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LETTERS

Intramolecular Diels-Alder Reactions Involving Boryl-3-propenoic Acid Derivatives

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Abstract: The coupling of 1,3-dienyl alcohols with boryl-3-propenoic acid **1** or of 1,3-dienyl secondary amines with the acid chloride **2** leads to the trienes **5** and **6** respectively. These are well suited precursors for an intramolecular Diels-Alder reaction leading to bicyclic cycloadducts having a carbon-boron bond which can be stereoselectively transformed into a C-O or C-C bond. Thus, the cycloadduct **9** gave the interesting compound **10** via a simple oxidation-reduction sequence or the new boronate **11** via a Matteson's homologation. The introduction of chirality at nitrogen or boron in the trienyl amide **6b** did not lead to interesting levels of asymmetric induction.

The intramolecular Diels-Alder reaction (IMDA) is widely used for the total synthesis of polycyclic natural products.[1] The main advantage of the IMDA is its capacity of creating several stereogenic centers in a single reaction. Intramolecular Diels-Alder reaction involving organometallic species like boronates or boranes are scarce.[2] We have synthesized esters and amides derived from the pinacolboryl-3-propenoic acid moiety and a dienyl alcohol or amine and studied furthermore their reactivity and diastereoselectivity in the intramolecular Diels-Alder reaction.

The coupling of boryl-3-propenoic acid **1** with dienyl alcohols **3a**[3] or **3b**[4] has been accomplished under Mitsunobu's reaction conditions[5] (Scheme 1). Trienyl esters **5a** and **5b**[6] were obtained after elimination of diethyl ether under vacuum, addition of cyclohexane and subsequent filtration of Ph_3PO on a short pad of celite. After elimination of cyclohexane under high vacuum, trienyl esters were obtained in more than 90% yields contaminated only by a few percent of Ph_3PO. Due to degradation on silica gel or during distillation, **5a** and **5b** were used directly without further purification. The addition of an ether solution of the acid chloride **2**[7] to an ether solution of the dienyl amine **4a**[8] in the presence of 1.5 equivalents of triethylamine at 0 °C afforded the trienyl amide **6a** after removal of triethylammonium chloride by filtration through a short pad of Celite in more than 90% yield. The ^1H and ^{13}C NMR spectra of **6a** showed the presence of several conformers at room temperature[9] and purification over silica gel or distillation induced degradation. Therefore, **6a** was used directly for the intramolecular cyclisation. Using the same reaction conditions as above, coupling of the acid chloride **2** with the dienyl amine **4b**[10] at 0 °C for 30 min did not lead to the trienyl amide **6b** but directly and quantitatively to a 85 / 15 mixture of cycloadducts **9**[11] and **9'** having respectively a *cis* and *trans* junction of the bicyclic structure. That the *cis* bicyclic structure **9** is the main adduct results from an endo approch of the diene and the dienophile in agreement with literature data.[12] The assignement of a *cis* configuration at the junction relies on the $^3J_{HH}$ = 5.5 Hz, whereas in the *trans* adduct **9'** a $^3J_{HH}$ = 11 Hz is observed. The Diels-Alder cycloaddition occured at 0°C in less than one hour showing the extreme reactivity of the intermediate trienyl amide **6b** in agreement with literature data.[13] Reaction of acid chloride **2** and dienyl amine **4b** at -78 °C with or without Et_2AlCl as catalyst showed the same yield and selectivity.

