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

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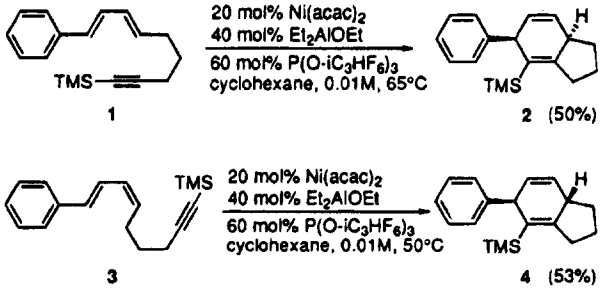
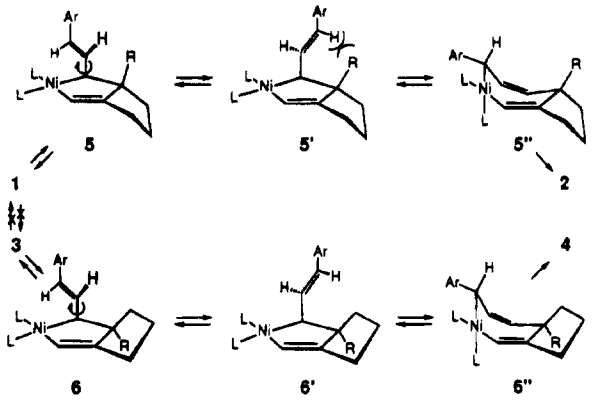
The nickel(0)-catalyzed intramolecular [4 + 2] cycloaddition between dienes and unactivated π-systems has been shown to be an efficient complement to the uncatalyzed (Diels–Alder) reaction.[1] Several representative examples have now been reported[1] for which the latter reaction[2] fails, or proceeds 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(0)-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 polycycles.[3]

The stereochemical course of the nickel(0)-catalyzed [4 + 2] cycloaddition was initially explored with the *E,E*- and *E,Z*-dienynes **1** and **3**. With a typical nickel(0) catalyst, prepared by the reduction of $Ni(acac)_2$ with Et_2AlOEt in the presence of tris(hexafluoro)isopropyl 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 stereocomplementary 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 σ-allyl complexes **5** and **6**. Subsequent rotation of the styryl group from an exo to an endo orientation as required for formation of the σ-allyl complexes **5″** and **6″** and reductive elimination with retention would provide a path to the cycloadducts in which stereochemical crossover is avoided.

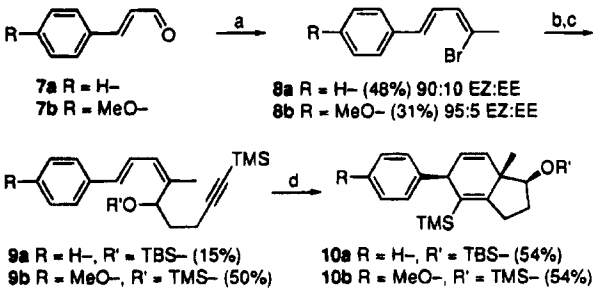


Implicit in the above mechanistic hypothesis is the expectation that the size of the diene group (R) destined to become an angular substituent in the cycloadduct would have a less pronounced steric effect on the cycloaddition of an *E,Z*-diene relative to that of the corresponding *E,E*-isomer (*e.g.*, **6′** vs **5′**, respectively). The significance of this analysis arises from the previous finding[1] that *E*-dienes bearing a methyl group (e.g., R = CH_3 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,

Scheme 1



Scheme 2



Reaction Conditions: (a) $Ph_3P^+CBr_2CH_3\ Br^-$, *t*-BuLi, THF, -78°C, inverse addition; (b) i. *t*-BuLi, THF, -78°C; ii. $MgBr_2$, Et_2O, PhH; iii. 5-trimethylsilyl-4-pentynal; (c) TBSOTf or TMS-imid; (d) 20 mol% $Ni(acac)_2$, 40 mol% Et_2AlOEt, 60 mol% $P(O\text{-}iC_3HF_6)_3$, cyclohexane, 0.01M, 80°C

(1) For the original work on intramolecular diene–diene and diene–alkyne cycloadditions, see: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6433. For more recent extensions to diene–alkene and diene–allene cycloadditions and other metal catalysts, see: Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145.

(2) For reviews of the intramolecular Diels–Alder reaction, see: Roush, W. R. In *Advances in Cycloaddition*; D. P., Curran, Ed.; JAI: Greenwich, 1990; Vol. 2, pp 91–146. Fallis, A. G. *Can. J. Chem. Soc.* **1984**, *62*, 183–234 and Ciganek, E. *Org. React.* **1984**, *32*, 1.

(3) Devon, T. K.; Scott, A. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972; Vol. 2 *Terpenes*.

(4) For the electronic and steric parameters of this versatile ligand, see: Van Leeuwen, P. W. N. M; Roobeek, C. F. *Tetrahedron* **1981**, *37*, 1973. For the best synthetic preparation, see: Sakatsume, O.; Yamane, H.; Takaku, H.; Yamamoto, N. *Nucleic Acids Res.* **1990**, *18*, 3327.

(5) Stereochemical assignments were made based on the characteristic homoallylic coupling of 1,4 cyclohexadienes (Rabideau, P. W., *Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*, VCH: New York, 1989 and references therein). **2**: $J_{1,4}$ cis = 9.07 Hz. **4**: $J_{1,4}$ trans = 5.28 Hz. In addition, treatment of both **2** and **4** with DDQ provided identical aromatic products.

