Lewis Base-catalysed Asymmetric Diels–Alder Reaction

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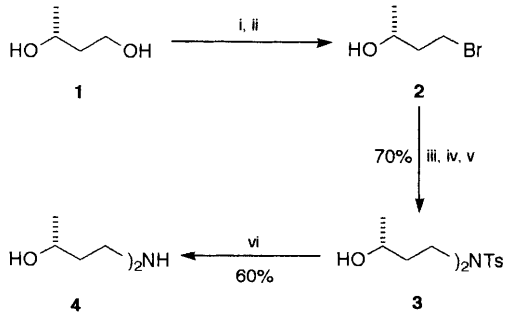
The 1,3-dienyldioxazaborecane **8**, derived from 1,3-dienylboronate **6** and the chiral aminodiol **4**, undergoes asymmetric Diels–Alder reaction with *N*-phenylmaleimide much faster and with higher stereoselectivity than does 1,3-dienylboronate **7**.

Diels–Alder reactions are often catalysed by Lewis acids.[1] Use of Lewis bases has attracted less attention. In this communication, we describe a chiral aminodiol of C_2 symmetry, which can act as a Lewis base and react with 1,3-dienylboronates *in situ* to generate a chiral diene for asymmetric Diels–Alder reactions.

The chiral aminodiol **4**† was synthesized from (*R*)-butane-1,3-diol **1** in three steps (Scheme 1). The first step was realized by adaption of a literature procedure.[2] The yield-determining steps are alkylation and detosylation, which were carried out smoothly by using a phase-transfer catalyst[3] and sodium in liquid ammonia.[4] Compound **4** is very water soluble, and was purified on a silica gel column with methylene chloride, methanol and aqueous ammonia (9 : 9 : 1) as eluent.

The 1,3-dienylboronate **5** has been synthesized previously.[5] Direct reaction of **5** with **4** was not clean owing to the production of the acidic catechol. The catechol group was therefore first removed by filtration of **5** through neutral Al_2O_3, using light petroleum and ethanol as eluents (Scheme 2). The product **6** thus obtained was a mixture of boronic acid, monoethyl ester and diethyl ester, which was converted quantitatively into a single isomer **7** or **8** by treatment with (+)-pinanediol or **4**, respectively.



Scheme 1 *Reagents and conditions*: i, TsCl (Ts = *p*-$MeC_6H_4SO_2$), pyridine; ii, LiBr, Me_2CO; iii, $EtOCH{=}CH_2$, pyridinium toluene-*p*-sulphonate, (PPTS), CH_2Cl_2; iv, $TsNH_2$; C_6H_6, aq. NaOH, Bu_4NHSO_4; v, PPTS, MeOH; vi, Na, NH_3

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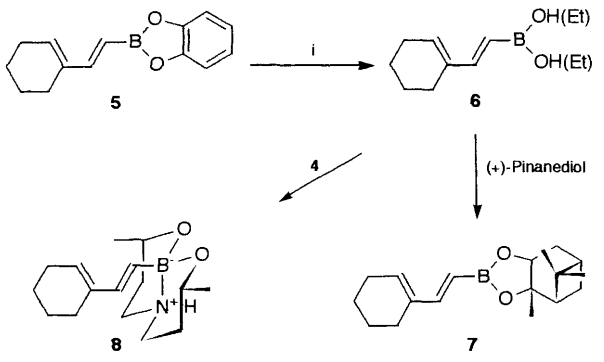
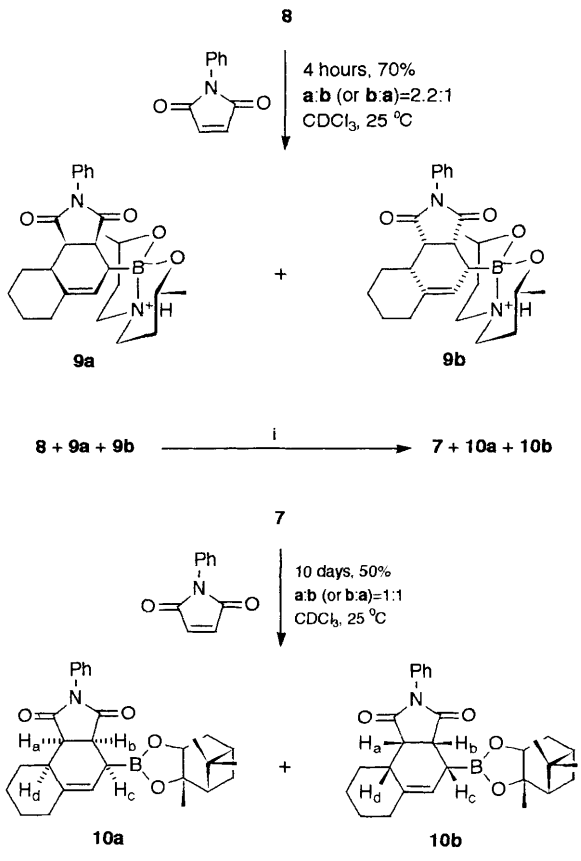
† Aminodiol **4**: IR (KBr) ν/cm^{-1} 3286, 2964, 1600, 1537, 1470, 1454, 1416, 1372, 1308, 1280 and 1132; FAB mass spectrum *m/z* 161 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$, δ 7.24) δ 3.91 (2H, m), 3.89 (3H, br), 2.84 (2H, m), 2.75 (2H, m), 1.56 (4H, m) and 1.16 (6H, d, *J* 6.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$, δ 77) 68.0, 47.7, 37.2 and 23.7.



