Transition Metal-Catalyzed Intramolecular [4 + 2] Cycloadditions: Initial Studies on Stereochemistry and on Stereo and Vitamin D Analog Syntheses

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The nickel(I)-catalyzed intramolecular [4 + 2] cycloaddition between dienes and unactivated π-systems has been shown to be an efficient complement to the uncatalyzed (Diels–Alder) reaction.1 Several representative examples have now been reported1 for which the latter reaction fails, or proceeds only slowly, even at elevated temperatures, while the former occurs efficiently and rapidly, often at room temperature. Notwithstanding the synthetic and operational advantages of the catalyzed cycloaddition, its full utilization in synthesis has been limited by the unknown relationship between the geometry of the starting diene and the stereochemistry of the cycloadduct. We describe herein the first study of this stereochemical feature of the nickel(I)-catalyzed intramolecular cycloaddition. Developed in the context of a strategy for the synthesis of steroids and vitamin D analogs, this study also furnishes the first solution to a problem previously encountered in attempts to apply this metal-catalyzed cycloaddition to the synthesis of bicyclic systems bearing an angular methyl group, a prominent feature of numerous natural and non-natural polyycles.2 The stereochemical course of the nickel(I)-catalyzed [4 + 2] cycloaddition was initially explored with the E,E- and E,Z-dienynes 1 and 3. With a typical nickel(I) catalyst, prepared by the reduction of Ni(acac)2 with Et2AlC1 in the presence of triis(hexafluoropropyl)phosphite,4 the E,E-dienyne 1 underwent stereocontrolled cycloaddition to produce only cycloadduct 2. Under the same conditions, the E,Z-dienyne 3 provided the stereo-complementary cycloadduct 4 in similar yield.5 Thus, while proceeding through a multistep pathway, the
catalyzed cycloaddition retains the stereochemical advantages of the concerted Diels–Alder process. A mechanism which accommodates the observed retention of stereochemistry in these reactions is given in Scheme 1. According to this sequence, initial syn selective oxidative addition would lead to the α-allyl complexes 5 and 6. Subsequent rotation of the styrly group from an exo to an endo orientation as required for formation of the α-allyl complexes 5′ and 6′ and reductive elimination with retention would provide a path to the cycloadducts in which stereochemical crossover is avoided.

Implicit in the above mechanistic hypothesis is the expectation that the size of the diene group (R) destined to become an angular substituent in the cycloadduct would have a less pronounced steric effect on the cycloaddition of an E,Z-diene relative to that of the corresponding E,E-isomer (e.g., 6′ vs 5′, respectively). The significance of this analysis arises from the previous finding6 that E-dienes bearing a methyl group (e.g., R = CH3 in Scheme 1) did not undergo metal-catalyzed cycloaddition, apparently precluding the application of this process to the synthesis of polycycles bearing angular methyl groups. The Z-isomer was not tested. However,

New results have been obtained on the synthesis of steroid and vitamin D analogs. The utility of the reaction of dienynes 14 in the presence of a catalyst which proceeds with a half-life of 109 h at 175 °C to provide only decomposition products. The stereochemistry of cycloadduct 15 was confirmed by its conversion to the steroid ketone 22, which was correlated with 8α-isoestradiol, 17β-acetate, 3-methyl ether, a known derivative of equilenin.

In summary, this study demonstrates that the stereochemistry of the diene component in nickel(0)-catalyzed dienynye cycloadditions is retained during the course of the reaction, even though the process involves multiple steps. In addition, it is shown that cycloadditions of methyl substituted Z-alkenes can be used to produce products containing angular methyl groups. Of further synthetic and mechanistic consequence, the cycloadditions of substrates with allylic substituents are found to occur with exceptional diastereoselectivities, as illustrated in a preliminary study of the utility of this process in the synthesis of steroid and vitamin D analogs.

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Supplementary Material Available: IR, NMR, and mass spectrometry data for compounds 1-4, 9a, 9b, 10a, 10b, 14, and 15 (6 pages).

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(9) Using Ni(cod)2 and in situ reduction with EtAlCl2 as the source of Ni(0) gave a lower yield (68%) for this particular transformation.

(10) As an added structural proof NOE experiments on a variant of 15 (MOM group replaced by TBS) showed a 4.4% enhancement of the o-hydrotgens of the ary1 ring when the angular methyl group was irradiated. This data suggests a syn relationship between these two groups. Stereochemical assignments for 10a and 10b were made by analogy to 15.

(11) Reduction products 16 and 17 were separated as their acetate derivatives 18 and 19. The former was converted to 22 by selective removal of the MOM ether by B-cromo catechol borane (Boeckman, K. R.; Potenza, J. C. Tetrahedron Lett. 1990, 26, 1411), oxidation, and Friedel-Crafts cyclization of the acid chloride (Johnson, W. S.; Glenn, H. J. J. Am. Chem. Soc. 1948, 72, 1199).

(12) Hydrogenolysis of 22 using the original conditions of Johnson (Johnson, W. S.; Christiansen, R. G.; Ireland, R. F. J. Am. Chem. Soc. 1987, 79, 10, 1965) gave the known steroid (rae-choi-isoestriadiol), 17α-acetate, 3-methyl ether (Ruffer, C. L.; Schröder, E.; Giblin, H. Liebigs Ann. Chem. 1967, 705, 211). Catalytic hydrogenation of equilin methyl ether (Sigma) gave a 1:1 mixture of 5α-isoestrone methyl ether and the B-ring aromatized product, equilenin, from which a small amount of the first component was isolated in pure form after medium-pressure column chromatography. The known NaBH4 reduction of this steroid ketone afforded the 17β alcohol (Smith, H. et al. J. Med. Chem. 1966, 9, 3332). Acetylation gave 5α-isoestriadiol, 17β-acetate, 3-methyl ether. The two isouestriol derivatives, both isolated from different sources, had identical "H-NMR spectra, IR spectra, and high-resolution mass spectrometry fragmentation patterns. A 1:1 mixture co-eluted on GC.