Supporting Information attached to manuscript:

**Solid-Phase Synthesis of Polysubstituted Piperidines by Imino-Diels-Alder Cycloaddition of 2-Amino-1,3-butadienes with Solid-Supported Imines**

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**Experimental**

**General Methods.** All reactions were carried out in fritted polypropylene syringes unless otherwise specified. Resin washings were performed three times with 5 mL of each solvent specified. All solvents were reagent grade or HPLC grade for the cleavage step. All chemicals used were reagent grade quality and used without previous purification except where noted. Chloromethyl polystyrene (Merrifield resin) was purchased to Aldrich Chemical Co. (loading 1.0-1.5 mmol/g, 2% cross-linked, 200-400 mesh). Wang resin was purchased to Polymer Laboratories (loading 1.70 or 1.83 mmol/g, 75-150 µm). All resins synthesized were dried under vacuum and stored in a desiccator at room temperature. For isolation, organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure.

¹H NMR spectra were recorded at 200 or 300 MHz, and ¹³C NMR spectra at 50 or 75 MHz in CDCl₃ at rt; chemical shift values are given in parts per million (ppm) relative to the residual solvent peak (δ) and coupling constants in Hz. Analytical TLC was carried out using Merck aluminium-backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using silica gel 60, 230-240 Mesh. Analytical HPLC was performed on a Shimadzu instrument using a Nucleosil 120-10 (10 µm, 150 x 4 mm) column and a flow rate of 0.8 mL/min, measuring at 220 nm.

2-Amino-1,3-butadienes were prepared as previously reported.¹ Resin-bound imines were obtained following literature procedures starting with BOBA² or modified Wang³ resins, and employing in both cases the trimethyl orthoformate method.⁴

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General procedures for the Imino-Diels Alder reactions:

- **Method A:** To a solution of Yb(OTf)$_3$ (125 mg, 0.2 mmol, 20 mol %) in THF (4 mL), the correspondent imine-resin 2 or 2’ was added and shaken for 5 min, when the aminodiene 1 (1 mmol) was added at rt. The reaction mixture was gently shaken for 12 h (the colour turned to dark brown). Filtration of the mixture and washing with DCM, MeOH, DMF and DCM afforded enaminic-adduct resins 3 or 3’. Following this method compounds 5aa, 5ab, 5ac, 5ad, 5ae, 5af, 5ag, 5ah, 5da, 5’aa and 5’ab were synthesized.

- **Method B:** To a solution of Yb(OTf)$_3$ (125 mg, 0.2 mmol, 20 mol %) in THF (10 mL) in a schlenk flask under a nitrogen atmosphere, the correspondent imine-resin 2 or 2’ was added and stirred for 5 min. The suspension was cooled (-60ºC) and the aminodiene 1 was added dropwise. Stirring was continued for 48 h, when the resin was rapidly filtered and washed with DCM, MeOH, DMF and DCM to provide the supported enaminic adduct 3 or 3’. Following this method compounds 5ba, 5ca, 5’ba and 5’ca were synthesized.

General procedures for the hydrolysis step:

- **TFA/DCM method:** The enaminic resin 3 or 3’ obtained in the first step was shaken with 2% TFA/DCM for 25 min, filtered and washed with DCM (6 x 5 mL) to afford the correspondent resin-bound piperidine-4-ones 4 or 4’. The combined filtrates can be concentrated to check whether the reaction sequence was successful. In this case, the essentially pure amine-TFA salt is obtained.

- **Aqueous HCl/THF method:** The enaminic resin 3 or 3’ was shaken overnight with a solution of aqueous HCl (0.1 mL, 0.01 M) in THF (3.5 mL). Filtration and washing with THF (3 x 5 mL) and DCM (4 x 5 mL) provided the correspondent resin-bound piperidones 4 or 4’.

