**, *41*, 2969.

(12) Fallis, A. G.; Lu, Y.-F. *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press Inc.: Greenwich, CT, 1993; Vol. 3.