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A novel design of roof-shaped anthracene-fused chiral prolines as organocatalysts for asymmetric Mannich reactions

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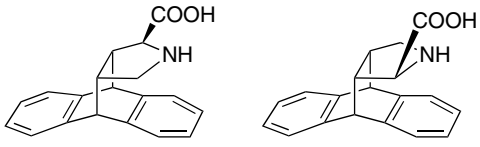
Abstract—A new class of artificial anthracene-fused chiral proline catalysts has been synthesized from the Diels–Alder adduct of anthracene and maleic anhydride via lithiation/carboxylation of **6** as a key step. Chiral resolution of racemic amino acids was carried out through the formation of diastereomeric esters with (−)-menthol. The absolute configuration of the chiral amino acid was determined by X-ray crystallographic analysis. The utility of the catalyst was confirmed by effecting asymmetric three-component Mannich reactions between aldehyde, ketone, and amine (yield up to 76%, ee up to 90%).

1. Introduction

Asymmetric organocatalysis is now recognized as an important tool for preparing enantiomerically enriched organic molecules due to its operational simplicity, high efficiency, and environmentally friendly processes.[1] Accordingly, numerous approaches have been used to devise new chiral organocatalysts and novel systems in unusual reaction media (water, ionic liquid, etc.), and to apply this method to natural product synthesis. In this rapidly expanding research area, proline and its derivatives occupy a pivotal position due to their ready availability in either enantiomeric form, ease of handling, and broad applicability since they were described by List et al.[2,3] However, there are still some limitations, particularly with regard to the reactivity and selectivity of asymmetric transformations through proline-based catalysis. Therefore, the discovery of more powerful proline-like catalysts is required.[4]

In our continuing research on the development of organocatalytic asymmetric synthesis,[5] we focused on the design of new proline-like catalysts that are more efficient than proline itself. We sought to incorporate planar steric hindrance in close proximity to the proline core skeleton. As a consequence, we used a Diels–Alder strategy with anthracene because of its rigid roof-shaped framework for the selective shielding of one side of a catalyst center,[6] since some successful examples have been reported of efficient asymmetric catalysts or chiral auxiliaries containing such a molecular architecture.[7]

We describe here our own contribution to the development of new anthracene-fused chiral proline catalysts **1** and **2**, and their use in asymmetric three-component Mannich reactions.[8]



1 **2**

2. Results and discussion

The synthesis of a new class of anthracene-fused proline catalysts **1** and **2** began with Diels–Alder adduct **3**,[9] which was readily available from anthracene and maleic anhydride (Scheme 1). Treatment of **3** with an equimolar amount of *p*-methoxybenzylamine ($PMBNH_2$) in hot THF produced the desired *N*-PMB-protected imide **4** in an almost quantitative yield. LAH-reduction followed by protective-group transformation cleanly provided *N*-Boc-protected isoindole **6** (66% yield over two steps). The

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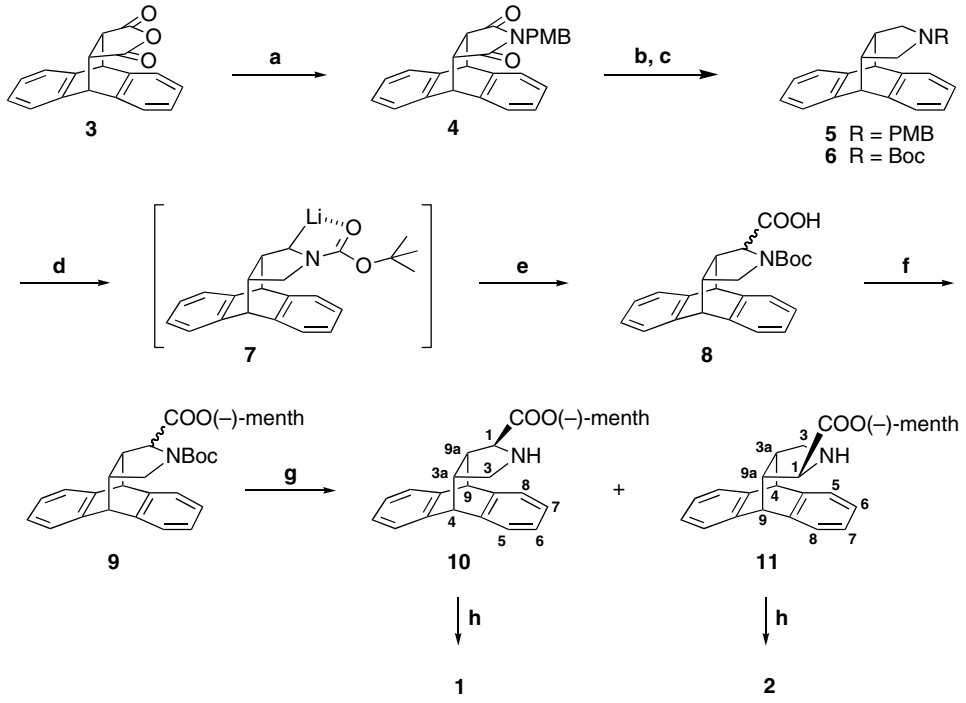


