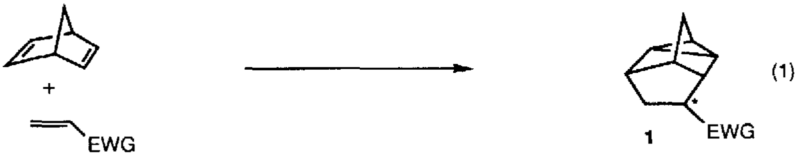
Tetrahedron Letters,Vol.30,No.49,pp 6813-6816,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Stereoselectivity in the Homo Diels-Alder Reaction

Mark Lautens[1] and Louise G. Edwards[2]
Department of Chemistry, University of Toronto
Toronto, Ontario Canada M5S 1A1

Abstract: $Ni(COD)_2/Ph_3P$ or $Ni(acac)_2/Et_3Al/Ph_3P$ have been shown to be effective catalysts for the stereoselective homo Diels-Alder reaction between norbornadiene and electron deficient olefins. High and opposite stereoselectivity was observed for cyclic and acyclic enones. Vinyl sulfoxides gave predominantly one isomer, whereas vinyl sulfones were non-selective.

The homo Diels Alder reaction has been known for more than 25 years and yet it has not found its way into the mainstream of synthetic organic chemistry.[3] In the reaction, a [2+2+2] cycloaddition occurs between a homoconjugated diene such norbornadiene and an olefin bearing an electron-withdrawing group (EWG). Two new rings, a substantial degree of strain and a new stereocentre (*) are created in the tetracyclic product **1** (eq. 1).



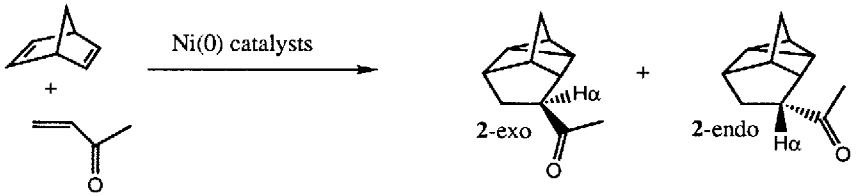
Our interest is in the development of approaches to the synthesis of linearly and angularly fused polycyclic compounds through a sequence of cycloaddition[4] and fragmentation. This report is concerned with the cycloaddition process; subsequent work will focus on fragmentation reactions. We demonstrate that in the presence of suitable nickel catalysts, stereoselective cycloaddition occurs at *room temperature*. Furthermore, the substituents on the olefin are shown to have a dramatic effect on the selectivity of the reaction.

Previous workers have reported that norbornadiene reacts with acrylonitrile, methyl acrylate or acrolein at 180 °C to give the cycloadduct in moderate yield. In the presence of $Ni(CO)_4$, $(Ph_3P)_2Ni(CO)_2$ or $Ni(AN)_2$/2 eq. Ph_3P, (AN=acrylonitrile), the reactions proceed at 80-100 °C with improved yields. An increase in selectivity for the [2+2+2] vs. [2+2] reaction is also observed.[5] However, the reported stereoselectivities are poor (exo/endo ratios of 1.5:1 to 4:1 commonly observed), and substituted norbornadienes are not reactive.[6] The temperature, the specific electron withdrawing group and the steric bulk of the phosphine have been shown to influence the stereoselectivity although no clear pattern has emerged.[7,8]

We investigated the cycloaddition between methyl vinyl ketone (MVK) and norbornadiene in the presence of 3 mol% $(Ph_3P)_2Ni(CO)_2$ at 80 °C. Cycloadduct **2** was isolated in 90% yield as a 2:1 mixture of exo:endo isomers (Table 1, entry 1[9]). Previous reports had indicated that with MVK polymerization rather than cycloaddition occurred.[5] We determined the ratio of isomers by integration of peaks in the ^1H NMR spectrum at

3.01 (dt, J= 4.4, 10.7 Hz) vs 2.90 (dd, J= 5.3, 9.0 Hz) ppm corresponding to the proton Hα. The major isomer (δ=2.90 ppm) was assigned as *exo* after comparison of the coupling constants in **2** with those in related cycloadducts.[7] This stereochemical assignment was confirmed chemically by a modification of a sequence first reported by Nickon.[9] Improvement in the stereoselectivity was noted when the reaction temperature was lowered to 60 °C although the yield of **2** decreased (entry 2). Any further decrease in temperature led to long reaction times and and low (< 10%) yields. Attempts to activate the catalyst using Me_3N-O (to oxidize a CO to a CO_2) or CuI (to complex a phosphine) yielded the cycloadducts but the temperature could not be lowered and no improvement in stereoselectivity was noted (entry 3). Clearly a more reactive complex was required. Yoshikawa had demonstrated that low valent nickel complexes generated by reduction of $Ni(acac)_2$ with sodium borohydride were catalysts but no yields were given.[8] Sodium borohydride is incompatible with an enone and therefore we required an alternative reducing agent. Triethylaluminum[10] proved to be very convenient and reaction of 5-10 mol% $Ni(acac)_2$ with 2 eqs. of the reducing agent in the presence of a phosphine ligand, (1.8 eqs.), gave **2** in 62% yield as a 19:1 mixture of stereoisomers (entry 4). Importantly, the reaction had taken place at room temperature. $Ni(COD)_2$ and 1.8 eqs. of triphenylphosphine was even more effective in promoting both high yields and good stereoselectivity in the cycloaddition (entry 5).[11] These findings may be contrasted to the low selectivity observed by Noyori in the reaction between norbornadiene and a variety of acrylates under similar conditions.[12]

