Pergamon

Tetrahedron 54 (1998) 4991–5004

TETRAHEDRON

Azetidine based Ligands in Boron catalyzed Asymmetric Diels-Alder Reactions

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Received 12 December 1997; revised 16 February 1998; accepted 5 March 1998

Abstract: The preparation of a new class of azetidine-based auxiliaries and their selectivity in the BBr_3 catalyzed Diels-Alder reaction is described. The results are compared with a similar proline-derived ligand and a known prolinol auxiliary. Results show that selectivities are highly dependent on the dienophile and the substituent of the chiral auxiliary.

INTRODUCTION

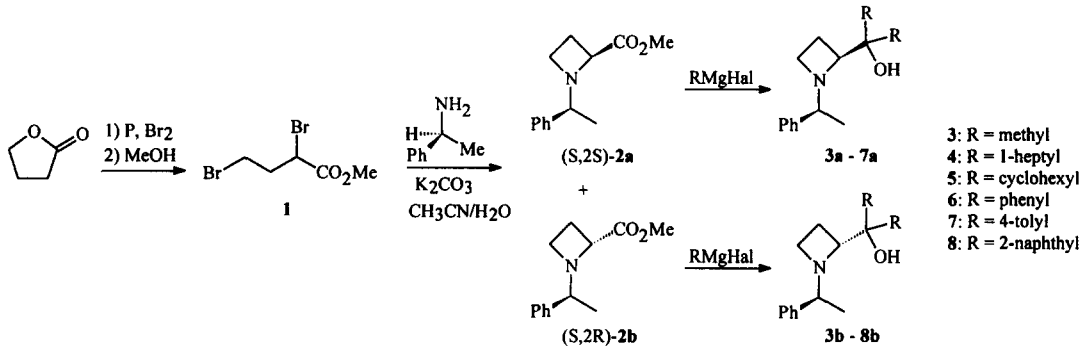
The Diels-Alder reaction is a very powerful synthetic methodology, especially for the synthesis of six-membered ring systems. The methodology has undergone a great improvement by the introduction of newly developed enantioselective versions using chiral Lewis acidic catalysis.[1] In many cases, various oxazaborolidines[2-6] or prolinol-derived catalysts are used and, in the latter case, the results reported range from moderate to excellent.[7-9] The high selectivities obtained with prolinol-derived auxiliaries, as opposed to other amino alcohols, is ascribed to the rigidity of the catalyst complex due to the cyclic backbone of the ligand. We now present even more rigid amino alcohols, *viz.* *N*-alkylazetidine-2-tertiairy alcohols, for asymmetric boron catalyzed Diels-Alder reactions with a variety of α,β-unsaturated aldehydes. For the sake of comparison, two prolinol-derived auxiliaries were investigated as well.

RESULTS

Optically active *N*-alkylazetidine-2-tertiairy alcohols were readily prepared in a three-step synthesis, starting from γ-butyrolactone. Standard Hell-Volhard-Zelinsky bromination and ring-closure of **1** with one equivalent of both (S)-α-methylbenzylamine and K_2CO_3 as a co-base led to a mixture of diastereomeric *N*-alkylazetidine

0040-4020/98/$19.00
PII: S0040-4020(98)00204-X

esters (**2**).[10] These esters were conveniently separated by flash chromatography and then converted into the corresponding carbinols by reaction with a variety of Grignard reagents in good yields (55-92 %). In this manner a series of ligands became available that may provide more insight in the electronic and stereochemical effect of the ligand substituents on the enantioselectivity of the Diels-Alder reaction (Scheme 1).



Scheme 1 Synthesis of diastereomeric azetidine ligands

The stereochemical configuration at C-2 relative to the known (S)-configuration of the α-methylbenzyl group of these ligands was unambiguously established by X-ray analysis of ligand **6a**[11] (Figure 1).

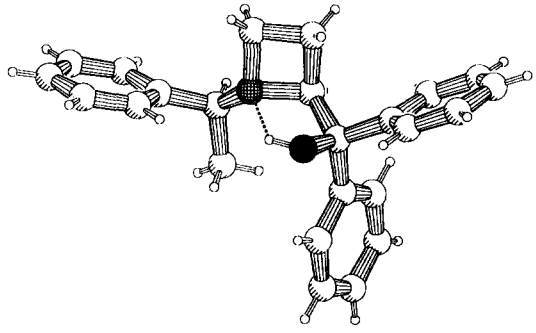
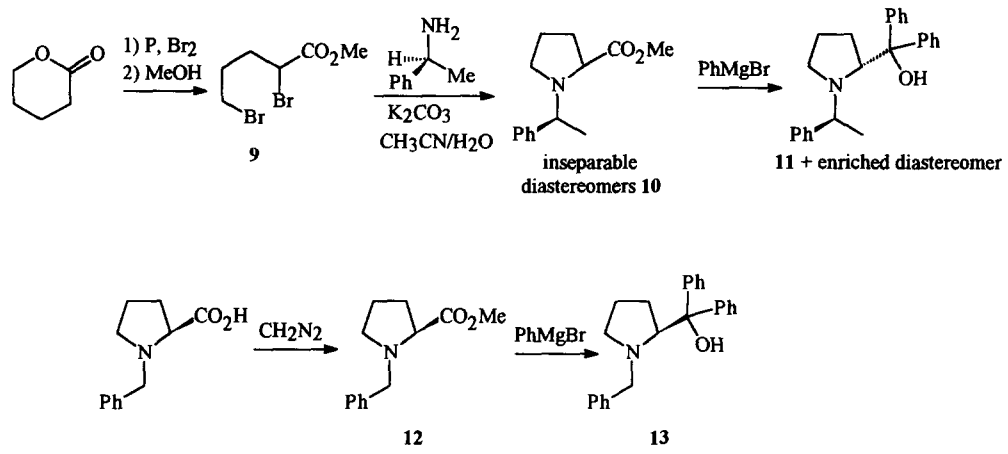


Figure 1 PLUTON[12] generated drawing of the X-ray crystal structure of chiral auxiliary **6a**

For the sake of comparison, two proline-derived ligands were prepared as well. The proline esters **10** were conveniently prepared from δ-valerolactone following a strategy analogous to that used for azetidine esters **2a/2b**. However, in the case of this 5-membered ring system, the separation of the diastereomeric products by flash chromatography proved to be impossible. Therefore, the mixture of esters was converted into the corresponding diphenylcarbinols. Only the (S,2R)-isomer **11** was obtained in pure form after flash chromatography (Scheme 2). The stereochemical configuration at C-2 in compound **11** was established by X-ray analysis by relating it to the known (S)-configuration of the α-methylbenzyl-group[11] (Figure 2).