Scheme 1. Reagents and conditions: (a) *p*-$MeOC_6H_4CH_2NH_2$, THF, reflux, 6 h, 100%; (b) $LiAlH_4$, THF, reflux, 12 h, 98%; (c) H_2, Boc_2O, 10% $Pd(OH)_2$/C, abs EtOH, rt, 15 h, 67%; (d) *sec*-BuLi, TMEDA, THF, −78 °C, 4 h; (e) CO_2 (gas), −78 °C, 3 h, 100% (2 steps); (f) (−)-menthol, DCC, DMAP, CH_2Cl_2, rt, 16 h, 80%; (g) TFA, CH_2Cl_2, rt, 3 h, 91%; (h) 1.0 M aq NaOH, MeOH, 45 °C, 16 h, then SiO_2 column, 73%.

crucial attachment of a carboxyl function onto **6** was successfully achieved by using Beak's protocol: *N*-Boc-directed lithiation/carboxylation.[10] Thus, lithiation using *sec*-BuLi/TMEDA in dry THF at −78 °C for 5 h provided the α-lithioamide intermediate **7**, which on exposure to bubbling CO_2 (gas) gave the desired carboxylic acid **8** in an excellent yield.

Based on its behavior in TLC and NMR, compound **8** exists as a diastereomeric mixture of *endo*- and *exo*-isomers. Fortunately, however, we found that the *endo*-isomer could be readily isomerized into the more stable *exo*-isomer after the following experiments.

Since initial attempts to enzymatically resolve racemic **8** after conversion to the corresponding methyl ester derivatives were not successful,[11] we decided to use the diastereomeric esters. Thus, treatment of **8** with (−)-menthol with the aid of DCC/DMAP gave menthyl ester **9** in 80% yield. At this stage, the side chain was isomerized quite smoothly. TFA-promoted deprotection of the *N*-Boc group gave nearly equal amounts of free amine **10** and **11** in a combined yield of 91%. Compounds **10** and **11** were isolated by silica gel column chromatography: **10** as a colorless gum, $[\alpha]_D^{22} = +20.9$ (*c* 1.62, MeOH) and **11** as mica crystals, mp 159–161 °C, $[\alpha]_D^{22} = -93.1$ (*c* 1.41, MeOH).

The stereochemistry of **11** was fully determined by X-ray crystallographic analysis, and the absolute configuration of the mother skeleton was unambiguously established to be (1*R*,3a*S*,9a*R*) (Fig. 1). This result leads to the conclusion that diastereomer **10** should have the (1*S*,3a*R*,9a*S*)-configuration.

Finally, alkaline hydrolysis of the menthyl ester of **10** gave the end product, anthracene-fused proline catalyst **1**, $[\alpha]_D^{22} = +57.6$ (*c* 0.62, MeOH), in an enantiomerically pure

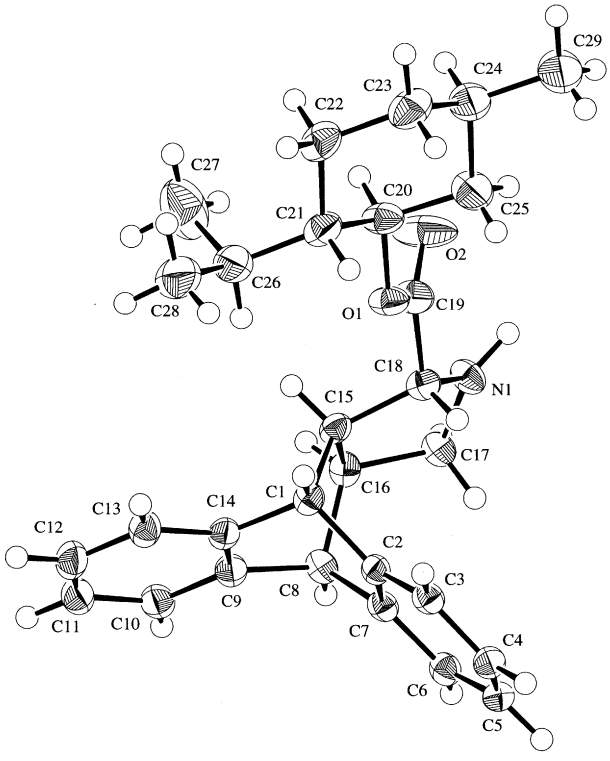
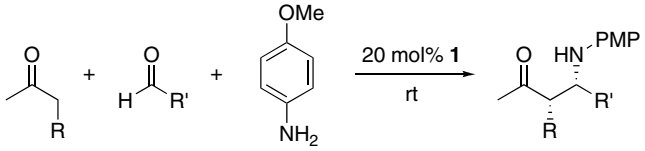
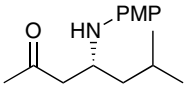
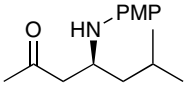
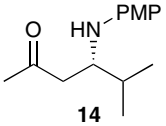
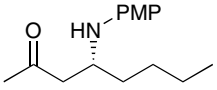
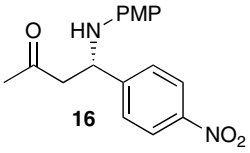
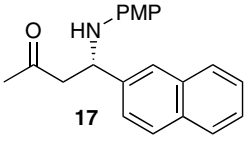
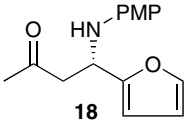
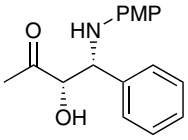
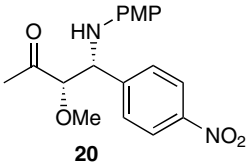


Figure 1. The ORTEP drawing of compound **11**.