General procedure for the cleavage step: Immobilized piperidones 4 or 4’ were suspended in a solution of TMSOTf (0.4 mL) in DCM (4 mL) and shaken for 3 h at rt. Then, the resin was filtered and washed with DCM, saturated aqueous NaHCO$_3$ solution (4 x 5 mL), and DCM. The filtrates were combined; the organic layer was separated, washed with saturated aqueous NaHCO$_3$ solution (2 x 10 mL) and brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The resultant residue was dried under high vacuum for 6 h to afford final 4-piperidones 5 or 5’.

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(2S*, 5S*)-N-(4-hydroxybenzyl)-5-methyl-2-phenylpiperidin-4-one (5aa). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5aa as a brown oil (23 mg, 93%). Rf= 0.34 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.48-7.07 (m; 7H), 6.79-6.72 (m; 2H), 3.69 (d, $^2$J=13.2; 1H), 3.49 (dd, $^3$J$_{aa}$=11.7, $^3$J$_{ae}$=3.5; 1H), 3.22 (dd, $^2$J=11.4; $^3$J$_{ae}$=5.8; 1H), 2.82-2.67 (m; 3H), 2.49 (dd, $^2$J=13.7, $^3$J$_{ae}$=3.5; 1H), 1.99 (dd, $^2$J=13.7, $^3$J$_{ae}$=11.6; 1H), 0.94 (d, $^3$J=6.6; 3H). 13C-NMR (CDCl$_3$, 75 MHz): 210.6 (C), 154.9 (C), 142.5 (C), 129.8 (CH), 129.6 (CH), 128.9 (CH), 127.2 (CH), 115.1 (CH), 69.3 (CH), 59.2 (CH$_2$), 57.3 (CH$_2$), 50.5 (CH$_2$), 44.4 (CH), 11.2 (CH$_3$). HRMS (EI): calcd. for C$_{19}$H$_{21}$NO$_2$: 295.1572, found 295.1569.

(2S*, 5S*)-N-(4-hydroxybenzyl)-5-methyl-2-(3-methoxyphenyl)piperidin-4-one (5ab). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5ab as a brown oil (21 mg, 80%). Rf= 0.42 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.34-6.92 (m; 5H), 6.88-6.75 (m; 3H), 3.84 (s; 3H), 3.82-3.71 (m; 2H), 3.50 (dd, $^3$J$_{aa}$=11.6, $^3$J$_{ae}$=3.6; 1H), 3.22 (dd, $^2$J=11.5, $^3$J$_{ae}$=5.9; 1H), 2.89-2.60 (m; 2H), 2.52 (dd, $^2$J=13.8, $^3$J$_{ae}$=3.6; 1H), 2.11 (dd, $^2$J=13.7, $^3$J$_{ae}$=11.6; 1H), 0.97 (d, $^3$J=6.6; 3H). 13C-NMR (CDCl$_3$, 75 MHz): 210.2 (C), 159.9 (C), 154.9 (CH), 144.2 (C), 143.4 (C), 129.8 (CH), 129.6 (CH), 119.5 (CH), 115.1 (CH), 112.9 (CH), 112.6 (CH), 69.2 (CH$_3$), 59.2 (CH$_2$), 57.2 (CH$_2$), 55.1 (CH), 50.3 (CH$_2$), 44.3 (CH). 11.1 (CH$_3$).

(2S*, 5S*)-2-(2-bromophenyl)-N-(4-hydroxybenzyl)-5-methylpiperidin-4-one (5ac). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5ac as a colourless oil (26 mg, 83%). Rf= 0.46 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.43-7.21 (m; 6H), 6.85-6.79 (m; 2H), 3.83 (d, $^2$J=13.7; 1H), 3.47 (dd, $^3$J$_{aa}$=11.4, $^3$J$_{ae}$=3.2; 1H), 3.17 (dd, $^2$J=11.6, $^3$J$_{ae}$=5.9; 1H), 2.89-2.65 (m; 3H), 2.49 (dd, $^2$J=13.9, $^3$J$_{ae}$=3.4; 1H), 2.10 (dd, $^2$J=13.7, $^3$J$_{ae}$=11.7; 1H), 0.94 (d, $^3$J=6.6; 3H). 13C-NMR (CDCl$_3$, 75 MHz): 210.0 (C), 154.9 (C), 141.2 (C), 133.0 (CH), 129.9 (CH), 129.7 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 123.4 (C), 115.2 (CH), 66.6 (CH), 58.9 (CH$_2$), 57.1 (CH$_2$), 48.4 (CH$_2$), 44.4 (CH), 11.2 (CH$_3$). HRMS (FAB): calcd. for C$_{19}$H$_{20}$NO$_2$Br: 374.0755, found 374.0737.

