alkylcuprates is further evidence that the conjugate addition reaction proceeds via the SET mechanism.

Supplementary Material Available: Details concerning the calculation methods, cartesian coordinates for optimized structures of 8 and 9, net atomic charges at C-2 and C-3 of 8 and 9 as a function of approaching nucleophile distance, and McLachlan spin densities for non-hydrogen atoms of the radical dianions derived from single-electron reduction of 8 and 9 (7 pages). Ordering information is given on any current masthead page.

Regiochemical Control in the Homo-Diels–Alder Reaction: Substituent Effects

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Summary: The regio- and stereoselectivity of the cycloaddition between substituted norbornadienes and electron-deficient olefins catalyzed by nickel complexes has been studied. The diene and dienophile substituents as well as the ligand were found to exert a dramatic effect on the selectivity.

We have recently reported improvements in the facility and stereoselectivity of the [2 + 2 + 2] homo-Diels–Alder reaction (HDA) between norbornadiene and activated olefins in the presence of nickel catalysts.[2a] This reaction has tremendous potential for use in the construction of complex polycycles since two new rings, as well as up to seven new stereocenters, are created in a single operation, eq 1.

(1)

Unlike the Diels–Alder reaction (where predictable and high regioselectivity is expected in a cycloaddition between an electron-rich diene and an electron-poor dienophile),[3] little is known about the regiochemical outcome of an analogous HDA reaction as there exists only one example of a successful cycloaddition between a substituted norbornadiene and a dienophile, eq 2.[4] In this instance,

(2)

TCNE, a symmetrical and highly reactive dienophile, approaches from the unsubstituted side of diene 2 to give the substituted cyclopropane derivative 3. Other attempts to promote the cycloaddition with substituted norbornadienes or other types of homoconjugated dienes have been unsuccessful.[4,5] With the advent of highly reactive catalysts,[2a,b] we chose to examine the cycloaddition between norbornadienes bearing an electron-donating or -withdrawing group and electron-deficient olefins. From the outset of this study, we were aware that as many as eight isomers *could* be formed when both the diene and dienophile are unsymmetrical; thus, high levels of regioselectivity would be necessary before the reaction could become synthetically useful. The structures of the isomers, designated ortho, meta, meta', and para, are shown in Scheme I. Exo and endo isomers are possible for each cycloadduct. This paper describes our preliminary studies in this area, which indicate that selective cycloadditions are possible.

Scheme I

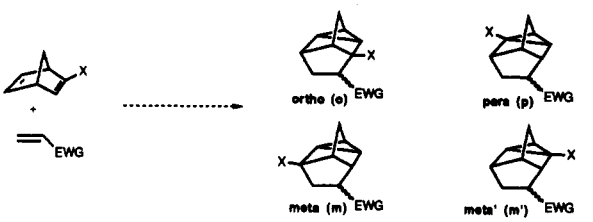

Table I. Cycloaddition of Methyl Norbornadiene-2-carboxylate (4) Using $Ni(COD)_2/2PPh_3$

			ratio of isomers (exo:endo)			
entry	dienophile	% yield	para	meta'	meta	ortho
1	acrylonitrile[a]	94	1 (1:2.3)[b]	0	0	0
2	acrylonitrile[a,c]	65	1 (1:1)	0	0	0
3	phenyl vinyl sulfone[a]	75[d]	2 (1:0)[e,f]	1 (1:0)[f]	0	0
4	methyl vinyl ketone[a]	88[g]	7 (2.8:1)	1 (1:1)	0	2 (0:1)
5	methyl vinyl ketone[a,h]	48	3.8 (1:3.2)	1 (0:1)	0	6.9 (0:1)

[a] At 80 °C in 1,2-dichloroethane. [b] The endo/exo ratio increased with increasing temperature. [c] Catalyst was $(Ph_3P)_2Ni(CO)_2$. [d] At room temperature, the yield decreased to 9%. [e] The ratio appeared to be unaffected by reaction temperature. [f] The regiochemistry assigned to the major and minor isomers may be reversed, see text. [g] At room temperature, the yield decreased to 25%. [h] Catalyst was $Ni(COD)_2/2P(O^iPr)_3$.