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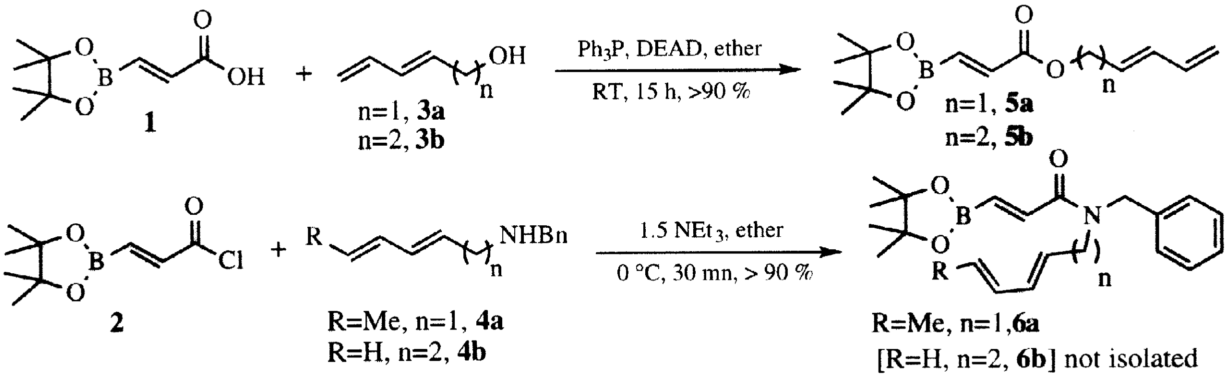
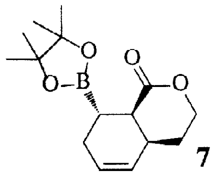
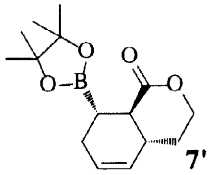
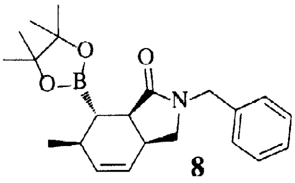
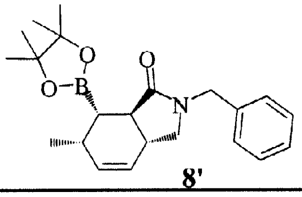
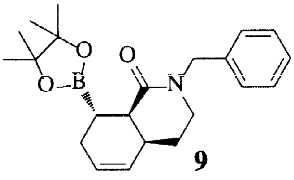
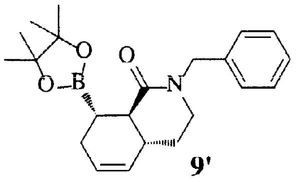
Scheme 1



Instead, intramolecular cyclisations of trienyl esters **5a**, **5b** and amide **6a** were induced by heating at different temperatures in toluene under high dilution conditions in the presence of a catalytic amount of hydroquinone as radical inhibitor. The experimental results are summarized in table I.

Table I : Reactivity and diastereoselectivity of the IMDA.

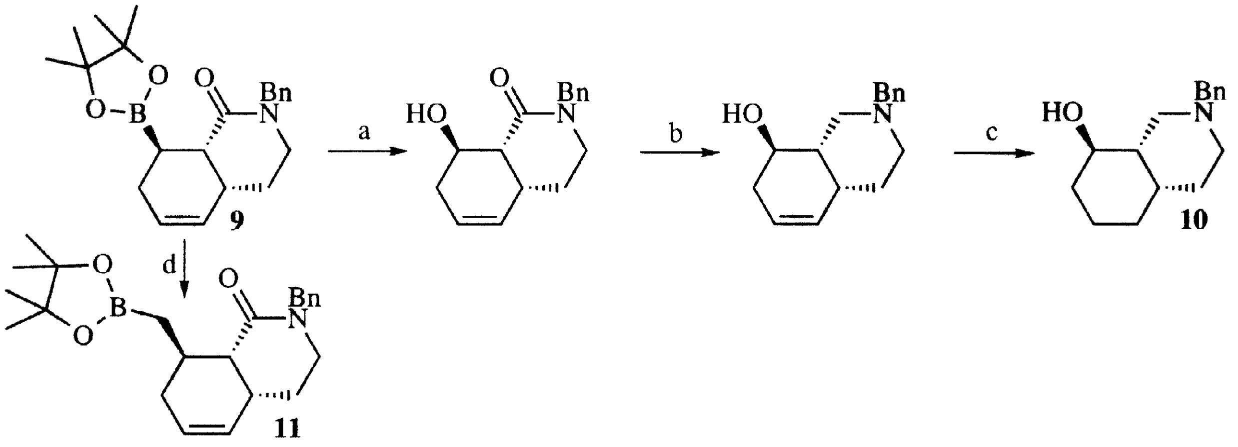
Substrates	Cycloadducts		Yields, ratios and reaction conditions
5a	---	---	0% only polymers
5b	 **7**	 **7'**	8% *cis* **7** / *trans* **7'** = 85 / 15 165°C, 30 h, toluene, 0.025 M
6a	 **8**	 **8'**	72% *cis* **8** / *trans* **8'** = 25 / 75 80°C, 15 h, toluene, 0.003 M
6b	 **9**	 **9'**	76% *cis* **9** / *trans* **9'** = 85 / 15 < 0°C, 30 mn, ether, 0.045 M