Scheme 2 Synthesis of proline-derived ligands **11** and **13**

As mentioned before, Kobayashi used the *N*-benzyl substituted proline-derived ligand **13** in the enantioselective Diels-Alder reaction.[9] This compound was also used as a reference ligand in the present study. It was prepared starting from *N*-benzyl proline by esterification with diazomethane and subsequent treatment of ester **12** with phenylmagnesium bromide as shown in Scheme 2. The molecular geometry of **13** was determined by X-ray analysis[11] (Figure 2). All three X-ray analyses show an intramolecular hydrogen bond between the carbinol hydroxyl group and the nitrogen atom.

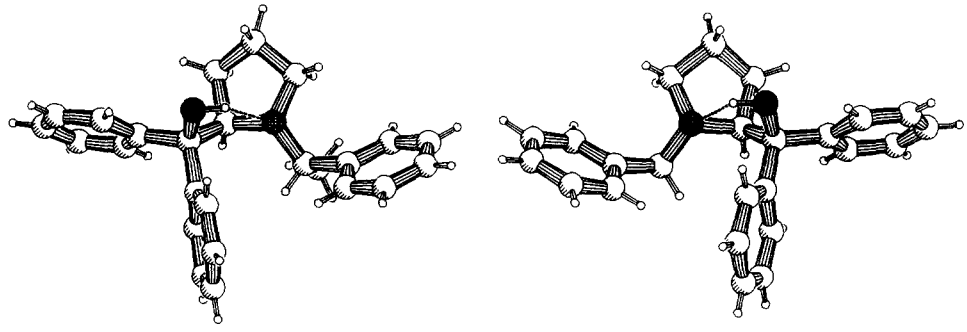
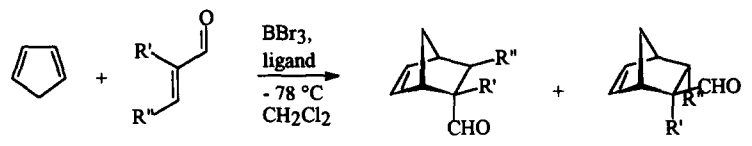


Figure 2 PLUTON[12] generated drawings of the X-ray crystal structures of ligands **11** (left) and **13** (right)

The reaction of cyclopentadiene with four dienophiles was investigated as a model reaction for testing the effectiveness of the respective ligands in the BBr_3-catalyzed Diels-Alder cycloaddition. These dienophiles were acrolein, 2-bromoacrolein, methacrolein and crotonaldehyde (Scheme 3). The results of these reactions are

collected in Table 1 and Table 2. In all cases the chemical yields were over 95 %. The *exo/endo* ratios were determined by capillary GC.



endo *exo*

14: R' = R" = H **16**: R' = CH_3, R" = H
15: R' = Br, R" = H **17**: R' = H, R" = CH_3

Scheme 3 Diels-Alder reaction of cyclopentadiene and α,β-unsaturated aldehydes

Table 1 Enantioselective Diels-Alder reaction catalyzed by chiral boron catalysts[a]

	14: R'=R"=H		**15**: R'=Br, R"=H		
Catalyst	*exo/endo*	e.e. *endo* [%][b]	*exo/endo*	e.e. *exo* [%][b,c]	e.e. *endo* [%][b]
3a	9 / 91	1.9	90 / 10	5.9 (S)	< 0.1
3b	10 / 90	3.4	90 / 10	16.0 (R)	9.5
4b	15 / 85	0.7	93 / 7	24.0 (R)	23.6
5a	11 / 89	0.5	89 / 11	2.0 (S)	1.8
5b	11 / 89	4.7	89 / 11	18.0 (R)	11.5
6a	10 / 90	0.7	90 / 10	3.3 (R)	1.6
6b	9 / 91	0.8	90 / 10	0.2 (R)	3.0
7a	8 / 92	< 0.1	92 / 8	5.8 (S)	2.9
7b	8 / 92	0.8	91 / 9	1.4 (S)	< 0.1
11	9 / 91	< 0.1	89 / 11	0.5 (R)	0.5
13	9 / 91	0.5	88 / 12	1.4 (R)	0.8

a Reactions were carried out in dichloromethane at -78 °C using 50 mol% catalyst and 2.5 equivalents of unsaturated aldehyde with respect to cyclopentadiene.
b Determined by chiral capillary GC using Alfa DEX 120 column by Supelco.
c Absolute configuration determined by comparison.[6]

These data show that the *exo/endo* ratio is not very much affected by the structural nature of the ligands with a few exceptions, *e.g.* ligand **4b** in the reaction with acrolein and ligand **6a** in the reaction with crotonaldehyde.