(2S*, 5S*)-2-(3-bromophenyl)-N-(4-hydroxybenzyl)-5-methylpiperidin-4-one (5ad). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5ad as a
colourless oil (28 mg, 91%). $R_f$= 0.32 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.67-7.11 (m; 6H), 6.85-6.74 (m; 2H), 3.72 (d, $^2$J=13.1; 1H), 3.49 (dd, $^3$J$_{aa}$=11.6, $^3$J$_{ae}$=3.9; 1H), 3.21 (dd, $^2$J=11.5; $^3$J$_{ae}$=5.9; 1H), 2.84-2.45 (m; 4H), 2.01 (dd, $^2$J= $^3$J$_{aa}$=11.6; 1H), 0.97 (d; $^3$J=6.4; 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): 209.7 (C), 155.1 (C), 145.1 (C), 130.9 (CH), 130.3 (CH), 130.1 (C), 129.9 (CH), 125.9 (CH), 122.9 (C), 115.2 (CH), 68.7 (CH), 59.1 (CH$_2$), 57.4 (CH$_2$), 50.3 (CH$_2$), 44.4 (CH), 11.2 (CH$_3$). HRMS (FAB): calcd. for C$_{19}$H$_{20}$NO$_2$Br: 374.0755, found 374.0774.

$(2S^*, 5S^*)$-2-(4-bromophenyl)-N-(4-hydroxybenzyl)-5-methylpiperidin-4-one (5ae). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5ae as a colourless oil (21 mg, 67%). $R_f$= 0.38 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.53-7.43 (m; 6H), 6.82-6.73 (m; 2H), 3.68 (d, $^2$J=13.3; 1H), 3.49 (dd, $^3$J$_{aa}$=11.6, $^3$J$_{ae}$=3.4; 1H), 3.19 (dd, $^2$J=11.7; $^3$J$_{ae}$=4.0; 1H), 2.84-2.59 (m; 3H), 2.47 (dd, $^2$J=13.9, $^3$J$_{ae}$=3.4; 1H), 2.00 (dd, $^2$J= $^3$J$_{aa}$=11.7; 1H), 0.95 (d; $^3$J=6.6; 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): 209.8 (C), 155.7 (C), 141.6 (C), 132.1 (CH), 131.8 (C), 129.9 (CH), 128.9 (CH), 121.4 (C), 115.2 (CH), 68.6 (CH), 59.1 (CH$_2$), 57.3 (CH$_2$), 50.3 (CH$_2$), 44.4 (CH), 11.2 (CH$_3$). HRMS (EI): calcd. for C$_{19}$H$_{20}$NO$_2$Br: 374.0755, found 374.0789.

$(2S^*, 5S^*)$-2-(furan-2-yl)-N-(4-hydroxybenzyl)-5-methylpiperidin-4-one (5af). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The aqueous HCl/THF method was used for the hydrolysis step. The cleavage step furnished compound 5af as a brown oil (17 mg, 71%). $R_f$= 0.38 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.34-7.26 (m; 2H), 6.89-6.80 (m; 2H), 6.39-6.28 (m; 1H), 6.12-6.08 (m; 1H), 4.37-4.32 (m; 1H), 3.72 (d, $^2$J=13.3; 1H), 3.52 (d, $^2$J=13.3, 1H), 2.98-2.83 (m; 2H), 2.63 (dd, $^2$J=14.4, $^3$J$_{ae}$=2.3; 1H), 2.37 (dd, $^2$J=14.4, $^3$J$_{aa}$=11.2; 1H), 1.04 (d; $^3$J=6.6; 3H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): 210.8 (C), 154.9 (C), 152.9 (C), 142.2 (CH), 131.2 (CH), 130.0 (CH), 115.3 (CH), 109.8 (CH), 109.1 (CH), 60.7 (CH), 58.0 (CH$_2$), 56.6 (CH), 54.0 (CH$_2$), 44.0 (CH$_2$), 11.8 (CH$_3$). HRMS (FAB): calcd. for C$_{17}$H$_{19}$NO$_3$ + H: 286.1443, found 286.1442.