In order to study the effect of substitution on the diene, substrates 4 and 5 were prepared[6] and reacted with several

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(6) (a) Methyl norbornadiene-2-carboxylate was prepared by adsorbing a mixture of methyl propiolate (791.5 mg, 9.4 mmol) and freshly cracked cyclopentadiene (1.60 g, 19.4 mmol) onto activated silica gel (22.5 g). This mixture was allowed to stand for 7–9 days, and the product was eluted with ether. After removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel or vacuum distillation (bp 78 °C (5 mmHg), 1.16 g, 82%). Yields ranged from 78–97%. This method was developed since existing methods proved to be capricious in our hands, see: Graham, P. J.; Buhle, E. L.; Pappas, N. *J. Org. Chem.* **1961**, *26*, 4658. Corey, E. J.; Shibasaki, M.; Nicolaou, K. C.; Malmsten, C. L.; Samuelsson, B. *Tetrahedron Lett.* **1976**, *17*, 737. For the use of silica gel to promote cycloadditions, see: Veselovsky, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenkov, A. M.; Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1988**, *29*, 175. (b) 2-Methoxynorbornadiene was prepared as described by Jefford, see: Jefford, C. W.; Huy, P. T. *Tetrahedron Lett.* **1980**, *21*, 755. Barbot, F.; Miginiac, P. *Helv. Chim. Acta* **1979**, *62*, 1451.

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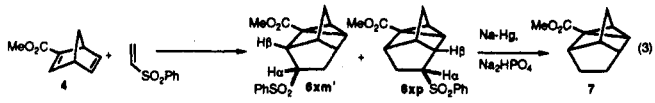
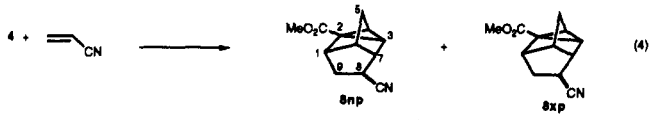
electron-deficient olefins. The reactive nickel catalyst formed in situ from $Ni(COD)_2/2PPh_3$ was found to be the most effective in the HDA cycloaddition for both electron-deficient and electron-rich norbornadienes.[7] Typical reaction conditions involved heating a mixture of the diene, dienophile, and catalyst at ca. 80 °C in order to obtain good yields and to maximize the consumption of the diene. Competition studies established that the electron-deficient diene **4** is more reactive than electron-rich diene **5**, although both are less reactive than norbornadiene.[8] The crude reaction mixtures were analyzed by capillary GC to measure the ratio of isomers, following which the products were separated by column chromatography or recrystallization.[9] As shown in Table I, only two of the eight isomers were formed to a significant extent. Furthermore, the reactions are highly orientationally selective with respect to the eventual position of the diene substituent. The placement of the dienophile substituent was, however, less predictable and less selective.

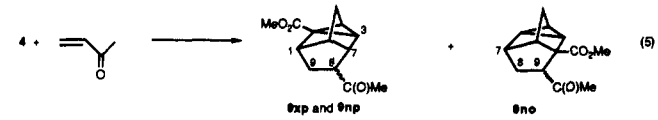
Specifically, good yields of cycloadducts between electron-deficient diene **4** and acrylonitrile, phenyl vinyl sulfone, and methyl vinyl ketone were obtained. Only two products were observed for acrylonitrile and phenyl vinyl sulfone. The determination of the structure of the cycloadducts relied on ^1H and ^{13}C NMR spectroscopy.[10] Cycloaddition with the unsaturated sulfone was highly stereoselective giving two exo isomers, **6xm'** and **6xp** in 75% yield, eq 3.[11] We did not determine the structure



of the major adduct, but following desulfonylation of the mixture (Na/Hg, Na_2HPO_4, MeOH), **7** was isolated as a single product in 87% yield, eq 3. Conversely, the nitrile cycloaddition gave a single regioisomer but a mixture of exo and endo stereoisomers **8xp** and **8np** (94% yield, 1:1–2.5 ratio of isomers depending on the conditions) as established by decoupling experiments, eq 4.[12]

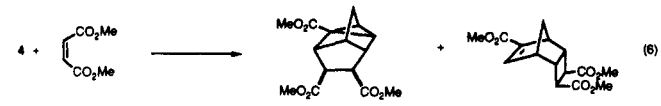


Cycloaddition with methyl vinyl ketone proved to be the most complex reaction studied. The major cycloadducts isolated from the reaction of **4** with MVK were identical with those obtained from the reaction with acrylonitrile, i.e., **9xp** and **9np**, the para exo and endo isomers, eq 5.