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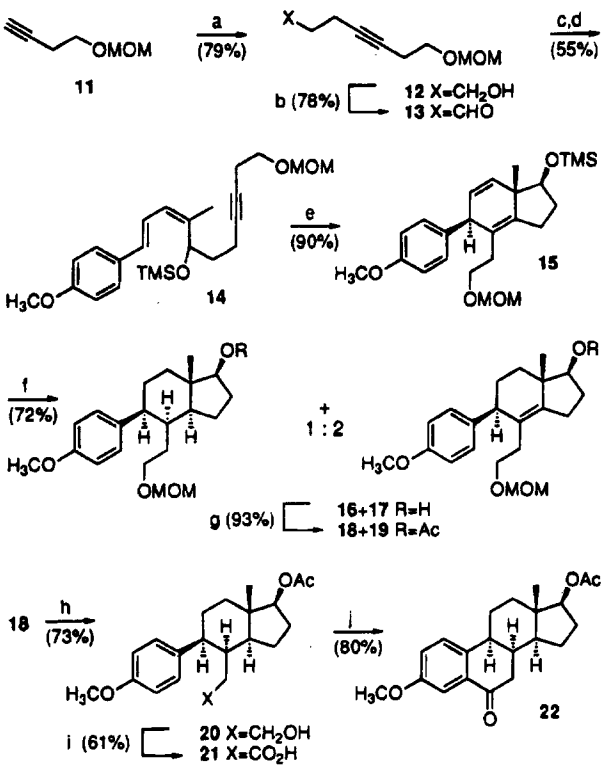
Scheme 3



Reaction Conditions: (a) EtMgBr, PhH, 0°C–rt, oxetane, reflux; (b) Swern; (c) **8b**, *t*-BuLi, THF, -78°C, ii. $MgBr_2$, Et_2O, PhH, i i i. inverse addition; (d) TMS-imid; (e) 20 mol% $Ni(COD)_2$, 40 mol% $P(O\text{-}iC_3HF_6)_3$, cyclohexane, 0.01M, 80°C; (f) 10% Pd/C, EtOH,1 atm H_2, rt; (g) Ac_2O / DMAP, pyr : CH_2Cl_2; 1:1, rt; (h) B-Br catechol borane, CH_2Cl_2, rt; (i) Jones' Reagent acetone, rt; (j) i. $SOCl_2$, rt–50°C, ii. $AlCl_3$, PhH, rt

as illustrated for the dienes **9a** and **9b** (Scheme 2), the use of the Z-isomer[6] leads to the formation of angularly substituted hydrindanes **10a** and **10b** under normal conditions of catalysis. In addition to the syn stereoselectivity of these cycloadditions, it is noteworthy that the relative stereochemical course of these reactions is controlled by the allylic stereogenic center of the starting diene (exo preference for the larger (OR) allylic group), in accord with the mechanism given in Scheme 1.

To corroborate the above stereochemical results as well as to explore preliminarily the utility of this process in the synthesis of steroid and vitamin D analogs, the cycloaddition of dienyne **14** (Scheme 3) was investigated. The synthesis of **14** started with the condensation of protected butynol **11**[7] with oxetane and oxidation of the resultant alcohol to aldehyde **13**. Reaction of this aldehyde with the metalated derivative of **8b** and protection of the resultant alcohol gave the cycloaddition substrate **14**. Importantly, when treated with *in situ* prepared nickel(0) catalyst, this dienyne was converted in 90% yield to only one cycloadduct, the desired hydrindane **15**, possessing natural steroidal stereochemistry at the pro-C9, C13, and C17 centers.[9] *The utility of this transition metal-catalyzed process is strikingly contrasted by the reaction of dienyne* **14** *in the absence 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[10] by its conversion to the steroidal ketone **22**,[11] which was correlated with 8α-isoestradiol, 17β-acetate, 3-methyl ether, a known derivative of equilenin.[12]

In summary, this study demonstrates that the stereochemistry of the diene component in nickel(0)-catalyzed dienyne 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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(6) Selective preparation of the *Z*-isomer was achieved by bromoolefination of the appropriately substituted cinnamaldehyde using the methodology of Smithers (Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833) and subsequent elaboration of the *E,Z* vinyl bromides **8a** and **8b** which were obtained in isomerically pure form by recrystallization.

(7) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373.

(8) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

(9) Using $Ni(acac)_2$ and *in situ* reduction with Et_2AlOEt 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 6.4% enhancement of the *o*-hydrogens of the aryl 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*-bromo catechol borane (Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411), oxidation, and Friedel–Crafts cyclization of the acid chloride (Johnson, W. S.; Glenn, H. J. *J. Am. Chem. Soc.* **1949**, *71*, 1092).

(12) Hydrogenolysis of **22** using the original conditions of Johnson (Johnson, W. S.; Christiansen, R. G.; Ireland, R. F. *J. Am. Chem. Soc.*, **1957**, *79*, 1995) gave the known steroid (rac)-8α-isoestradiol, 17β-acetate, 3-methyl ether (Rufer, C. L.; Schröder, E.; Gibian, H. *Liebigs Ann. Chem.* **1967**, *705*, 211). Catalytic hydrogenation of equilin methyl ether (Sigma) gave a 1:1 mixture of 8α-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 $NaBH_4$ reduction of this steroidal ketone afforded the 17β alcohol. (Smith, H.; *et al. J. Med. Chem.* **1966**, *9*, 338). Acetylation gave 8α-isoestradiol, 17β-acetate, 3-methyl ether. The two isoestrone derivatives, prepared from different routes, had identical ^1H-NMR spectra, IR spectra, and high-resolution mass spectroscopy fragmentation patterns. A 1:1 mixture co-eluted on GC.