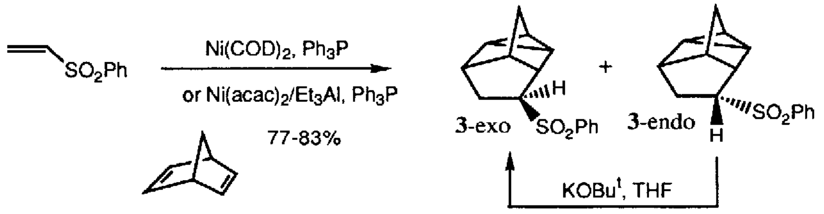
Table 1



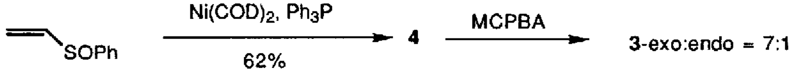
Entry	Catalyst[1]	Temperature	Exo:endo	Yield
1	$(Ph_3P)_2Ni(CO)_2$[2]	80 °C	2:1	90 %
2	$(Ph_3P)_2Ni(CO)_2$[2]	60 °C	9:1	62 %
3	$(Ph_3P)_2Ni(CO)_2$[2]	80 °C	see footnote 4	
4	$Ni(acac)_2/Et_3Al$, 2 Ph_3P[3]	r.t.	19:1	62 %
5	$Ni(COD)_2$., $2Ph_3P$[3]	r.t.	14:1	88 %

1. 5 mol% Ni(0), **2.** no solvent, **3.** $ClCH_2CH_2Cl$ as solvent, **4.** With added CuI the exo/endo ratio = 8:1 (23 % yield), with added Me_3NO the exo/endo ratio = 5:1 (44 % yield)

We wished to determine the generality of the selectivity as well as the compatibility of other functional groups with the reactions conditions. Increasing steric hindrance α to the ketone reduces the selectivity: e.g. tert-butyl vinyl ketone was less selective (3:1 exo:endo) than MVK. An unsaturated sulfone (eq. 2a) reacted with norbornadiene in the presence of $Ni(COD)_2$ or $Ni(acac)_2/Et_3Al$ and added phosphine to generate **3** in high yield (77-83%). The stereoselectivity was poor, (i.e. 1-1.5:1) in this instance and it was not influenced by changes in the temperature or catalyst. Nevertheless, it was possible to increase the amount of the exo isomer to 9:1 exo:endo by epimerization under basic conditions (KOBu^t in THF at rt). The assignment of stereochemistry was based on a comparison of the ^{1}H NMR spectra of **3** and **2**-exo. On the other hand, phenyl vinyl sulfoxide was far more stereoselective (exo:endo=7:1, unknown configuration at sulfur; 10 mol% Ni(COD)$_2$/20 mol% Ph$_3$P, r.t. 2 days, 62% yield, ratio measured after oxidation of the crude sulfoxide **4** to **3** with MCPBA).

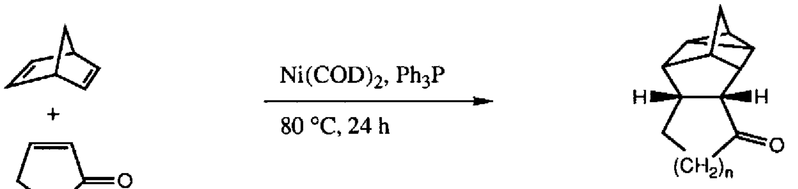


(2a)



(2b)

Cyclic enones have not been previously examined in the homo Diels-Alder reaction. We found that this class of compounds was moderately reactive in the presence of Ni(COD)$_2$/Ph$_3$P. One feature of this cycloaddition is that pentacyclic compounds are created with high stereoselectivity in a single step (>20:1 ratio of stereoisomers). β-substitution does slow the reaction, but this was simply overcome by the use of higher temperatures with no loss of selectivity. For example, with 15-20 mol% Ni(COD)$_2$/2Ph$_3$P, cyclohexenone gave **5b** in 23% yield at 80°C, while cyclopentenone gave **5a** in 56% yield. In contrast to acyclic enones, the stereochemistry of the newly formed ring in **5a** was shown to be *endo*![13]



5 a n=1, 56%
b n=2, 23%

It is premature to offer an explanation for the observed changes in stereoselectivity that have been observed. In general, enones that are unable to adopt an s-*cis* geometry seem to give the opposite isomer to those that can. It may be that complexation of the oxygen in the ketone or sulfoxide locks in one conformation and thereby promotes the formation of one isomer. Further studies are required to test these proposals.