Table 1. Asymmetric three-component Mannich reactions between ketone, *p*-anisidine, and aldehyde[a]



Entry	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	 **12**	0.5	71	56
2[e]		0.5	76	65
3		0.5	76	75
4[f]	 **13**	0.5	76	68
5[g]	 **14**	0.5	56	54
6	 **15**	0.5	62	64
7[g]	 **16**	2	54	90
8[g]	 **17**	3	59	90
9[g]	 **18**	2	65	84
10[g]	 **19**	3	72 (dr > 19:1)[h]	79
11[g]	 **20**	3	67 (dr > 17:1)[h]	86

[a] Unless otherwise noted, all reactions were conducted at rt in pure ketone (5 mL) using aldehyde (0.5 mmol) and *p*-anisidine (0.55 mmol) in the presence of 20 mol % of **1**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] At 0 °C in the presence of 5 mol % of **1**.
[e] 10 mol % of **1** was used.
[f] 20 mol % of **2** was used as the catalyst.
[g] The reaction was conducted in DMSO/ketone = 4:1.
[h] Determined by NMR.

form in 73% yield. In the same manner, catalyst **2**, $[\alpha]_D^{22} = -57.6$ (*c* 1.31, MeOH), was obtained from **11**.

The overall sequence in the above strategy requires only seven steps from the starting anhydride **3** and the product is relatively easy to access in multigram quantities. In addition, one of the favorable points of this work is the ready availability of either enantiomer of the catalysts, which provides a highly flexible way to conduct research on organocatalytic asymmetric synthesis.

By analogy to previously established examples using L-proline as a catalyst,[8] the utility of the newly formed anthracene-fused chiral proline catalysts was then tested in asymmetric three-component Mannich reactions between ketone donors, *p*-anisidine, and aldehyde acceptors. The results are summarized in Table 1.

A mixture of isovaleraldehyde (1 equiv), *p*-anisidine (1.1 equiv), and catalyst **1** (20 mol %) in pure acetone was subjected to the standard conditions (entry 3).[12] After 30 min at room temperature, the reaction was completed and the *N*-PMP-protected β-amino ketone **12** was obtained in 76% yield with 75% ee. The absolute configuration of **12** was determined to be (*R*) by comparison with that of the authentic sample prepared by L-proline catalysis. Slight decreases in enantioselectivity were observed at a lower loading of the catalyst or at lower temperatures (entries 1 and 2 vs entry 3).

On the other hand, the use of catalyst **2** gave (*S*)-enantiomer **13** (entry 4). The general applicability of the present method was established by Mannich reactions using isobutyraldehyde, pentanal, *p*-nitrobenzaldehyde, 2-naphthaldehyde, and 2-furaldehyde as an aldehyde component (entries 5–9). Other ketones (hydroxyacetone and methoxyacetone) were also used as a donor, and with *p*-anisidine and aldehyde furnished the desired products **19** and **20** in high regio-, diastereo-, and enantioselectivities (entries 10 and 11).

3. Conclusion

In summary, we have developed an efficient synthetic pathway for the construction of anthracene-fused chiral proline catalysts **1** and **2** via a seven-step conversion from Diels–Alder adduct **3**. The utility of this novel class of artificial catalysts was exemplified by applying it to asymmetric Mannich-type reactions that provide chiral β-amino ketone compounds. Although the catalytic activities of **1** and **2** do not exceed our expectations, the present system offers several advantages, including easy construction of the catalysts and short reaction times. Further studies to improve the catalyst design and to apply this approach to other types of asymmetric transformations are now in progress.

4. Experimental

4.1. General

All reactions were performed in an oven-dried glassware under a positive pressure of nitrogen or argon. Air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. All melting points were measured on a Yanagimoto MP-S3 micro-melting point apparatus and are uncorrected. The NMR spectra were recorded on a JEOL LA 400 (400 MHz for ^{1}H NMR analysis and 100 MHz for ^{13}C NMR analysis) instrument in $CDCl_3$ unless otherwise stated and are reported in parts per million (δ) downfield from TMS as an internal standard. The infrared spectra were measured with a JASCO FTIR-5300 or FTIR-460plus Fourier Transform Infrared Spectrophotometer and are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC analysis was carried out using a Hitachi L-6200 HPLC system.

Thin-layer chromatography (TLC) was conducted using Merck Kieselgel 60F-254 plates (0.25 mm). Fuji silicia BW-300 was used for column chromatography, and Merck Kieselgel (230–400 mesh) was used for flash chromatography.

4.2. *N*-(*p*-Methoxybenzyl)-4,9[1′,2′]benzeno-3a,4,9,9a-tetrahydro-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione 4

To a solution of **3**[9] (5.53 g, 20 mmol) in dry THF (60 mL) was added *p*-methoxybenzylamine (2.74 g, 20 mmol) at room temperature, and the mixture was refluxed for 6 h. After the reaction was complete, the mixture was filtered, and the precipitate was dried in vacuo to give **4** (7.91 g, 100%) as a white solid. R_f 0.29 (hexane/EtOAc = 2:1); mp 224–226 °C (from $CHCl_3$–hexane); FTIR (KBr) ν 1773, 1707, 1615, 1516, 1250, 1034; ^{1}H NMR δ 3.20 (2H, s), 3.76 (3H, s), 4.20 (2H, s), 4.76 (2H, s), 6.65 (2H, d, $J_{AB} = 8.4$ Hz), 6.70 (2H, d, $J_{AB} = 8.4$ Hz), 6.97 (2H, dd, $J = 5.4$, 3.2 Hz), 7.14–7.17 (4H, m), 7.35 (2H, dd, $J = 4.6$, 3.2 Hz); ^{13}C NMR δ 41.5, 45.4 (×2), 46.8 (×2), 55.2, 113.7 (×2), 124.2 (×2), 124.8 (×2), 126.6 (×2), 127.0 (×2), 127.3, 129.3 (×2), 138.4 (×2), 141.7 (×2), 158.8, 176.5 (×2). Anal. Calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54. Found: C, 78.95; H, 5.59; N, 3.76.