The next most abundant product isolated, **9no**, has the ester group not attached to the cyclopropane, i.e., ortho isomer,[10] and the acyl group was shown to be endo. Additionally minor amounts of meta' isomers were isolated.[13] Thus, the (ortho + para) to meta ratio is a respectable 9:1. The observation that MVK could form an ortho adduct suggested that by changing the phosphine ligand we might further influence the regioselectivity. Triisopropyl phosphite was most effective at "switching" the regiochemistry such that the major product became **9no**. Cycloadditions with acrylonitrile and phenyl vinyl sulfone were less selective and gave complicated mixtures upon changing the ligand to $(^iPrO)_3P$.

Dimethyl maleate reacts with **4** at 110 °C in toluene to give a 4.5:1 mixture of an HDA adduct and a metal-catalyzed [2 + 2] cycloadduct in 63% overall yield, eq 6.[14]



Partial isomerization of the maleate to fumarate was observed under the reaction conditions. The maleate–fumarate isomerization is problematic since fumarate is significantly less reactive than maleate as a dienophile in the homo-Diels–Alder reaction.[15]

Of the dienophiles studied, only methyl vinyl ketone underwent successful [2 + 2 + 2] cycloaddition with the electron-rich diene **5**. In contrast to the electron-withdrawing group, the alkoxy group favored the formation of the ortho endo adduct **10no** in 51% yield, eq 7.[16] An

improvement in selectivity toward this cycloadduct was observed upon changing the ligand to triisopropyl phos-

(7) General procedure: $Ni(COD)_2$ (10–25 mol %) and PPh_3 (20–50 mol %) were mixed under nitrogen, and the diene (1 molar equiv) was added in solvent followed by dienophile (1–2 molar equiv depending on ease of removal). Phenyl vinyl sulfone (1 molar equiv) was added as the solid prior to the diene. The reaction mixture was heated at 60–80 °C for 16–48 h and filtered through a plug of silica gel, eluting with CH_2Cl_2 to obtain the crude product, which was purified by distillation or chromatography. $(Ph_3P)_2Ni(CO)_2$ gave synthetically useful quantities of the cycloadducts only with **4** and acrylonitrile.

(8) Competition studies using MVK and $Ni(COD)_2/2PPh_3$ catalysis showed the relative rates of product formation from dienes **4**, **5**, and NBD to be 4.5, 1.0, and 7.6, respectively. Details will be reported in the full account of this work.

(9) All new compounds for which structures are shown were fully characterized by appropriate spectral data (IR, ^1H NMR, ^{13}C NMR, and HRMS) and by satisfactory microanalysis.

(10) The position of the substituent with respect to the cyclopropane ring was readily determined by ^{13}C NMR spectroscopy. In the cycloadduct with an electron-withdrawing group on the cyclopropane ring, the ^{13}C shifts of the three cyclopropane carbons (one quaternary) resonate below 20 ppm. Adducts lacking a substituent on the cyclopropane show shifts from 14–20 ppm. See: Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley-Interscience: New York, 1980.

(11) The exo stereochemistry was easily established by analysis of the ^1H NMR spectrum of the mixture, which shows a doublet of doublets at 3.75 and 3.45 ppm assigned to the protons H_α for the **6xm'** and **6xp**. Had either compound been the endo isomer, coupling to the bridgehead proton H_β would have given ddd's (i.e., eight line patterns).

(12) In **8np**, H^8 appeared as a ddd due to coupling to the bridgehead proton H^7. Identification of H^7 and subsequent decoupling established that H^7 is coupled to H^3, establishing it as the para isomer. By an analogous sequence of decouplings, identification of protons H^{9n}, H^{9x}, H^1, and H^7 in **8xp** showed that H^7 is coupled to a cyclopropane hydrogen while H^1 was not, and therefore **8xp** and **8np** are stereoisomers not regioisomers.