Table 2 Enantioselective Diels-Alder reaction catalyzed by chiral boron catalysts[a]

	16: R'=CH_3, R"=H		**17**: R'=H, R"=CH_3	
Catalyst	*exo* / *endo*	e.e. *exo* [%][b,c]	*exo* / *endo*	e.e. *endo* [%][d]
3a	93 / 7	16.6 (R)	8 / 92	< 0.1
3b	92 / 8	7.0 (S)	12 / 88	3.0
4b	93 / 7	30.1 (S)	6 / 94	7.4
5a	93 / 7	7.8 (R)	7 / 93	4.1
5b	92 / 8	2.0 (S)	7 / 93	0.6
6a	95 / 5	33.4 (S)	26 / 74	32.2
6b	92 / 8	2.5 (R)	10 / 90	17.7
7a	93 / 7	20.3 (S)	11 / 89	4.2
7b	90 / 10	1.8 (R)	7 / 93	2.4
8b	90 / 10	3.7 (R)	6 / 94	6.3
11	90 / 10	0.7 (R)	9 / 91	26.9
13	91 / 9	0.7 (S)	10/90 (31/69)[e]	65 (59)[e]

a Reactions were carried out in dichloromethane at -78 °C using 50 mol% catalyst and 2.5 equivalents of unsaturated aldehyde with respect to cyclopentadiene.
b Determined by chiral capillary GC using Alfa DEX 120 column by Supelco.
c Absolute configuration determined by comparison.[6]
d Determined by chiral capillary GC using Beta DEX 120 column by Supelco.
e Values in parentheses determined by Kobayashi *et al.*[9]

DISCUSSION

The data presented in Table 1 and Table 2 clearly indicate that the observed enantioselectivities are strongly dependent on the structure of the dienophile as well as that of the ligand: only poor selectivities were obtained in the reaction with acrolein, whereas reactions with the other α,β-unsaturated aldehydes showed only moderate e.e.'s in a few cases. It is important to note that even Kobayashi's proline-derived auxiliary **13** showed only good selectivity in the reaction with crotonaldehyde.

The reaction of 2-bromoacrolein and cyclopentadiene is best catalyzed with catalysts **3b**, **4b** and **5b**. These azetidine-based catalysts all bear aliphatic carbinol substituents and have a (S,2R)-configuration. It is of interest to point out that ligands that have (S,2S)-configuration give much worse results. This may indicate that the (S,2R)-configuration of the catalysts leads to a matching effect of the two chiral centers of the ligand as far as the chirality transfer is concerned, whilst the (S,2S)-configuration of the ligand apparently causes a mismatch. All ligands with aromatic carbinol substituents showed poor selectivities for either product.

The best selectivities for the cycloaddition of methacrolein and cyclopentadiene were obtained with azetidine ligands **4b**, **6a** and **7a**, all giving the same norbornene-enantiomer in excess. The proline-derived ligands

showed selectivities smaller than 1 %. These results are in sharp contrast to those reported by Kobayashi[9] and Aggarwal[7] for the same reaction with the corresponding diphenyl carbinol derived from *N*-methyl-proline that showed very good selectivity. This points at a substantial effect of the *N*-alkyl substituent on the enantioselectivity. The sterically more demanding (α-methyl-)benzyl group apparently hinders the complexation of the dienophile, resulting in a less effective chirality transfer from the ligand/boron complex to the substrate. The diphenyl carbinols **6a**, **6b**, **11** and **13** were the ligands of choice in the Diels-Alder reaction of crotonaldehyde and cyclopentadiene giving moderate to good selectivities. Both ligands with (S,2S)-configuration gave the same norbornene enantiomer, whereas the opposite enantiomer was formed preferentially when the ligands with (S,2R)-configuration were used. Disappointingly, the selectivities with the azetidine based ligands were somewhat lower than those with the proline derived ligands. The better *exo/endo* ratio obtained with the 4-membered ring catalyst as compared to Kobayashi's results with **13** is however remarkable. The overall conclusion is that the catalytic capability of the ligands is governed by subtle structural features and depends strongly on the substrates studied.

EXPERIMENTAL

General remarks

All reactions were carried out in an inert atmosphere of nitrogen or argon unless stated otherwise. Melting points were determined using a Reichert thermopan microscope and are uncorrected. Optical rotations were measured with a Perkin Elmer automatic polarimeter, model 241 MC, using concentrations c in g/100 ml at 20 °C in the solvents indicated. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 100 spectrometer at 100 and 25 MHz, respectively. The chemical shift δ is denoted in ppm relative to the internal standard (TMS for ^{1}H NMR, $CDCl_3$ for ^{13}C NMR). IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. The wavenumber σ is listed in cm^{-1}. For (high resolution) mass spectra a double focusing VG7070E mass spectrometer was used. GC-MS were measured using a Varian Saturn II GC-MS by on-column injection (DB-1 column, length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Elemental analyses were performed using a Carlo Erba Instruments CHNS-O EA 1108 element analyzer.

Solvents and reagents

Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride and stored over sodium wire. Hexane was distilled from calcium hydride and stored over molsieves (4Å). Ethyl acetate was distilled from potassium carbonate. Dichloromethane was distilled from calcium hydride. Triethylamine was distilled from calciumhydride and stored over KOH pellets. Dicyclopentadiene was cracked at 180 °C to obtain cyclopentadiene as a colorless liquid with a boiling point of 41 °C that was stored at -70 °C to prevent dimerization.

Acrolein, methacrolein and crotonaldehyde were distilled and stored at -70 °C. 2-Bromoacrolein was prepared following literature procedures[2, 13] and stored at -70 °C. Stock solutions of BBr_3, cyclopentadiene and the unsaturated carbonyl compounds in freshly distilled dichloromethane were prepared in advance and stored at -70 °C. 1-Benzyl-(2S)-proline was a generous gift of Dr. G.H.L. Nefkens. *N*-Tosyl-phenylalanine and *N*-tosyl-*iso*-leucine were generous gifts of Mr. P.J. Hermsen.

Methyl 2,4-dibromobutyrate (1)

Compound **1** was prepared following literature procedure.[14]

Yield: 102.7 g, 85 %. Bp. 53 °C (0.03 mm Hg). ^{1}H NMR ($CDCl_3$): δ 4.54 (t, J = 7.1 Hz, 1H, CHBr), 3.81 (s, 3H, $COOCH_3$), 3.55 (t, J = 6.2 Hz, 2H, CH_2Br), 2.53 (dt, J = 6.3 Hz and J = 9.4 Hz, 2H, CH_2). IR (CCl_4): σ 1742 (s, $COOCH_3$). GC-MS: *m/z* 227 (M^+ - OCH_3, isotope pattern of 2 bromines), 199 (M^+ - $COOCH_3$, isotope pattern of 2 bromines), 179 (M^+ - ^{79}Br, isotope pattern of 1 bromine).

