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Intramolecular Diels-Alder Reactions of Alkenylboranes - A Stereoselective Route to Functionalized Bicyclo[4.3.0]nonenes.

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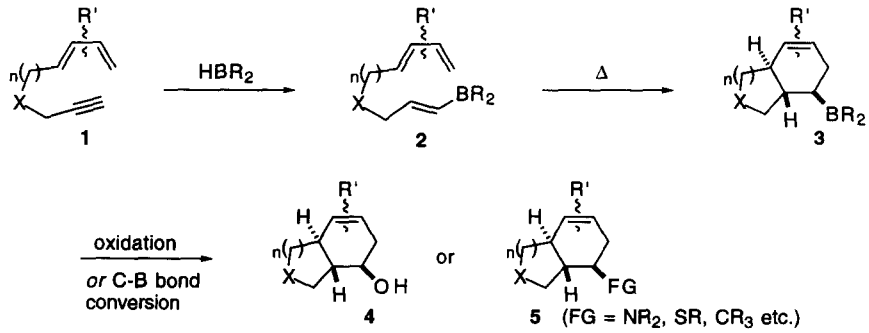
Key words: Intramolecular Diels-Alder Reaction, Alkenylborane, Hydroboration, Masked Dienophile, *E*-Enol Dienophile Equivalent.

Abstract: A one-pot procedure for the synthesis of bicyclo[4.3.0]alkenols is described. Alkenylboranes, formed *in situ* by hydroboration, undergo stereoselective intramolecular Diels-Alder reactions to give alkylboranes, which upon oxidation, yield the products corresponding to *endo* addition.

The intramolecular Diels-Alder reaction is a powerful method for the formation of bicyclic and polycyclic molecules.[3] The major difficulties associated with this methodology are the formation of the requisite precursors, and the potential limitations inherent in the steric and electronic requirements of the dienophile and diene, and the resultant effect upon the stereoselectivity and rate of cycloaddition. As part of a wider interest in the use of boron substituents in controlling reactivity,[4] we have investigated the utility of alkenylboranes in intramolecular Diels-Alder reactions.[5] The general strategy (Scheme 1) that we envisaged employs a three-stage "one-pot" reaction, in which an enyne **1** is used as a precursor for the cycloaddition substrate alkenylborane **2**. Conversion of **2** to the cycloadduct borane **3** under thermal conditions, is followed by transformation to the desired adducts **4** or **5**, which contain three new contiguous stereocentres. For example, straightforward oxidation would yield alcohol **4**. Such an approach is attractive, since the boron substituents can in principle be used to control the diastereo- and enantioselectivity of addition, and the C-B bond in the cycloadduct **3** can be



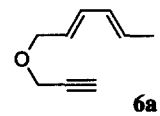
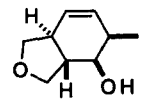
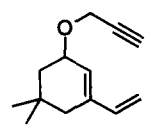
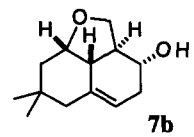
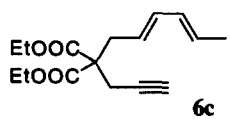
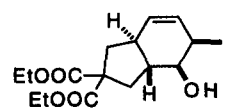
Scheme 1

converted using standard procedures[6] to a wide variety of potential functionalities **5**. The alkenylborane group thus acts as a "masked" dienophile. In the case of oxidation to **4**, the alkenylborane acts as a synthetic equivalent to an *E*-enol dienophile, a group which is not normally suitable for intramolecular Diels-Alder reactions.

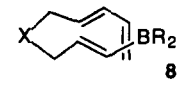
Intermolecular Diels-Alder reactions using alkenylboron species have been known for over thirty years, the first example reported by Matteson using alkenylboronic esters.[7] More recently, Singleton and co-workers have firmly established alkenylboron compounds as practical dienophiles in intermolecular reactions.[8] During the initial stages of our study, Singleton reported the first example of an intramolecular Diels-Alder reaction using an alkenylborane, in which a *trans*-fused bicyclo[4.4.0]decenol **10** (Figure 1) was formed, using either hydroboration or transmetallation to form the requisite alkenylborane.[9] In contrast, our work has focussed on the formation of bicyclo[4.3.0]nonenols **4** (n=1, X=O or CR_2), through a "one-pot" procedure involving (i) hydroboration, (ii) cycloaddition, and (iii) oxidation (Scheme 1).