(13) See supplementary material for a complete spectral analysis of the products.

(14) The stereochemistry of the cyclobutane ring has not been established. [2 + 2] adducts were isolated as the exclusive products in some cases. Lautens, M.; Edwards, L. G. Manuscript in preparation.

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(16) A minor product (3%) was also observed whose structure was not determined. The structure of **10no** was determined by NMR spectroscopy; for full details see the supplementary material. Briefly, the presence of three distinct cyclopropyl protons and the characteristic shift of the corresponding carbons rule out the meta' and para isomer. The splitting pattern of protons H^{8x}, H^{8n}, and H^9 could arise only from compound **10no**. H^9 appears as a dd, thus eliminating the endo meta isomer, which would have a coupling to the bridgehead proton and appear as a ddd. Positive identification of H^{8x} (ddd) and H^{8n} (dd) protons by decoupling H^9 confirmed the location of the methoxy substituent in the ortho position. The coupling constants for H^{8x} and H^{8n} to H^9 suggest that the endo isomer was formed. A similar approach was used to assign the structure of **9no**: see supplementary material.

phite, but the yield of the reaction decreased to 33%.

In conclusion, we have found that nickel catalysts promote the cycloaddition of norbornadienes bearing electron-withdrawing and -donating substituents and that ligands can affect the regioselectivity. Importantly, the substituents exhibited complementary behavior in that *an electron-deficient diene favored the adduct with the diene substituent attached to the cyclopropane, while an electron-donating substituent was strongly disfavored on the cyclopropane carbon.* The overall tendency follows the Diels-Alder reaction in that ortho and para orientations are greatly preferred. The homo-Diels-Alder reaction is complicated by the possibility that both ortho and para isomers can arise from the *same* substrates depending on the direction of approach of the dienophile. The absence of the meta isomer in any of the cycloaddition reactions we have carried out is noteworthy. A mechanistic interpretation of these results is difficult in light of the complex multistep mechanism that is undoubtedly involved, and we will resist speculation prior to the results of further experimentation which is now in progress.

Acknowledgment. We thank the A. P. Sloan Foundation, the Natural Science and Engineering Research Council (NSERC) of Canada, Bio-Mega, and the University of Toronto for financial support.

Supplementary Material Available: General and specific procedures and characterization for the compounds reported (6 pages). Ordering information is given on any current masthead page.

Articles

Sequential Directed Ortho Metalation-Boronic Acid Cross-Coupling Reactions. A General Regiospecific Route to Oxygenated Dibenzo[*b*,*d*]pyran-6-ones Related to Ellagic Acid

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A general regiospecific synthesis of dibenzo[*b*,*d*]pyran-6-one derivatives **1a**,**c** and **8a-i** related to ellagic acid is described (Scheme I, Table I). The sequence involves directed ortho metalation-boronation of benzamides **4** to give the arylboronic acids **5**, which, upon palladium-catalyzed cross-coupling with alkoxybromobenzenes **6** leads to the biphenylamides **7**. BBr_3 demethylation followed by acid-catalyzed cyclization affords pyranone **8**. In this manner, the naturally occurring dibenzopyranones **1a**, autumnariol (**1c**), and the heterocyclic analogue **13** (Scheme III) were efficiently prepared.

The dibenzo[*b*,*d*]pyran-6-one skeleton **1** is a somewhat neglected condensed heterocycle, which, nevertheless, is embodied in a small group of oxygenated natural products consisting of **1a** (from castoreum, the secretion of the scent gland of the Canadian beaver *Castor fiber*),[1] alternariol **1b** (*Dematiaceae* moulds),[2] autumnariol **1c**,[3] autumnariniol **1d**,[3] **1e**[4] (*Tamarix nilotica*), and altenuisol **1f** (*Alternaria tenius*).[5] Recently, the benzo[*d*]naphthopyran-6-one nucleus **2**, a benzannelated analogue of **1**, has surfaced as common ring system of a group of antibiotics isolated from various strains of *Streptomyces*,[6-9] which, mainly as a result of promising antitumor activity, has stimulated noteworthy synthetic efforts.[10] Structurally related to **1**

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