(2S) and (2R) Methyl 1-((1S)-phenylethyl)azetidine-2-carboxylate (2a and 2b)

Azetidine esters **2a** and **2b** were prepared following literature procedure[10] using **1** (25.001 g, 96.18 mmol), potassium carbonate (13.294 g, 96.2 mmol) and (S)-α-methylbenzylamine (12.4 ml, 96.18 mmol) in 85 % total yield. The diastereomeric esters were purified and separated by flash chromatography (hexane:ethyl acetate, 4:1, *v/v*).

Methyl 1-((1S)-phenylethyl)azetidine-(2S)-carboxylate (**2a**)

R_f: 0.25. Bp.: 76-77 °C (0.03 mm Hg).$[\alpha]_D^{20}$: -124.5° (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.30 (m, 5H, Ph), 3.75 (s, 3H, $COOCH_3$ and t, J = 8.3 Hz, 1H, NC*H*), 3.45 (q, J = 6.6 Hz, 1H, NC*H*(CH_3), 3.20-3.02 and 2.91-2.66 (m, 2H, NCH_2), 2.37-2.10 (m, 2H, CH_2), 1.22 (d, J = 6.6 Hz, 3H, NCH(C*H*$_3$)). ^{13}C NMR ($CDCl_3$): δ 173.6 (s, C(O)O), 142.4 (s, aromatic C), 128.1, 127.4, 127.1 (d, aromatic C), 67.1 and 63.6 (d, NCH and N*C*H(CH_3), 51.8 (q, OCH_3), 49.5 (t, NCH_2), 20.9 (t, CH_2), 20.7 (q, NCH(*C*H_3)). IR (CCl_4): σ 1735 (s, $COOCH_3$), 700 (s, monosubstituted phenyl). GC-MS: *m/z* 220 (M^+ + 1), 204 (M^+ - CH_3), 160 (M^+ - $COOCH_3$), 105 (Methyl-tropilium). HR-MS: Calculated for $C_{13}H_{17}NO_2$ 219.1259, found 219.1260.

Methyl 1-((1S)-phenylethyl)azetidine-(2R)-carboxylate (**2b**)

R_f: 0.20. Bp.: 79 °C (0.02 mm Hg). $[\alpha]_D^{20}$: +35° (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.26 (m, 5H, Ph), 3.67-3.50 (m, 2H, NCH and NC*H*(CH_3)), 3.36 (m, 1H, NCH_2), 3.33 (s, 3H, $COOCH_3$), 3.13-2.89 (m, 1H, NCH_2), 2.39-2.08 (m, 2H, CH_2), 1.29 (d, J = 6.5 Hz, 3H, NCH(C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 172.8 (s, C(O)O), 141.8 (s, aromatic C), 128.1, 128.0, 127.6 (d, aromatic C), 66.3 and 64.6 (d, NCH and N*C*H(CH_3), 51.6 (q, OCH_3), 50.7 (t, NCH_2), 20.9 (t, CH_2), 19.8 (q, NCH(*C*H_3)). IR (CCl_4): σ 1745 (s, $COOCH_3$), 700 (s, monosubstituted phenyl). GC-MS: *m/z* 220 (M^+ + 1), 204 (M^+ - CH_3), 160 (M^+ - $COOCH_3$), 105 (Methyltropilium). HR-MS: Calculated for $C_{13}H_{17}NO_2$ 219.1259, found 219.1258.

General procedure for the azetidine-carbinol syntheses

The glassware was oven-dried and assembled under argon. To a suspension of magnesium turnings (1.11 g, 45.65 mmol) in diethyl ether (10 ml) 1 ml of a solution of 5 equivalents of alkyl- or arylhalide in diethyl ether (10 ml) was added to start the reaction. If the reaction started sluggishly, a spoontip of iodine or some drops of 1,2-dibromoethane were added. As soon as the reaction started, the remaining alkyl- or arylhalide was gradually added and the solution was refluxed for an additional 30 min. Then, a solution of **2a** or **2b** (2.00 g, 9.13 mmol) in diethyl ether (5 ml) was added dropwise and the reaction mixture was stirred for 2 h. After addition of an excess of saturated NH_4Cl solution, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude carbinols were purified by flash chromatography (hexane:ethyl acetate, 10:1 - 5:1, *v/v*) to give the ligands in up to 92 % yield.

2-(1-((1S)-phenylethyl)azetidin-(2S)-yl)-propan-2-ol (3a)

Yield: 1.44 g, 72 %. $[\alpha]_D^{20}$: -64.0° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.45-7.14 (m, 5H, Ph), 3.78 (q, J = 6.9 Hz, 1H, NC*H*(CH_3)), 3.59 (s, 1H, OH), 3.18-2.76 (m, 3H, NCH_2 and NCH), 2.17-1.54 (m, 2H, CH_2), 1.31 (d, J = 6.9 Hz, 3H, NCH(C*H*$_3$)), 1.24 (s, 3H, C*H*$_3$-C-OH), 1.01 (s, 3H, C*H*$_3$-C-OH). ^{13}C NMR ($CDCl_3$): δ 140.9 (s, aromatic C), 128.3, 128.2, 127.2 (d, aromatic C), 69.6 (s, carbinol C), 69.2 and 62.3 (d, N*C*H(CH_3) and NCH), 44.7 (t, NCH_2), 29.1, 24.0, 20.1 (q, *C*H_3C*C*H_3 and NCH(*C*H_3)), 17.3 (t, CH_2). IR (CCl_4): σ 3550 (broad, OH), 700 (s, monosubstituted phenyl). GC-MS: *m/z* 220 (M^+ + 1), 204 (M^+ - CH_3), 160 (M^+ - $C(CH_3)_2OH$), 105 (Methyltropilium). HR-MS: Calculated for $C_{14}H_{21}NO$ 219.1623, found 219.16236.