4.3. *N*-(*p*-Methoxybenzyl)-4,9[1′,2′]benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole 5

To a suspension of $LiAlH_4$ (1.02 g, 26.9 mmol) in dry THF (60 mL) at 0 °C was added **4** (3.95 g, 10 mmol) in dry THF (140 mL), and the mixture was gently refluxed overnight. After cooling, the mixture was carefully quenched by the addition of a minimum amount of water, dried (K_2CO_3), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 4:1) to give **5** (3.31 g, 98%) as a yellowish gum. R_f 0.28 (hexane/EtOAc = 2:1); FTIR (neat) ν 1613, 1512, 1464, 1244, 1036; ^{1}H NMR δ 1.71 (2H, dd, $J = 9.0$, 6.6 Hz), 2.68 (2H, m), 2.80 (2H, m), 3.17 (2H, s), 3.78 (3H, s), 4.09 (2H, s), 6.77 (2H, d, $J = 8.5$ Hz), 6.97 (2H, d, $J = 8.5$ Hz), 7.07 (2H, dd, $J = 5.4$, 3.2 Hz), 7.14 (2H, $J = 5.4$, 3.2 Hz), 7.20–7.24 (4H, m); ^{13}C NMR ($CDCl_3$) δ 44.3 (×2), 47.3 (×2), 55.2, 56.9 (×2), 59.5, 113.4 (×2), 123.6 (×2), 125.6 (×2), 125.6 (6) (×2), 125.6 (7) (×2), 128.2, 129.8 (×2), 141.9 (×2), 144.1 (×2), 158.5. Anal. Calcd

for $C_{26}H_{25}NO{\cdot}H_2O$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.70; H, 7.19; N, 3.88.

4.4. *N*-(*tert*-Butoxycarbonyl)-4,9[1′,2′]benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole 6

To a solution of **5** (3.53 g, 9.6 mmol) in abs EtOH (50 mL) were added Boc_2O (3.14 g, 14.4 mmol) and 10% $Pd(OH)_2$/C (100 mg), and the mixture was stirred under H_2 at room temperature for 15 h. The catalyst was removed by filtration through Celite, and the crude product was recrystallized from CH_2Cl_2–hexane to give **6** (2.24 g, 67%; a ca. 3:1 mixture of amide rotamers) as a white solid (minor rotamer peaks denoted by an *). R_f 0.41 (hexane/EtOAc = 2:1); mp 211–215 °C (from $CHCl_3$–hexane); FTIR (KBr) ν 1691, 1470, 1418, 1175, 1115; ^{1}H NMR δ 1.29 (9H, s), 2.73 (2H, br s), 2.90 (1H, d, $J = 10.2$ Hz), 3.01 (1H, d, $J = 10.2$ Hz), 3.39 (2H, m), 4.17 (2H, d, $J = 13.7$ Hz), 7.09 (2H, dd, $J = 5.4$, 3.2 Hz), 7.11 (2H, dd, $J = 5.8$, 2.9 Hz), 7.24–7.29 (4H, m); ^{13}C NMR δ 28.3 (×3), 43.4*, 44.2*, 48.4 (×6), 48.6*, 77.2*, 78.8, 123.6 (×4), 125.1*, 125.6*, 125.9 (×4), 126.1*, 126.2*, 140.2 (×4), 143.2*, 143.5*, 153.3. Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.26; H, 7.53; N, 4.06.

4.5. *N*-(*tert*-Butoxycarbonyl)-4,9[1′,2′]benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole-1-carboxylic acid 8

To a solution of **6** (3.0 g, 8.63 mmol) in dry THF (36 mL) at −78 °C were added *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA; 1.5 mL, 9.94 mmol), and *sec*-BuLi (0.98 M in cyclohexane; 10 mL, 9.8 mmol). The mixture was stirred at −78 °C for 4 h and CO_2 gas was then bubbled into the reaction mixture. After being stirred for 3 h, the mixture was carefully quenched by the addition of aq NH_4Cl to make the solution acidic (pH ca. 4). The organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL × 3). The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to afford **8** (3.38 g, 100%) as a white solid. R_f 0.24 (hexane/EtOAc = 1:1); mp 235–238 °C (from $CHCl_3$–hexane); FTIR (KBr) ν 3441, 1732, 1692, 1399; ^{1}H NMR δ 1.40 and 1.42 (total 9H, s), 2.74 (1H, t, $J = 10.1$ Hz), 2.93 (1H, m), 3.13 (1H, m), 3.77 (1H, m), 4.14 (1H, br), 4.52 (1H, br s), 4.62 (1H, br), 7.06–7.28 (8H, m); ^{13}C NMR (major peaks; Boc carbonyl is missing) δ 28.3 (×3), 44.9 (×2), 46.2 (×3), 59.9, 80.1, 123.7, 123.8, 125.7, 125.9 (8), 126.0 (3), 126.3, 126.5, 127.3, 141.4, 143.8 (×2), 143.9, 171.2. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.31; H, 6.63; N, 3.63.