Scheme 2 *Reagents and conditions*: i, Al_2O_3, EtOH, light petroleum



Scheme 3 *Reagents and conditions*: i, (+)-pinanediol, Et_2O, NH_4Cl

The Diels–Alder reactions of **8** and **7** at the same concentration (0.06 mol dm^{-3}) with *N*-phenylmaleimide (1.3 equiv.) in $CDCl_3$ were carried out in two separate NMR tubes at 25 °C (Scheme 3). After 4 hours, the reaction involving **8** proceeded to 70% completion as indicated by ^1H NMR integration, while the reaction involving **7** did not show any notable changes. The excess dienophile of the first reaction was quenched by addition of an equivalent amount of imidazole at −10 °C. To preserve the actual ratio of the products, **9a**, **b** and the remaining starting material **8** were not isolated, but transformed cleanly to **10a**, **b** and **7**,‡ by treating the mixture with (+)-pinanediol in ether and by removing the aminodiol moiety with saturated aqueous ammonium chloride.§ Compounds **10a** and **b** were also obtained in a 1 : 1 ratio from the second reaction after 10 days.

Both reactions proceeded with formation of *endo* adducts exclusively, as suggested by previous work[5] and confirmed by the following coupling constants for **10a** and **b**: J_{ab} 8.5, J_{bc} 6.2 and J_{ad} 8.6 Hz. The ^1H NMR chemical shift of the methyl group attached to the five-membered boronates in **10a** (δ 1.41) is different from that in **10b** (δ 1.40). The ratio of the two diastereoisomers **9a** and **b** is estimated from ^1H NMR integration of these nonequivalent methyl groups of **10a** and **b**. Approximately the same ratio can be obtained from ^{13}C NMR integration.

The 1,3-dienyldioxazaborecane **8** contains a complex N → B bond.[6] The donation of electrons from nitrogen to boron activates the diene. As a consequence, the difference in chemical shift between the unsaturated carbon atoms and hydrogens is smaller in **8** than that in **7**,[7] and the rate of the reaction of **8** with *N*-phenylmaleimide is greatly accelerated. The pinanediol group in **7** is too far from the reaction centre to have any steric effect on the reaction rate, and therefore no stereoselectivity is observed. Addition of 1 equivalent of diethylamine to **7** had no effect on the ^1H NMR spectrum of **7**. The corresponding Diels–Alder reaction was not catalysed.

The structure of **8** resembles that of two *trans* fused six-membered rings,[6] in which one methyl group is in the axial position, blocking one face of the diene. Therefore, the dienophile prefers to attack from the sterically less congested side, where the other methyl group is equatorial. The stereoselectivity for the reaction of **8** with *N*-phenylmaleimide was found to be 2–3 times higher than that of **7**. Higher stereoselectivity would be expected if rotation of the diene moiety in **8** was restricted.

Further investigation is underway to confirm the three-dimensional structure of **8**, to elucidate the relative configuration of the major adducts from Diels–Alder reactions, to change the methyl groups in **4** to larger groups or other functional groups, to vary the structure of dienes and dienophiles, to manipulate the allylborate functionality of the adducts and to explore the utilization of chiral aminodiol derivatives for resolution of racemic boronic acids and for other types of asymmetric reactions in organic chemistry.