Ester **5a** polymerized entirely after 15 hours at 230 °C and catalysis with Et_2AlCl gave only decomposition products. Ester **5b** was heated at 165°C under inert atmosphere for over 30 hrs to give a mixture of *cis* and *trans* cycloadducts **7** and **7'** and a large proportion of tars. **7** and **7'** were unseparable by preparative TLC and isolated as a 85 / 15 mixture in an 8% yield.[14] Catalysis with Et_2AlCl gave only decomposition products. According to literature data, the reactivity of trienyl amides is higher to that of trienyl esters.[9] Intramolecular cyclisation of the amide **6a** was completed after 15 hours at 80 °C in toluene to give a mixture of cycloadducts *cis* **8** / *trans* **8'** = 25 / 75 in 72% yield, which were separated by chromatography over silica gel.

Catalysis with Et_2AlCl, $ZnCl_2$ or $Cl_2Ti(O\text{-}iPr)_2$[15] did not give cycloadducts and only decomposition of the substrate was observed.

Heterocycles having the 2-alkyl-decahydro-isoquinolin-8-ol framework such as **10** are known to have a high antiarhythmic activity.[16] **10** was easily accessible from **9** as it is described in Scheme 2. Further transformation of **9** was realized using Matteson's homologation[17] which led stereoselectively to the new boronate **11** in a 70% isolated yield thus opening the way to a variety of new derivatives.

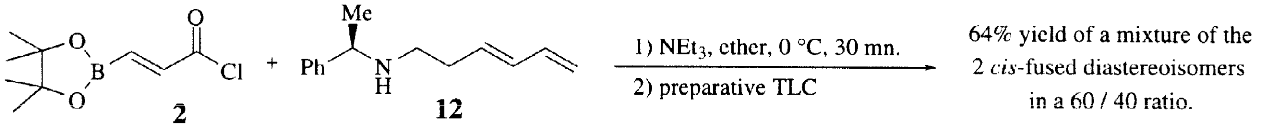
Scheme 2 : Some further transformations of the IMDA adduct **9**.



(a) H_2O_2, THF-phosphate buffer, 71%; (b) $LiAlH_4$, ether, 71%; (c) H_2, Pd / C, AcOEt, 63%; (d) $LiCH_2Br$, THF, -95°C, 70%.

To perform the Diels-Alder reaction in an asymmetric way, trienyl amide **6b** (which gave the best reactivity and selectivity) was modified with optically active groups. Two possibilities have been studied with chirality on the amide moiety (Scheme 3) or on the boronate moiety (Scheme 4). To test the asymmetric induction with a tertiary amide function, acid chloride **2** was coupled with dienyl amine **12** prepared from R(+) α-methylbenzylamine instead of benzylamine under standard conditions. Cycloaddition occured at low temperature during the coupling reaction and gave directly a mixture of four diastereoisomeric adducts. The purification by preparative TLC allowed the isolation in a 64% yield of a 40 / 60 mixture of the *cis*-fused diastereoisomers whereas the two *trans*-fused diastereoisomers could not be obtained pure. To evaluate asymmetric induction induced by the boronate moiety, the two acid chlorides **13** or **14** issued from (+)-pinanediol or (R,R)-1,2-dicyclohexylethane-1,2-diol respectively were synthesized. Cycloaddition occured at low temperature during the coupling of acid chloride **13** or **14** with dienylamine **4b.** In both cases, we obtained directly a mixture of four diastereoisomeric adducts *cis*1, *cis*2, *trans*1 and *trans*2 in 45 / 45 / 5 / 5 ratios respectively. These adducts were isolated after filtration on a short pad of Celite and elimination of ether.