2-(1-((1S)-phenylethyl)azetidin-(2R)-yl)-propan-2-ol (3b)

Yield: 1.10 g, 55 %. $[\alpha]_D^{20}$: -9.3° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.38-7.23 (m, 5H, Ph), 3.78 (q, J = 6.6 Hz, 1H, NC*H*(CH_3)), 3.29-2.88 (m, 3H, NCH_2 and NCH), 2.31 (broad s, 1H, OH), 2.11-1.77 (m, 2H, CH_2), 1.29 (d, J = 6.6 Hz, 3H, NCH(C*H*$_3$)), 0.96 (s, 3H, C*H*$_3$-C-OH), 0.64 (s, 3H, C*H*$_3$-C-OH). ^{13}C NMR ($CDCl_3$): δ 144.4 (s, aromatic C), 126.5, 127.7, 127.4 (d, aromatic C), 73.1 and 65.1 (d, NCH and N*C*H(CH_3)), 69.6 (s, carbinol C), 46.8 (t, NCH_2), 26.6, 23.9, 17.9 (q, *C*H_3C*C*H_3 and NCH(*C*H_3)), 18.0 (t, CH_2). IR (CCl_4): σ 3550 (broad, OH), 700 (monosubstituted phenyl). GC-MS: *m/z* 220 (M^+ + 1), 204 (M^+ - CH_3), 160 (M^+ - $C(CH_3)_2OH$), 105 (Methyltropilium). HR-MS: Calculated for $C_{14}H_{21}NO$ 219.1623, found 219.16235.

8-(1-((1S)-phenylethyl)azetidin-(2R)-yl)-pentadecan-8-ol (4b)

Yield: 3.26 g, 92 %. $[\alpha]_D^{20}$: +32.2° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.34-7.26 (m, 5H, Ph), 3.64 (q, J = 6.6 Hz, 1H, NC*H*(CH_3)), 3.42 (t, J = 8.0 Hz, 1H, NCH), 3.09 (dd, J = 8.2 Hz and J = 6.2 Hz, 2H, NCH_2), 2.26-1.64 (m, 2H, CH_2), 1.32 (d, J = 6.7 Hz, 3H, NCH(C*H*$_3$)), 1.3-0.9 (broad m, 14 H, alkyl chain CH_2), 0.87 (t, J =

5.7 Hz, 6H, alkyl chain CH_3). ^{13}C NMR ($CDCl_3$): δ 144.5 (s, aromatic C), 126.5, 127.6, 127.3 (d, aromatic C), 72.9 (s, carbinol C), 70.0 and 63.4 (d, NCH and NC*H*(CH_3)), 45.9 (t, NCH_2), 36.6 (t, CH_2), 33.4, 31.9, 30.4, 30.2, 29.3, 29.3, 23.6, 23.2, 22.7 (t, alkyl CH_2), 17.1, 16.7, 14.2 (q, NCH(*C*H_3) and alkyl CH_3). IR (CCl_4): σ 3300 (broad, OH). GC-MS: *m/z* 388 (M^+ + 1), 288 (M^+ - C_7H_{15}), 105 (Methyltropilium). HR-MS: Calculated for $C_{26}H_{45}NO$ 387.3501, found 387.3483.

Dicyclohexyl-(1-((1S)-phenylethyl)azetidin-(2S)-yl)-methanol (5a)

Yield: 2.89 g, 89 %. Mp.: 66-67 °C (diethyl ether). $[\alpha]_D^{20}$: +42.6° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.45-7.15 (m, 5H, Ph), 3.88-3.58 (m, 2H, NCH and NC*H*(CH_3)), 3.46 (broad s, 1H, OH), 3.23-2.84 (m, 2H, NCH_2), 2.3-0.9 (m, 27H, CH_2, NCH(*C*H_3) and cyclohexyl). ^{13}C NMR ($CDCl_3$): δ 141.4 (s, aromatic C), 128.4, 128.2, 127.3 (d, aromatic C), 75.4 (s, carbinol C), 64.9 and 62.9 (d, NCH and NCH(CH_3)), 46.5, 43.5 (d, cyclohexyl), 45.2 (t, NCH_2), 29.3, 29.0, 28.7, 27.8, 27.7, 27.6, 27.4, 27.1, 27.0 (t, cyclohexyl), 20.1 (q, NCH(*C*H_3)), 18.3 (t, CH_2). IR (CCl_4): σ 3400 (broad, OH), 700 (monosubstituted phenyl). GC-MS: *m/z* 356 (M^+ + 1), 340 (M^+ - CH_3), 272 (M^+ - cyclohexyl), 160 (M^+ - $C(C_6H_{11})_2OH$), 105 (Methyltropilium). Elemental analysis: Calculated for $C_{24}H_{37}NO$ %C 81.07, %H 10.49, %N 3.94. Found %C 81.06, %H 10.56, %N 4.02.

Dicyclohexyl-(1-((1S)-phenylethyl)azetidin-(2R)-yl)-methanol (5b)

Yield: 2.14 g, 66 %. Mp.: 107-108 °C (diethyl ether). $[\alpha]_D^{20}$: -94.2° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.35-7.15 (m, 5H, Ph), 4.03-3.71 (m, 2H, NCH and NC*H*(CH_3)), 3.31-3.09 (m, 2H, OH and NCH_2), 2.87 (dt, J = 7.8 Hz and J = 3.5 Hz, 1H, NCH_2), 2.4-0.9 (m, 27H, CH_2, NCH(*C*H_3) and cyclohexyl). ^{13}C NMR ($CDCl_3$): δ 144.0 (s, aromatic C), 128.3, 127.1, 126.8 (d, aromatic C), 75.4 (s, carbinol C), 65.1 and 59.8 (d, NCH and NCH(CH_3)), 47.1, 43.5 (d, cyclohexyl), 42.9 (t, NCH_2), 29.3, 29.1, 29.0, 27.9, 27.7, 27.5, 27.0 (t, cyclohexyl), 18.5 (q, NCH(*C*H_3)), 13.3 (t, CH_2). IR (CCl_4): σ 3390 (broad, OH), 700 (monosubstituted phenyl). GC-MS: *m/z* 356 (M^+ + 1), 340 (M^+ - CH_3), 272 (M^+ - cyclohexyl), 160 (M^+ - $C(C_6H_{11})_2OH$), 105 (Methyltropilium). Elemental analysis: Calculated for $C_{24}H_{37}NO$ %C 81.07, %H 10.49, %N 3.94. Found %C 80.93, %H 10.60, %N 3.99.