4.6. *N*-(*tert*-Butoxycarbonyl)-4,9[1′,2′]benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole-1-carboxylic acid (−)-menthyl ester 9

To a solution of **8** (4.04 g, 10.3 mmol), *N*,*N*′-dicyclohexylcarbodiimide (DCC; 3.61 g, 17.5 mmol), and 4-dimethylaminopyridine (DMAP; 370 mg, 3.0 mmol) in dry CH_2Cl_2 (150 mL) was added (−)-menthol (1.75 g, 11.2 mmol), and the mixture was stirred at room temperature for 16 h. After the reaction was complete, the mixture was concentrated, and the insoluble substance was removed by filtration. Evaporation of the solvent gave a crude product, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 99:1) to afford **9** (4.36 g, 80%; an inseparable 1:1 diastereomeric mixture) as a white solid. R_f 0.53 (hexane/acetone = 2:1); mp 179–185 °C (from hexane); FTIR (KBr) ν 1730, 1703, 1468, 1399, 1175; ^{1}H NMR δ 0.71 (3H, m), 0.86 (6H, d, $J = 6.4$ Hz), 0.90–1.15 (2H, m), 1.21 and 1.24 (total 9H, s), 1.32–1.50 (2H, m), 1.62–1.70 (3H, m), 1.78–1.96 (2H, m), 2.72 (2H, m), 3.17–3.19 and 3.37–3.50 (total 2H, m), 3.85 and 3.98 (total 1H, s), 4.17 and 4.21 (total 1H, s), 4.41 (1H, m), 4.66 (1H, m), 7.11–7.13 (4H, m), 7.26–7.34 (4H, m); ^{13}C NMR (major peaks; Boc carbonyl is missing) δ 16.1, 20.8, 21.9, 23.2, 26.0, 28.1 (×3), 31.3, 34.1, 40.7, 42.9, 46.9, 49.0 (×2), 49.1 (×2), 63.2, 74.9, 79.3, 123.6, 123.7, 123.8, 126.0, 126.1, 126.2 (×2), 126.5, 139.4, 139.7, 142.1, 143.1, 172.6. Anal. Calcd for $C_{34}H_{43}NO_4{\cdot}H_2O$: C, 74.56; H, 8.28; N, 2.56. Found: C, 74.77; H, 8.21; N, 2.83.

4.7. 4,9[1′,2′]Benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole-1-carboxylic acid (−)-menthyl ester 10 and 11

To a solution of **9** (2.06 g, 3.9 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added trifluoroacetic acid (TFA; 3.0 mL, 40.4 mmol), and the mixture was stirred at room temperature for 3 h. After being quenched by the addition of aq NaOH, the mixture was extracted with EtOAc. The extracts were dried (K_2CO_3) and concentrated. The crude product was purified repeatedly by column chromatography on silica gel (hexane/EtOAc = 2:1) to give **10** (762 mg, 46%) and **11** (758 mg, 45%).

Compound **10**: colorless gum; R_f 0.41 (hexane/EtOAc = 2:1); $[\alpha]_D^{22} = +20.9$ (c 1.62, MeOH); FTIR (neat) ν 3316, 1732, 1458, 1179; ^{1}H NMR δ 0.75 (3H, d, $J = 6.8$ Hz), 0.91 (6H, d, $J = 6.8$ Hz), 0.95–1.12 (2H, m), 1.45–1.51 (2H, m), 1.58–1.80 (4H, m), 1.86 (1H, ddt, $J = 16.0$, 7.1, 2.7 Hz), 1.98 (1H, m), 2.36 (1H, dd, $J = 11.5$, 5.6 Hz), 2.70 (2H, m), 3.10 (1H, d, $J = 5.6$ Hz), 3.15 (1H, dd, $J = 11.5$, 7.4 Hz), 4.12 (1H, d, $J = 2.7$ Hz), 4.34 (1H, d, $J = 2.7$ Hz), 4.73 (1H, dt, $J = 10.9$, 4.3 Hz), 7.07–7.12 (2H, m), 7.13–7.17 (2H, m), 7.23–7.30 (4H, m); ^{13}C NMR δ 16.4, 20.7, 22.0, 23.6, 26.4, 31.4, 34.2, 40.9, 46.8, 47.1, 47.7 (×2), 50.1, 51.9, 63.7, 74.7, 123.6, 123.8, 125.5, 125.7, 125.8, 126.0, 126.2 (6), 126.2 (7), 140.9, 141.1, 143.4, 144.1, 173.1. Anal. Calcd for $C_{29}H_{35}NO_2{\cdot}H_2O$: C, 77.82; H, 8.33; N, 3.13. Found: C, 77.46; H, 8.27; N, 3.39.

Compound **11**: mica crystals; R_f 0.38 (hexane/EtOAc = 2:1); mp 159–161 °C (from hexane); $[\alpha]_D^{22} = -93.1$ (c 1.41, MeOH); FTIR (KBr) ν 3322, 1725, 1456, 1233, 1181; ^{1}H NMR δ 0.77 (3H, d, $J = 7.1$ Hz), 0.92 (3H, d, $J = 6.6$ Hz), 1.01 (3H, d, $J = 6.8$ Hz), 0.87–1.13 (2H, m), 1.26 (1H, m), 1.43–1.57 (2H, m), 1.71–1.76 (2H, m), 1.96–2.04 (2H, m), 2.27 (1H, dd, $J = 11.5$, 7.8 Hz), 2.65 (1H, br), 2.69 (1H, ddd, $J = 10.8$, 7.8, 3.0 Hz), 2.78–2.85 (1H, m), 3.07 (1H, d, $J = 7.6$ Hz), 3.27