In conclusion, we have shown that Ni(COD)$_2$ or Ni(acac)$_2$/Et$_3$Al in the presence of triphenylphosphine effectively promote the homo Diels Alder reaction. Reaction occurs at *room temperature* for several dienophiles or at 80 °C for more highly substituted and therefore less reactive substrates. High stereoselectivity has been observed in the cycloadditon reaction with methyl vinyl ketone, cyclic enones, and phenyl vinyl sulfoxide. With more active catalysts in hand, opportunities emerge for studies of the regioselectivity of couplings between unsymmetrical norbornadienes and dienophiles. Such investigations represent one direction of our present research in this area.

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada and the Bickell Foundation. We thank Prof. Dave Farrar for valuable dicussions.

References and Notes

1. NSERC(Canada) University Research Fellow 1987-1992.
2. NSERC(Canada) Postgraduate Scholarship 1987-1991.
3. a) Cookson, R.C.; Dance, J.; Hudec, J. *J. Chem. Soc.***1964**, 5416. b) Blomquist, A.T.; Meinwald, Y.C. *J. Am. Chem. Soc.* **1959**, 81, 667. c) Schrauzer, G.N. *Adv. Catal.* **1968**, 18, 373 and references therein. d) Lyons, J.E.; Myers, H.K. Schneider, A. "Transition Metal Mediated Organic Synthesis" *Ann. N.Y. Acad. Sci.* **1980**, 333, 273. Slocum, D.W.; Hughes, O.R. Eds. and references therein.
4. For related cycloaddition studies with Co catalysts see: Lautens, M.; Crudden, C.M. *Organometallics*
5. Schrauzer, G.N.; Eichler, S. *Chem. Ber.* **1962**, 95, 2764.
6. Kelly, T.R. *Tetrahedron Lett.* **1973**, 437.
7. Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T.*J. Am. Chem. Soc.*, **1972**, 94, 3633.
8. Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Bull. Chem. Soc. Jpn.* **1975**, 48, 3239.
9. Nickon, A.; Kwasnik, H.R.; Mathew, C.T.; Swartz, T.D.; Williams, R.O.; DiGiorgio, J.B. *J. Org. Chem.* **1978**, 43, 3904. We treated *exo*-**2** with MCPBA/$NaHCO_3$ in CH_2Cl_2 for 7 days (quant.), the derived ester was hydrolyzed (K_2CO_3, MeOH, 90%), and the alcohol was oxidized (pyridinium dichromate, CH_2Cl_2, 96%) to deltacyclanone. Reduction with L-selectride gave a single alcohol with stereochemistry opposite to that of the starting alcohol. For the reduction with $NaBH_4$ to give a 7:1 exo: endo mixture, see: Freeman, P.K.; Balls, D.M.; Blazevich, J.N. *J. Am. Chem. Soc.*, **1970**, 92, 2051.
10. Triethylaluminum is the reducing agent used in the preparation of $Ni(COD)_2$ from $Ni(acac)_2$. Schunn, R.A. *Inorganic Synthesis*, **1974**, 15, 5. This catalyst system is also reported to promote the Diels-Alder reaction between butadiene and methyl sorbate, see: Garratt, P.J.; Wyatt, M. *J. Chem. Soc. Chem. Commun.* **1974**, 251.
11. A typical procedure is as follows: $Ni(COD)_2$ (5 -15 mol %) was transferred to a flame dried flask along with Ph_3P (2 eq.). The flash was flushed with argon, the solvent (1,2-dichloroethane), and norbornadiene were added and the flask was placed in a water bath at room temperature. The mixture was stirred for the indicated time and then passed through a plug of silica gel which was washed repeatedly with CH_2Cl_2 to obtain a solution free of metallic impurities. Removal of the solvent yielded an oil. Purification by bulb-to-bulb distillation or flash chromatography provided the product. The ratios we observe are kinetic ratios. Similar results have been obtained with acrylonitrile as dienophile, see: ref. 8.
12. Noyori, R.; Umeda, I.; Kawauchi, H.; Takaya, H. *J. Am. Chem. Soc.* **1975**, 97, 812. Typical selectivities of 1.2:1 were observed. Phosphines are avoided in his work as they are claimed to reduce the reactivity.
13. Baeyer-Villiger oxidation of **5a** differentiates the proton at the stereocentre in question. It appeared as a dd, J=9.6, 4.5 Hz, indicative of an exo proton which is known to couple to **both** adjacent protons.

(Received in USA 23 August 1989)