Scheme 3 :

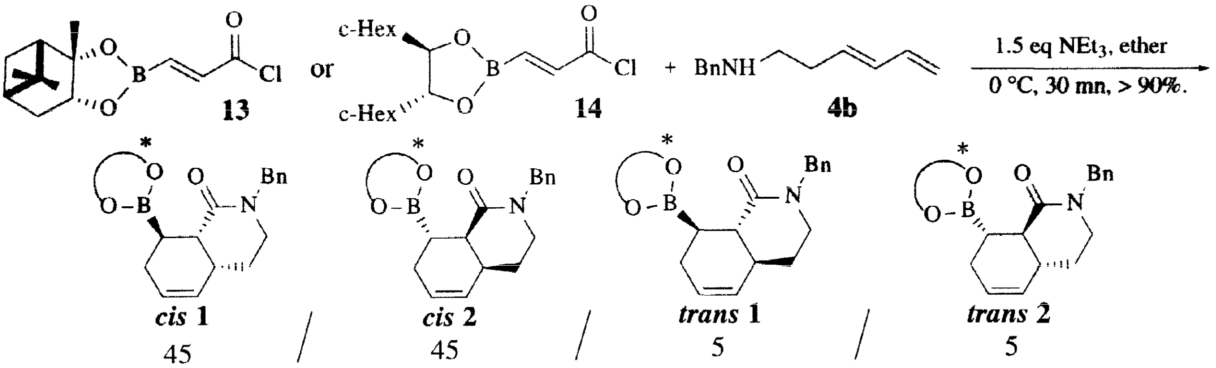


1) NEt_3, ether, 0 °C, 30 mn.

2) preparative TLC

64% yield of a mixture of the 2 *cis*-fused diastereoisomers in a 60 / 40 ratio.

Scheme 4 :



In conclusion, we have explored the ability of trienyl esters and amides derived from boryl-3-propenoic acid to cyclize via an intramolecular Diels-Alder reaction. With ester derivatives, harsh conditions for cyclisation were necessary, leading to low yields of cycloadducts. On the opposite, trienyl amides gave cycloadducts in good yields and high diastereoselectivity under very mild conditions. One of the cycloadducts has been used in a simple stereoselective construction of a decahydro-isoquinolin-8-ol. The introduction of a chiral unit on nitrogen of the trienyl amide **6b** or on boron led to a poor diastereoselectivity in the intramolecular Diels-Alder reaction. Further work is on the way in these laboratories to improve the diastereoselectivity.

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[11] Compound **9** was characterized as follows : white cristals; mp 133 °C (recrystallized from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35- 7.12 (5H, m), 5.89 (1H, ddd, J = 10.1, 5.8, 4.3 Hz), 5.46 (1H, dd, J = 10.1, 1.8 Hz), 4.70 (1H, d, J = 14.8 Hz), 4.47 (1H, d, J = 14.8 Hz), 3.07 (2H, m), 2.84 (1H, dd, J = 5.8, 5.5 Hz), 2.73 (1H, m), 2.09 (2H, m), 1.88 (1H, m), 1.66 (1H, m), 1.24 (12H, s), 0.88 (1H, dd, J = 5.8, 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 137.5, 130.5, 128.4, 128.1, 127.8, 127.1, 83.1, 50.6, 44.8, 41.6, 32.0, 27.5, 24.8, 24.7, 24.1, 20.0; IR (KBr) 1630, 1599 cm^{-1}; Anal. Calcd for $C_{22}H_{20}BNO_3$: C, 71.94; H, 8.23%, found: C, 71.87; H, 8.37%.

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[13] This is reminiscent of what is known concerning IMDA of an identical triene with an hydrogene instead of a boronate fonction performed at 25°C for 20 hours to give a 89 / 11 mixture of *cis* / *trans* cycloadducts : Martin, S.F.; Williamson, S.A.; Gist, R.P.; Smith, K.M. J. Org. Chem. 1983, *48*, 5170-5180.

[14] Experimental conditions were not optimized. The IMDA of an identical triene bearing an ester instead of a boronate performed at 140 °C for 15 hours to give a 78 / 22 mixture of *cis* / *trans* cycloadducts : Chen, C-Y.; Hart, D.J. *J. Org. Chem.* **1993**, 58, 3840-3849.

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