(1H, dd, $J = 11.5$, 8.1 Hz), 4.11 (1H, d, $J = 2.8$ Hz), 4.34 (1H, d, $J = 2.7$ Hz), 4.76 (1H, dt, $J = 11.0$, 4.5 Hz), 7.03–7.11 (2H, m), 7.13–7.18 (2H, m), 7.20–7.22 (1H, m), 7.23–7.27 (2H, m), 7.30–7.33 (1H, m); ^{13}C NMR δ 16.1, 21.0, 22.0, 23.2, 26.3, 31.4, 34.2, 40.8, 47.1 (6), 47.2 (0), 47.4, 47.5, 49.9, 52.3, 63.6, 74.7, 123.6 (×2), 125.7, 125.8, 125.8 (8), 125.9 (2), 126.2, 126.3, 140.1, 141.3, 143.6, 144.2, 173.2. Anal. Calcd for $C_{29}H_{35}NO_2$: C, 81.08; H, 8.21; N, 3.26. Found: C, 79.97; H, 8.64; N, 3.45.

4.8. X-ray crystal structure determination of compound 11

A colorless platelet crystal of $C_{29}H_{35}NO_2$ with approximate dimensions of $0.80 \times 0.40 \times 0.05$ mm, mounted in a loop, was used for the X-ray study. All measurements were made on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 4010 observed reflections and 289 variable parameters and converged with unweighted and weighted agreement factors of $R = 0.063$ and $R_w = 0.101$. Crystal data: $C_{29}H_{35}NO_2$, $M = 429.60$, crystal system: orthorhombic, space group: $P2_12_12_1$ (#19). Lattice parameters: $a = 7.1814$ (2) Å, $b = 8.6301(3)$ Å, $c = 38.797(1)$ Å, $V = 2404.5(1)$ Å^3, $Z = 4$, $D_{calc} = 1.187$ g/cm^3, $F(000)$ 928.00, μ(Mo-Kα) 0.73 cm^{-1}. CCDC-626851 contains the supplementary crystallographic data for this complex. These data are available free of charge via www.ccdc.cam.ac.uk/data_request/cif.

4.9. (1*S*,3a*R*,9a*S*)-4,9[1′,2′]Benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole-1-carboxylic acid 1

To a solution of **10** (180 mg, 0.42 mmol) in MeOH (5 mL) was added aq NaOH (1.0 M; 2.5 mL, 2.5 mmol), and the mixture was stirred at 45 °C for 16 h. Evaporation of the solvent gave a crude product, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 4:1) to give pure **1** (89 mg, 73%) as a white solid. R_f 0.19 ($CHCl_3$/MeOH = 4:1); mp 261–265 °C; $[\alpha]_D^{22} = +57.6$ (*c* 0.62, MeOH); FTIR (KBr) *v* 3434, 1735, 1675, 1198, 1140; ^{1}H NMR (CD_3OD) δ 2.26 (1H, dd, $J = 11.7$, 9.5 Hz), 2.73 (1H, m), 2.90 (1H, m), 3.04 (1H, d, $J = 9.3$ Hz), 3.46 (1H, dd, $J = 11.7$, 8.3 Hz), 4.28 (1H, d, $J = 2.7$ Hz), 4.58 (1H, d, $J = 2.7$ Hz), 7.09–7.14 (2H, m), 7.19–7.24 (2H, m), 7.28–7.37 (3H, m), 7.46–7.50 (1H, m); ^{13}C NMR (CD_3OD) δ 45.2, 47.1, 47.7, 48.0, 50.0, 65.2, 124.9, 125.2, 127.3 (9) (×2), 127.4 (4), 127.7, 127.8, 127.9, 141.7, 141.8, 144.1, 144.2, 172.7. Anal. Calcd for $C_{19}H_{17}NO_2 \cdot 0.6H_2O$: C, 75.52; H, 6.07; N, 4.64. Found: C, 75.14; H, 6.38; N, 4.58.

4.10. (1*R*,3a*S*,9a*R*)-4,9[1′,2′]Benzeno-1,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]isoindole-1-carboxylic acid 2

Compound **2** was also prepared in the same manner as for **1**: mp 262–265 °C; $[\alpha]_D^{22} = -57.6$ (*c* 1.31, MeOH).

4.11. General procedure for anthracene-fused proline-catalyzed asymmetric Mannich reactions

A suspension of **1** (29 mg, 0.1 mmol), *p*-anisidine (67 mg, 0.55 mmol), and an aldehyde (0.5 mmol) in 5 mL of pure ketone (or DMSO/ketone = 4:1) was stirred at room temperature for 30–120 min. The mixture was worked up by filtration to remove the insoluble materials, concentrated, and purified by column chromatography on silica gel (hexane/EtOAc = 4:1 to 2:1). In the reactions in DMSO–ketone, the mixture was quenched by the addition of phosphate buffer solution (pH 7.4) and extracted with EtOAc. The extracts were dried ($MgSO_4$), concentrated, and purified by column chromatography on silica gel (hexane/EtOAc = 4:1 to 2:1). The enantiomeric purity of the substance was determined by chiral HPLC analysis.