Diphenyl-(1-((1S)-phenylethyl)azetidin-(2S)-yl)-methanol (6a)[11]

Crystals of **6a** suitable for X-ray diffraction studies were obtained by crystallization from hexane.

Yield: 2.26 g, 72 %. Mp.: 90-92 °C (hexane). $[\alpha]_D^{20}$: -14.5° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.66-6.80 (m, 15H, Ph), 5.60 (broad s, 1H, OH), 4.26 (t, J = 7.7 Hz, 1H, NCH), 3.30-2.82 (m, 3H, NCH_2 and NC*H*(CH_3)), 2.08-1.66 (m, 2H, CH_2), 0.85 (d, J = 6.7 Hz, 3H, NCH(*C*H_3)). ^{13}C NMR ($CDCl_3$): δ 148.1, 145.3, 140.6 (s, aromatic C), 128.2, 128.2, 128.1, 127.1, 126.8, 126.5, 126.0, 125.7 (d, aromatic C), 75.7 (s, carbinol C), 69.8, 61.2 (d, NCH and NCH(CH_3)), 45.0 (t, NCH_2), 19.8 (q, NCH(*C*H_3)), 19.6 (t, CH_2). IR (CCl_4): σ 3230 (broad,

OH), 700 (monosubstituted phenyl). GC-MS: *m/z* 343 (M^+), 328 (M^+ - CH_3), 266 (M^+ - Ph), 238 (M^+ - methylbenzyl), 105 (Methyltropilium). Elemental analysis: Calculated for $C_{24}H_{25}NO$ %C 83.93, %H 7.34, %N 4.08. Found %C 83.61, %H 7.28, %N 4.19.

Diphenyl-(1-((1S)-phenylethyl)azetidin-(2R)-yl)-methanol (6b)

Yield: 2.35 g, 75 %. Mp.: 89.5-90.0 °C (hexane). $[\alpha]_D^{20}$: -52.0° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.60-6.97 (m, 15H, ArH), 5.25 (broad s, 1H, OH), 4.65 (t, J = 7.6 Hz, 1H, NCH_2), 3.41-2.81 (m, 3H, NCH_2 and $NCH(CH_3)$), 2.21-1.81 (m, 2H, CH_2), 1.16 (d, J = 6.9 Hz, 3H, $NCH(CH_3)$). ^{13}C NMR ($CDCl_3$): δ 147.4, 144.7, 142.6 (s, aromatic C), 128.1, 128.0, 127.0, 126.9, 126.5, 126.3, 125.5, 125.5 (d, aromatic C), 75.5 (s, carbinol C), 66.4, 57.7 (d, NCH and $NCH(CH_3)$), 42.6 (t, NCH_2), 19.0 (t, CH_2), 12.8 (q, $NCH(CH_3)$). IR (CCl_4): σ 3200 (broad, OH), 700 (monosubstituted phenyl). GC-MS: *m/z* 343 (M^+), 328 (M^+ - CH_3), 238 (M^+ - methylbenzyl), 105 (Methyltropilium), 91 (Tropilium). Elemental analysis: Calculated for $C_{24}H_{25}NO$ %C 83.93, %H 7.34, %N 4.08. Found %C 84.02, %H 7.32, %N 4.24.

Di-(4-methylphenyl)-(1-((1S)-phenylethyl)azetidin-(2S)-yl)-methanol (7a)

Yield: 2.41 g, 71 %. $[\alpha]_D^{20}$: -41.7° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.90 (d, J_{ortho} = 8.2 Hz, 2H, tolyl), 7.76 (d, J_{ortho} = 8.2 Hz, 2H, tolyl), 7.59-7.32 (m, 9H, Ph and tolyl), 5.60 (broad s, 1H, OH), 4.97 (t, J = 7.6 Hz, 1H, NCH), 3.76 (q, J = 7.0 Hz, 1H, $NCH(CH_3)$), 3.74-3.3 (m, 2H, NCH_2), 2.58 (s, 6H, 4-CH_3-phenyl), 2.4-2.0 (m, 2H, CH_2), 1.51 (d, J = 7.0 Hz, 3H, $NCH(CH_3)$). ^{13}C NMR ($CDCl_3$): δ 145.4, 142.6, 140.8, 136.0, 135.9 (s, aromatic C), 128.9, 128.4, 128.2, 127.3, 125.9, 125.6 (d, aromatic C), 75.6 (s, carbinol C), 69.6, 61.2 7 45.0 (t, NCH_2), 21.1, 19.9 (q, 4-CH_3-phenyl and $NCH(CH_3)$), 19.6. (t CH_2). IR (CCl_4): σ 3300 (broad, OH). GC-MS: *m/z* 372 (M^+ + 1), 160 (M^+ - $C(4\text{-}CH_3\text{-}C_6H_4)_2OH$), 105 (Methyltropilium). HR-MS: Calculated for $C_{26}H_{29}NO$ 371.2249, found 371.2248.