Three substrates **6a-c** were chosen to test this methodology, but initial optimization was carried out on the readily available propargyl ether **6a**[10] (Table 1). The choice of hydroborating agent is critical for the success of this procedure, since chemoselective hydroboration of the alkyne in the presence of the diene is necessary, and the alkenylborane must also be a good dienophile. Several hydroborating agents that are selective for alkynes over alkenes are known,[6] and four of these were screened: dicyclohexylborane, disiamylborane, catecholborane and dimesitylborane. Dicyclohexylborane and disiamylborane both led to the formation of product **7a**. Initial studies were complicated by varying yields of products. However, the addition of a small quantity (5 mol%) of butylated hydroxytoluene (BHT), as a radical inhibitor, prior to heating the reaction led to increased yields of cycloadducts **7a-c**. In general, dicyclohexylborane gave better yields than disiamylborane, and experimentally was easier to use, since the success of the initial hydroboration step could be followed by the dissolution of the dicyclohexylborane. Optimized conditions for the Diels-Alder step occurred on refluxing the alkenylborane in a benzene / THF solvent mixture overnight. Several oxidation procedures were screened, but oxidation by trimethylamine-*N*-oxide gave the best results, and had the added advantage that functional groups such as esters, which are normally labile to the traditional alkaline hydrogen peroxide work-up, were unaffected. Thus, under optimized conditions,[11] **7a** was formed as a single diastereomer.[12] Catecholborane[13] did not undergo selective hydroboration of **6a** at 80°C, and the only isolable product was that derived from

Table 1. Conversion of dienynes **6** into cycloadducts **7**, using dicyclohexylborane.[11]

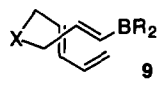
Substrate	Cycloadduct	Isolated Yield
 **6a**	 **7a**	70 %
 **6b**	 **7b**	35 %
 **6c**	 **7c**	44 %

direct intramolecular [4+2] cycloaddition of the alkyne to the diene. Dimesitylborane selectively hydroborated the alkyne, but the resultant dimesitylalkenylborane did not undergo cycloaddition, presumably because of the increased steric hindrance of the dienophile. Substrates **6b**[10] and **6c**[10] were also subjected to the optimized conditions, leading in both cases to the formation of single isolable diastereomers **7b** and **7c** in moderate yields (Table 1). NOE experiments revealed that the stereochemistry of each of the cycloadducts **7a-7c** contained a *trans*-fused ring junction between the newly formed rings. In the case of **7a**, the relative stereochemistry was proven by an X-ray crystal structure of the corresponding *p*-nitrobenzoate ester.



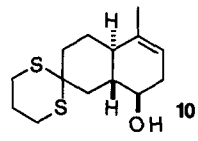
8

"*endo*" transition state

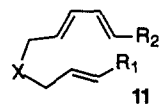


9

"*exo*" transition state



10



11

	Ref.	X	R_1	R_2	*trans* : *cis*
11a	14a	CH_2	H	H	1 : 3
11b	14b	CH_2	$COOCH_3$	H	6 : 4
11c	14b	CH_2	$COOCH_3$	*i*-Pr	72 : 28
11d	14c	CH_2	NO_2	H	89 : 11
11e	14d	O	H	H	1 : 3
11f	14d	O	$CH=CHCH_3$	H	4 : 1
11g	14a	$(CH_2)_2$	H	H	48 : 52
11h	14e	$(CH_2)_2$	$COOCH_3$	H	51 : 49
11i	14f	CH_2O	COOEt	H	3 : 2

Figure 1: Some Comparative Data for Thermal Intramolecular Diels-Alder Cycloadditions