‡ 1,3-Dienylboronate **7**: IR (KBr) ν/cm^{-1} 2970, 2930, 2968, 1632, 1605, 1386, 1375, 1356, 1334 and 1031; FAB mass spectrum *m/z* 286 (M^+); ^1H NMR (400 MHz, $CDCl_3$, δ 7.24 for $CHCl_3$) δ 7.01 (1H, d, *J* 18.2 Hz), 5.94 (1H, br), 5.42 (1H, d, *J* 18.3 Hz), 4.29 (1H, dd *J* 1.6, 8.4 Hz), 2.33 (1H, m), 2.18 (1H, m), 2.13 (4H, m), 2.05 (1H, m), 1.89 (1H, m), 1.87 (1H, m), 1.64 (2H, m), 1.57 (2H, m), 1.38 (3H, s), 1.27 (3H, s), 1.14 (1H, d, *J* 10.8 Hz) and 0.83 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$, δ 77) δ 153.2, 137.2, 134.1, 111.5(br),[7] 85.5, 77.6, 51.4, 39.5, 38.1, 35.6, 28.6, 27.1, 26.4, 26.1, 24.0, 23.8, 22.4 and 22.3; ^{13}C NMR (300 MHz, C_6D_6, δ 128) δ 153.8, 137.6, 133.8, 112.7(br),[7] 85.4, 77.9, 51.8, 39.9, 38.1, 35.9, 28.9, 27.1, 26.8, 26.3, 24.1, 23.9, 22.7 and 22.6.

1,3-Dienyldioxazaborecane **8**; ^1H NMR (400 MHz, $CDCl_3$, δ 7.24 for $CHCl_3$) δ 6.37 (1H, d, *J* 18.3 Hz), 5.63 (1H, br), 5.62 (1H, d, *J* 18.3 Hz), 4.12–4.05 (2H, m), 4.01 (1H, br), 3.54 (1H, m), 3.40 (1H, m), 3.25 (1H, br), 3.09 (1H, br), 2.79–2.70 (2H, m), 2.07 (4H, m), 1.84 (1H, br), 1.68–1.47 (4H, m), 1.35 (1H, m), 1.94 (d, 3H, *J* 6.1 Hz) and 1.15 (d, 3H, *J* 6.2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$, δ 77) δ 141.3, 137.7, 129.0(br),[7] 127.5, 66.4, 63.8, 47.6, 44.9, 34.9, 29.0, 25.8, 24.4, 23.9, 23.7, 22.8 and 22.7.

Diels–Alder adducts **10a** and **b**: IR (KBr) ν/cm^{-1} 2927, 2867, 1711, 1499, 1456, 1379, 1312, 1283, 1239, 1182, 1122, 1077 and 1031; EI high res. mass spectrum *m/z* 458.2564 for $C_{28}H_{34}O_4NB$ (calc. 458.2581); ^1H NMR (400 MHz, $CDCl_3$, δ 7.24 for $CHCl_3$) δ 7.41 (2H, m), 7.32 (1H, m), 7.20 (2H, m), 5.73 (5.72 for **b**) (1H, br), 4.35 (4.34 for **b**) (1H, dd *J* 2.1, 8.9 Hz), 3.47 (1H, dd, *J* 6.2, 8.5 Hz), 3.27 (1H, dd, *J* 8.5, 8.6 Hz), 2.43 (1H, m), 2.35–2.11 (3H, m), 2.10–2.02 (3H, m), 1.99–1.93 (1H, m), 1.91–1.86 (2H, m), 1.85–178 (1H, m), 1.68–1.57 (2H, m), 1.51–1.29 (2H, m), 1.41 (1.40 for **b**) (3H, s), 1.32 (1H, d, *J* 10.8 Hz), 1.27 (3H, s) and 0.83 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$, δ 77) δ 179.0, 177.5, 140.8, 132.2 (134.2 for **b**), 129.0, 128.3, 126.5, 119.3 (119.4 for **b**), 86.3 (86.2 for **b**), 78.0 (77.2 for **b**), 51.5 (51.3 for **b**), 43.5, 42.6, 39.5, 38.2, 36.8, 35.4, 32.1 (32.0 for **b**), 29.7, 28.3 (28.5 for **b**), 27.1, 26.9 (26.7 for **b**), 26.3, 24.4 (24.3 for **b**), 24.0 and 19.8 (br).[7] The stereochemistry cannot be assigned to **a** and **b**.

§ Aminodiol **4** can be recycled.

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