4.11.1. (*R*)-4-(4-Methoxyphenylamino)-6-methylheptan-2-one 12. Yellow oil, 76%, ee = 75%. FTIR (neat) *v* 3367, 1709, 1618, 1512, 1241; ^{1}H NMR δ 0.91 (3H, d, $J = 6.6$ Hz), 0.93 (3H, d, $J = 6.8$ Hz), 1.32 (1H, ddd, $J = 14.0$, 8.1, 5.9 Hz), 1.47 (1H, ddd, $J = 14.0$, 8.3, 6.3 Hz), 1.74 (1H, m), 2.12 (3H, s), 2.55 (1H, dd, $J = 16.4$, 6.3 Hz), 2.65 (1H, dd, $J = 16.4$, 4.9 Hz), 3.37 (1H, br), 3.74 (3H, s), 3.81 (1H, m), 6.57 (2H, m), 6.77 (2H, m); ^{13}C NMR δ 22.3, 22.9, 25.0, 31.0, 44.7, 48.0, 49.1, 55.7, 115.0 (×4), 141.3, 152.1, 208.6. HPLC: Daicel Chiralpak AS, $\lambda = 315$ nm, 10% *i*-PrOH/hexane, flow rate = 0.5 mL/min, major t_R (*R*-enantiomer) 16.08 min, minor t_R (*S*-enantiomer) 20.08 min.

4.11.2. (*S*)-4-(4-Methoxyphenylamino)-5-methylhexan-2-one 14. Yellow oil, 56%, ee = 54%. FTIR (neat) *v* 3376, 1709, 1618, 1513, 1236; ^{1}H NMR δ 0.90 (3H, d, $J = 6.8$ Hz), 0.96 (3H, d, $J = 7.1$ Hz), 1.93 (1H, m), 2.14 (3H, s), 2.53 (1H, dd, $J = 15.9$, 7.1 Hz), 2.58 (1H, $J = 15.9$, 5.4 Hz), 3.36 (1H, br), 3.65 (1H, dt, $J = 7.1$, 5.4 Hz), 3.74 (3H, s), 6.58 (2H, m), 6.76 (2H, m); ^{13}C NMR: δ 18.4, 18.8, 30.6, 31.2, 45.2, 55.8, 56.2, 114.9 (×4), 141.6, 152.1, 208.5. HPLC: Daicel Chiralpak AS, $\lambda = 315$ nm, 15% *i*-PrOH/hexane, flow rate = 0.5 mL/min, major t_R (*S*-enantiomer) 16.14 min, minor t_R (*R*-enantiomer) 23.31 min.

4.11.3. (*R*)-4-(4-Methoxyphenylamino)octan-2-one 15. Yellow oil, 62%, ee = 64%. FTIR (neat) *v* 3366, 1709, 1512, 1237; ^{1}H NMR δ 0.88 (3H, t, $J = 7.5$ Hz), 1.23–1.43 (4H, m), 1.53 (2H, m), 2.13 (3H, s), 2.57 (1H, dd, $J = 16.4$, 6.4 Hz), 2.65 (1H, dd, $J = 16.4$, 5.4 Hz), 3.38 (1H, br), 3.72 (1H, m), 3.74 (3H, s), 6.57 (2H, m), 6.76 (2H, m); ^{13}C NMR δ 14.0, 22.6, 28.4, 30.9, 34.9, 47.9, 51.0, 55.8, 115.0 (×2), 115.1 (×2), 141.3, 152.2, 208.4. HPLC: Daicel Chiralpak AD, $\lambda = 315$ nm, 2% *i*-PrOH/hexane, flow rate = 0.5 mL/min, major t_R (*S*-enantiomer) 24.04 min, minor t_R (*R*-enantiomer) 27.26 min.

4.11.4. (*S*)-4-(4-Nitrophenyl)-(4-methoxyphenylamino)-butan-2-one 16. Yellow oil, 54%, ee = 90%. FTIR (neat) *v* 3361, 1713, 1600, 1512, 1346, 1239; ^{1}H NMR δ 2.15 (3H, s), 2.94 (2H, d, $J = 6.4$ Hz), 3.69 (3H, s), 4.28 (1H, br), 4.85 (1H, t, $J = 6.4$ Hz), 6.46 (2H, m), 6.69 (2H, m), 7.55 (2H, d, $J = 8.8$ Hz), 8.17 (2H, d, $J = 8.8$ Hz); ^{13}C NMR δ 30.7, 50.7, 54.7, 55.6, 55.7, 114.8 (×2), 115.4 (×2),

116.4, 124.0 (×2), 127.4 (×2), 140.1, 150.6, 152.8, 206.1. HPLC: Daicel Chiralpak AD, $\lambda = 280$ nm, 50% *i*-PrOH/hexane, flow rate = 0.5 mL/min, major t_R (*S*-enantiomer) 17.36 min, minor t_R (*R*-enantiomer) 14.38 min.

4.11.5. (*S*)-4-(2-Naphthyl)-(4-methoxyphenylamino)-butan-2-one 17. Light yellow solid, 59%, ee = 90%. FTIR (KBr) *v* 3386, 1709, 1512, 1238; ^{1}H NMR δ 2.12 (3H, s), 2.98 (2H, d, $J = 6.8$ Hz), 3.67 (3H, s), 4.27 (1H, br), 4.92 (1H, t, $J = 6.8$ Hz), 6.55 (2H, m), 6.67 (2H, m), 7.44–7.50 (3H, m), 7.78–7.83 (4H, m); ^{13}C NMR δ 30.8, 51.4, 55.5, 55.6, 114.7 (×2), 115.4 (×2), 124.4, 125.1, 125.8, 126.2, 127.7, 127.9, 128.7, 132.8, 133.4, 140.2, 140.9, 152.4, 207.2. HPLC: Daicel Chiralpak AS-H, $\lambda = 315$ nm, 15% *i*-PrOH/hexane, flow rate = 1.0 mL/min, major t_R (*R*-enantiomer) 17.11 min, minor t_R (*S*-enantiomer) 20.24 min.