Reaction via the "*endo*" transition state **8** leads to the formation of *trans*-fused adducts, whereas reaction via the "*exo*" transition state **9** would yield the *cis*-fused adducts (Figure 1). However, thermal intramolecular Diels-Alder reactions are known not to follow the "endo rule", with non-bonded interactions in the tethering chain having profound effects on the stereoselectivity.[3] Substituted nonatrienes **11b-d**, analogs of **6a** and **6c**, show a preference for formation of the *trans*-fused-[4.3.0]nonenes under thermal conditions (Figure 1).[14] Interestingly, the oxygen tethered substrate **11e** yields mainly *cis*-fused adducts, whereas **11f** yields mainly *trans*-fused adducts.[15] Singleton has proposed using *ab initio* calculations that a [4+3] transition state occurs for the *intermolecular* reaction of alkenylboranes with dienes, in which there is substantial bonding character between the boron atom and the terminal position of the diene in the *endo*-transition state.[16] Similar interactions were also calculated to be important in the corresponding intramolecular cases leading to the formation of *trans*-fused-[4.4.0]decenes, such as **10** (Figure 1).[9] By comparison, the cycloaddition of simple substituted decatrienes **11g-i** results in poor diastereoselectivity, but the addition of a methyl group at the 3-position of the diene (i.e. 3-methyl-1,3,9-decatriene)[17] leads to exclusive formation of *trans*-fused bicyclo[4.4.0]decenes (*cf.* **11g**). Thus, in the case of compound **10**,[9] the methyl group may have a strong influence on the observed stereoselectivity. The current work demonstrates the formation of *trans*-fused bicyclo[4.3.0]adducts **7a-7c**,[18] and is consistent with reaction via a [4+3] transition state, although this remains speculative because of a lack of appropriate comparative experimental data for thermal intramolecular Diels-Alder reactions. In any case, the reactivity of **6a-c** is notably higher than trienes in similar reported thermal cycloadditions (e.g. **11a-i**),[14] demonstrating the activating effect of a boron substituent on the dienophile in thermal intramolecular Diels-Alder reactions. Also, the observed stereoselectivity is comparable to that achieved in Lewis acid catalyzed intramolecular Diels-Alder reactions, although the reactivity is lower than for Lewis acid activated dienophiles.[3]

In summary, we have developed methodology for the synthesis of *trans*-fused[4.3.0] bicycloalkenols, using a three-step hydroboration-cycloaddition-oxidation strategy. Optimized conditions employ dicyclohexylborane for the hydroboration step, with BHT as a radical inhibitor for the thermal cycloaddition step. The boron substituent both activates the cycloaddition and is a synthetic equivalent for an *E*-enol as a dienophile. The observed stereoselectivity corroborates the [4+3] transition state model for the cycloadditions of alkenylboranes. Further studies in the application of organoboranes to cycloaddition chemistry are now in progress in our laboratory and will be reported in due course.

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(2) Undergraduate Research Participants.

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(10) Compounds **6a** and **6b** were synthesized by propargylation of the corresponding sodium alkoxides. Compound **6c** was synthesized by standard malonate alkylation techniques.

(11) Dieneyne **6a-c** (1.9 mmol) was added dropwise to a suspension of dicyclohexylborane (2.0 mmol in 4 ml of THF). After stirring for 2 h, BHT (0.1 mmol) in freshly distilled benzene (50 mL) was added to the reaction and the reaction mixture was heated at reflux for 17-20 h. After cooling to room temperature, trimethylamine-*N*-oxide dihydrate (6.5 mmol) was added and the reaction was reheated to reflux for 24 h. Upon cooling to room temperature, distilled water (20 mL) was added and the reaction mixture was heated to 60 °C for 30 min. Aqueous work-up and purification by flash column chromatography (silica gel, EtOAc / hexanes) afforded the desired bicyclo[4.3.0]alkenols **7a-c**. In each case only a single diastereomer was observed by NMR and t.l.c.

(12) Selected spectral data for compound **7a**: IR (neat) υ 3418, 3021 2933, 2869, 1632, 1455, 1160, 1117, 1102, 1070, 1040, 1016, 981, 881, 867, 806, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (2H, m), 4.06 (3H, m), 3.58 (1H, dd, J = 11.0, 7.4 Hz), 3.38 (1H, dd, J = 11.7, 7.0 Hz), 2.67 (1H, m), 2.48 (1H, m), 2.06 (1H, dq, J = 11.2, 6.9 Hz), 1.71 (1H, s, OH), 1.04 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.94, 122.77, 72.59, 70.64, 70.00, 45.22, 45.09, 37.55, 14.53; HRMS (EI) *m/e* calcd. ($M-H^+$) 153.0915, found 153.0911.

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(15) The selectivity observed in the cycloaddition of **11f**, is presumably complicated by considerable diradical character for the transition states.

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(18) *Trans*-fused products similar to that of tricycle **7b** are also formed from the allylated analog of **6b**, see: Burke, S. D.; Smith Strickland, S. M.; Powner, T. H. *J. Org. Chem.* **1983**, *48*, 454-459.

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