Di-(4-methylphenyl)-(1-((1S)-phenylethyl)azetidin-(2R)-yl)-methanol (7b)

Yield: 2.31 g, 68 %. $[\alpha]_D^{20}$: +45.3° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.58 (d, J_{ortho} = 8.2 Hz, 2H, tolyl), 7.35-6.8 (m, 11H, Ph and tolyl), 4.23 (t, J = 7.8 Hz, 1H, NCH), 3.3-2.8 (m, 3H, $NCH(CH_3)$ and NCH_2), 2.28 and 2.25 (s, 6H, 4-CH_3-phenyl), 2.0-1.7 (m, 2H, CH_2), 0.91 (d, J = 6.9 Hz, 3H, $NCH(CH_3)$). ^{13}C NMR ($CDCl_3$): δ 145.2, 143.3, 142.6, 136.0, 135.8 (s, aromatic C), 129.1, 128.5, 127.4, 127.0, 125.8 (d, aromatic C), 75.6 (s, carbinol C), 68.9, 58.3 (d, NCH and $NCH(CH_3)$), 43.1 (t, NCH_2), 21.4, 21.3 (q, 4-CH_3-phenyl), 19.4 (t, CH_2), 13.3 (q, $NCH(CH_3)$). IR (CCl_4): σ 3300 (broad, OH). GC-MS: *m/z* 372 (M^+ + 1), 160 (M^+ - $C(4\text{-}CH_3\text{-}C_6H_4)_2OH$), 105 (Methyltropilium). HR-MS: Calculated for $C_{26}H_{29}NO$ 371.2249, found 371.2248.

Di-(2-naphthyl)-(1-((1S)-phenylethyl)azetidin-(2R)-yl)-methanol (8b)

Yield: 2.75 g, 68 %. Mp.: 141 °C (diethyl ether). $[\alpha]_D^{20}$: -51.2° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.1-7.3 (m, 14H, naphthyl), 7.1-6.9 (m, 5H, Ph), 5.25 (broad s, 1H, OH), 4.87 (t, J = 7.7 Hz, 1H, NCH), 3.4-2.9 (m, 3H, NCH_2 and $NCH(CH_3)$), 2.2-1.85 (m, 2H, CH_2), 1.17 (d, J = 6.7 Hz, 3H, $NCH(CH_3)$). ^{13}C NMR ($CDCl_3$): δ 144.5, 142.8, 142.1, 133.1, 132.2 (s, aromatic C), 128.3, 128.2, 128.0, 127.7, 127.5, 127.3, 126.9, 126.7, 125.8, 125.6, 124.5, 124.3, 124.0, 123.7 (d, aromatic C), 75.9 (s, carbinol C), 68.6, 59.1 (d, NCH and $NCH(CH_3)$), 43.6 (t, NCH_2), 19.3 (t, CH_2), 14.1 (q, $NCH(CH_3)$). IR (CCl_4): σ 3300 (broad, OH). Mass (EI): *m/z* 443 (M^+), 160 (M^+ - $C(C_{10}H_7)_2OH$), 105 (Methyltropilium). Elemental analysis: Calculated for $C_{32}H_{29}NO$ %C 86.65, %H 6.58, %N 3.16. Found %C 86.43, %H 6.64, %N 3.26.

Methyl 2,5-dibromo-pentanoate (9)

Compound **9** was prepared from δ-valerolactone (5.00 g, 49.9 mmol), following the same procedure as was used for the synthesis of **1**. The product was purified by distillation *in vacuo*.

Yield: 12.284 g, 90 %. Bp.: 91-93 °C (0.12 mmHg). ^1H NMR ($CDCl_3$): δ 4.28 (dd, J = 6.0 Hz and J = 7.7 Hz, 1H, CHBr), 3.80 (s, 3H, $COOCH_3$), 3.43 (t, J = 6.1 Hz, 2H, CH_2Br), 2.35-1.91 (m, 4H, CH_2CH_2). IR (CCl_4): σ 1745 (s, $COOCH_3$). GC-MS: *m/z* 279 (M^+, isotope pattern of 2 bromines), 212 (M^+ - $COOCH_3$, isotope pattern of 2 bromines).

Methyl 1-((1S)-phenylethyl)pyrrolidine-2-carboxylate (10)

To a refluxing solution of **9** (1.00 g, 3.65 mmol) and potassium carbonate (1.009 g, 7.3 mmol) in acetonitrile (10 ml) and distilled water (1 ml) a solution of (S)-α-methylbenzylamine (491 mg, 4.05 mmol) in acetonitrile (5 ml) was added dropwise. When no more **9** was present as was determined by GC, the reaction was stopped by concentrating the mixture *in vacuo* and taking-up the residue in 1N HCl solution. The aqueous solution was extracted once with ethyl acetate, brought to pH > 8 by adding 1N NaOH solution and extracted with dichloromethane. The latter extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The diastereomers were purified, but not separated, by flash chromatography (hexane:ethyl acetate, 7:1, *v/v*) to give **10** in 72 % total yield. The mixture of esters **10** was used as such in the Grignard reaction.

Diphenyl-(1-((1S)-phenylethyl)pyrrolidin-(2R)-yl)-methanol (11)[11]

Auxiliary **11** was obtained by standard Grignard reaction of the mixture of diastereomeric esters **10** and subsequent separation of the resulting carbinols by flash chromatography (toluene:diethyl ether, 7:1, *v/v*). Crystals of **11** suitable for X-ray diffraction studies were obtained by crystallization from hexane.

Yield: 28 % starting from δ-valerolactone. Mp.: 115.5 °C (hexane). $[\alpha]_D^{20}$: +0.5° (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.76-7.01 (m, 15H, Ph), 5.0 (broad s, 1H, OH), 4.3 (t, J = 6.2 Hz, NCH), 3.10-2.57 (m, 3H,

NC*H*(CH_3) and NCH_2), 1.75-1.25 (m, 4H, CH_2CH_2), 1.18 (d, J = 7.1 Hz, 3H, NCH(CH_3)). ^{13}C NMR ($CDCl_3$): δ 148.9, 146.7, 140.3 (s, aromatic C), 128.8, 128.3, 128.1, 127.2, 126.5, 126.3, 126.1, 125.8 (d, aromatic C), 78.1 (s, carbinol C), 67.9, 57.7 (d, NCH and NCH(CH_3)), 47.5 (t, NCH_2), 30.1, 24.5 (t, CH_2CH_2), 20.6 (q, NCH(CH_3)). IR (CCl_4): σ 3450 (broad, OH), 710, 700 (s, monosubstituted phenyl). Mass (EI): *m/z* 358 (M^+ + 1), 280 (M^+ - C_6H_5), 174 (M^+ - $C(C_6H_5)_2OH$), 105 (Methyltropilium). Elemental analysis: Calculated for $C_{25}H_{27}NO$ %C 83.99, %H 7.61, %N 3.92. Found %C 83.71, %H 7.69, %N 3.96.