4.11.6. (*S*)-4-(2-Furyl)-(4-methoxyphenylamino)butan-2-one 18. Yellow oil, 65%, ee = 84%. FTIR (neat) *v* 3362, 1712, 1618, 1513, 1239; ^{1}H NMR δ 2.15 (3H, s), 2.97 (1H, dd, $J = 16.4$, 6.1 Hz), 3.02 (1H, dd, $J = 16.4$, 6.1 Hz), 3.73 (3H, s), 3.96 (1H, br), 4.91 (1H, t, $J = 6.1$ Hz), 6.15 (1H, d, $J = 3.3$ Hz), 6.27 (1H, dd, $J = 3.3$, 2.0 Hz), 6.63 (2H, m), 6.75 (2H, m), 7.32 (1H, m); ^{13}C NMR δ 30.7, 47.3, 49.6, 55.6, 106.4, 110.3, 114.7 (×2), 115.9 (×2), 140.5, 141.6, 152.9, 154.9, 206.8. HPLC: Daicel Chiralpak AS-H, $\lambda = 315$ nm, 10% *i*-PrOH/hexane, flow rate = 1.0 mL/min, major t_R (*R*-enantiomer) 25.83 min, minor t_R (*S*-enantiomer) 35.55 min.

4.11.7. (3*S*,4*R*)-3-Hydroxy-4-phenyl-(4-methoxyphenylamino)butan-2-one 19. Colorless solid, 72% (dr >19:1), ee = 79%. FTIR (KBr) *v* 3381, 1714, 1619, 1513, 1241; ^{1}H NMR δ 2.33 (3H, s), 3.68 (3H, s), 3.77 (1H, d, $J = 2.8$ Hz), 4.34 (1H, br), 4.43 (1H, t, $J = 2.8$ Hz), 4.90 (1H, br s), 6.50 (2H, m), 6.68 (2H, m), 7.23–7.38 (5H, m); ^{13}C NMR δ 25.2, 55.6, 59.1, 80.8, 114.8 (×2), 115.1 (×2), 127.0 (×2), 127.6, 128.7 (×2), 139.3, 140.1, 152.4, 207.4. HPLC: Daicel Chiralpak AD, $\lambda = 254$ nm, 8% *i*-PrOH/hexane, flow rate = 1.0 mL/min, minor t_R (3*R*,4*S*-enantiomer) 14.56 min, major t_R (3*S*,4*R*-enantiomer) 20.30 min.

4.11.8. (3*S*,4*R*)-3-Methoxy-4-(4-nitrophenyl)-(4-methoxyphenylamino)butan-2-one 20. Yellow oil, 67% (dr >17:1), ee = 86%. FTIR (neat) *v* 3379, 1717, 1605, 1514, 1347, 1243; ^{1}H NMR δ 2.23 (3H, s), 3.32 (3H, s), 3.68 (3H, s), 3.81 (1H, d, $J = 2.5$ Hz), 4.59 (1H, br), 4.86 (1H, d, $J = 2.5$ Hz), 6.45 (2H, m), 6.67 (2H, m), 7.53 (2H, m), 8.18 (2H, m); ^{13}C NMR δ 27.3, 55.6, 59.3, 59.9, 89.8, 114.9 (×2), 115.1 (×2), 115.6, 123.8 (×2), 128.1 (×2), 139.5, 147.9, 152.7, 209.5. HPLC: Daicel Chiralpak AD, $\lambda = 280$ nm, 5% *i*-PrOH/hexane, flow rate = 0.5 mL/min, minor t_R (3*R*,4*S*-enantiomer) 49.04 min, major t_R (3*S*,4*R*-enantiomer) 54.48 min.

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References

1. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (c) Houk, K. N., List, B., Eds. *Acc. Chem. Res.* **2004**, *37*; (d) List, B., Bolm, C., Eds.. *Adv. Synth. Catal.* **2004**, *346*; (e) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005; (f) Kocovosky, P., Malkov, A. V., Eds. *Tetrahedron* **2006**, *62*.
2. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
3. Reviews: (a) List, B. *Synlett* **2001**, *11*, 1675–1686; (b) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532; (c) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Eur. J.* **2002**, *8*, 37–44; (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495; (e) List, B. *Tetrahedron* **2002**, *58*, 5573–5590.
4. For example, see: (a) Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962–963; (b) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055–3057; (c) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409; (d) Cheong, P. H.-Y.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 811–814; (e) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041; (f) Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423–7426.
5. (a) Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* **2003**, 1655–1658; (b) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; (c) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron* **2006**, *62*, 311–316.
6. Atherton, J. C. C.; Jones, S. *Tetrahedron* **2003**, *59*, 9039–9057.
7. Reviews: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943; (b) Matsunaga, H.; Ishizuka, H.; Kunieda, T. *Tetrahedron* **2005**, *61*, 8073–8094; See also: (a) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2004**, *45*, 8203–8206; (b) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Org. Lett.* **2006**, *8*, 1487–1490.
8. For reviews of proline-catalyzed asymmetric Mannich reactions, see: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591; (c) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352.
9. (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437; See also: (b) Kloetzel, M. C. *Org. React.* **1948**, *4*, 1–59.
10. Reviews: (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523; (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560.
11. Stürmer, R.; Schäfer, B.; Wolfart, V.; Stahr, H.; Kazmaier, U.; Helmchen, G. *Synthesis* **2001**, 46–48.
12. (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833; (c) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208–11209; (d) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131–1140.