Methyl 1-benzylpyrrolidine-(2S)-carboxylate (12)

An excess of a 0.3 M solution of diazomethane in diethyl ether was added to a suspension of 1-benzyl-(2S)-proline in THF. After the initial gas evolution had stopped the yellow solution was stirred for 30 min., after which the excess diazomethane was removed by bubbling nitrogen gas through the solution. The product was obtained in quantitative yield after concentration *in vacuo*.

Yield: > 99 %. $[\alpha]_D^{20}$: -69.3° (c=1, $CHCl_3$), lit. $[\alpha]_D^{20}$: -79.2° (c=1.203, $CHCl_3$)[15], $[\alpha]_D^{18}$: -85.7° (c=4.0, $CHCl_3$)[16]. ^{1}H NMR ($CDCl_3$): δ 7.4-7.3 (m, 5H, Ph), 3.73 (AB quartet, J = 12.7 Hz and J = 33.2 Hz, 2H, NC*H*$_2$Ph), 3.65 (s, 3H, $COOCH_3$), 3.32-2.95 (m, 2H, NCH_2), 2.43 (t, J = 7.9 Hz, 1H, NCH), 2.28-1.7 (m, 4H, CH_2CH_2). IR (CCl_4): σ 1740 (s, $COOCH_3$), 700 (s, monosubtituted phenyl).

Diphenyl-(1-benzylpyrrolidin-(2S)-yl)-methanol (13)[11]

Auxiliary **13** was obtained by standard Grignard reaction using 5 equivalents of phenylmagnesium bromide with respect to ester **12**. Crystals of **13** suitable for X-ray diffraction studies were obtained by crystallization from diethyl ether.

Yield: 76 %. Mp.: 116 °C (diethyl ether). $[\alpha]_D^{20}$: -94.5° (c=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.8-6.9 (m, 15 H, Ph), 4.87 (broad s, 1H, OH), 3.97 (dd, J = 8.7 Hz and J = 4.8 Hz, 1H, NCH), 3.11 (AB quartet, J = 12.5 Hz and J = 23.2 Hz, 2H, NC*H*$_2$Ph), 3.0-2.8 and 2.49-2.22 (m, 2H, NCH_2), 2.2-1.4 (m, 4H, CH_2CH_2). ^{13}C NMR ($CDCl_3$): δ 148.2, 146.8, 139.8 (s, aromatic C), 128.7, 128.3, 128.2, 128.2, 126.9, 126.5, 126.3, 125.7, 125.7 (d, aromatic C), 76.0 (s, carbinol C), 70.8 (d, NCH), 60.7, 55.6 (t, NCH_2Ph and NCH_2), 29.9, 24.3 (t, CH_2CH_2). IR (CCl_4): 3450 (broad, OH). GC-MS: 160 (M^+ - $C(C_6H_5)_2OH$), 91 (Tropilium). Elemental analysis: Calculated for $C_{24}H_{25}NO$ %C 83.93, %H 7.34, %N 4.08. Found %C 83.96, %H 7.34, %N 4.22.

General remarks concerning the asymmetric catalytic Diels Alder reactions

All reactions were carried out under an inert atmosphere of argon, using standard Schlenk techniques. First, racemic mixtures of both *endo* and *exo* adducts were obtained by carrying out the BBr_3-catalyzed Diels-Alder reaction without any chiral auxiliary. *Endo/exo* ratios were determined by capillary GC and ^{1}H NMR. Enantiomeric excesses (e.e.'s) of the Diels Alder products were determined by GC using chiral columns:

Supelco, Beta-DEX™ 120 fused silica column (length 60 m, internal diameter 0.25 mm, film thickness 0.25 μm) and Supelco, Alfa-DEX™ 120 fused silica column (length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm).

General procedure for asymmetric Diels-Alder reactions

In a dry 10 ml Schlenktube 0.16 mmol chiral ligand was dissolved in dichloromethane (1 ml) containing 0.16 mmol BBr_3. After 1 h. the solvent and any non-coordinated BBr_3 were removed in high vacuum. The residue was then dissolved in dichloromethane (5.0 ml) containing 0.8 mmol (5 equivalents) of unsaturated carbonyl compound and cooled to -78 °C. Finally, a solution of 0.3 mmol (2 equivalents) cyclopentadiene in dichloromethane (5 ml) was added and the reaction mixture was stored at -70 °C for 19 h. The reaction was quenched at -70 °C with saturated $NaHCO_3$ solution and the aqueous layer extracted with diethyl ether. The combined organic layers were extracted with 1 N HCl solution to separate the chiral ligand and dried with $MgSO_4$, filtered and concentrated *in vacuo* after which the *endo/exo* ratios and the e.e.'s were determined. All yields were over 95 %. The chiral ligand was recovered by adding 1 N NaOH solution to the acidic aqueous extract and extraction of the alkaline solution with dichloromethane. Typical recovery yield: 80 %.

Bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (14)

The enantioselectivity of the *endo* adduct was determined by chiral capillary GC using the Alfa DEX 120 column.

2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (15)

The enantioselectivity of both the *endo* and *exo* adduct was determined by chiral capillary GC using the Alfa DEX 120 column (100 °C isotherm). The absolute configuration of the *exo* adduct was determined by comparison to the known compound (1R,2R,4R)-**15** obtained from the N-tosyl-*L*-phenylalanine-derived oxazaborolidine catalyzed reaction.[6]

2-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (16)

The enantioselectivity of the *exo* adduct was determined by chiral capillary GC using the Alfa DEX 120 column (85 °C isotherm). The absolute configuration of this adduct was determined by comparison to the known compound (1R,2R,4S)-**16** obtained from the N-tosyl-*L-iso*-leucine-derived oxazaborolidine catalyzed reaction.[6]

3-Methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (17)

The enantioselectivity of the *endo* adduct was determined by chiral capillary GC using the Beta DEX 120 column.

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