$(2S^*, 5S^*)$-2-(furan-3-yl)-N-(4-hydroxybenzyl)-5-methylpiperidin-4-one (5ag). Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The aqueous HCl/THF method was used for the hydrolysis step. The cleavage step furnished compound 5ag as a brown oil (18 mg, 76%). $R_f$= 0.31 (DCM : MeOH, 20 : 1). $^1$H-NMR (CDCl$_3$, 300 MHz): 7.42-7.15 (m; 4H), 6.84-6.62 (m; 3H), 4.25-4.20 (m; 1H), 3.68 (d, $^2$J=13.0; 1H), 3.61 (d, $^2$J=13.0, 1H), 2.98-
(2S*, 5S*)-N-(4-hydroxybenzyl)-5-methyl-2-(pyridin-3-yl)piperidin-4-one (5ah).
Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5ah as a brown oil (18 mg, 71%). \( R_f = 0.14 \) (DCM: MeOH, 20:1). \(^1\)H-NMR (CDCl\(_3\), 300 MHz): 8.61-8.56 (m; 1H), 7.84-7.77 (m; 1H), 7.45-7.37 (m; 1H), 7.25-7.19 (m; 1H), 7.15 (d, \(^3\)J=8.2, 2H), 6.89 (d, \(^3\)J=8.2, 2H), 3.72 (d, \(^2\)J=13.1, 1H), 3.63 (dd, \(^3\)J\(_{aa}=11.5, \)^3J\(_{ae}=3.8; 1H), 3.38-3.21 (m; 2H), 2.86-2.63 (m; 2H), 2.53 (dd, \(^2\)J=14.1, \(^3\)J\(_{ac}=3.8; 1H), 2.06 (dd, \(^3\)J\(_{ac}=11.7, \)^2J=11.6; 1H), 0.98 (d, \(^3\)J=6.5; 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): 208.9 (C), 156.5 (C), 148.1 (CH), 139.1 (C), 136.2 (CH), 129.9 (CH), 128.8 (C), 124.3 (CH), 121.4 (CH), 115.4 (CH), 66.9 (CH), 59.1 (CH\(_2\)), 57.7 (CH\(_2\)), 50.2 (CH\(_2\)), 44.4 (CH). 11.2 (CH\(_3\)).

(2S*, 5S*, 6S*)-N-(4-hydroxybenzyl)-2-phenyloctahidroquinolin-4-one (5ca).
Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5ca as a colourless oil (25 mg, 90%). \( R_f = 0.51 \) (DCM: MeOH, 20:1). \(^1\)H-NMR (CDCl\(_3\), 300 MHz): 7.45-7.09 (m; 7H), 7.09-7.69 (m; 2H), 3.88 (d, \(^2\)J=15.4; 1H), 3.82 (dd, \(^3\)J\(_{aa}=11.5, \)^3J\(_{ae}=3.1; 1H), 3.57-3.44 (m; 2H), 2.83-2.42 (m; 2H), 2.10-1.97 (m; 1H), 1.84-1.67 (m; 4H), 1.32-1.15 (m; 4H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): 209.8 (C), 154.2 (C), 143.0 (C), 129.1 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 127.0 (CH), 114.5 (CH), 67.3 (CH), 67.2 (CH), 53.2 (CH), 52.2 (CH\(_2\)), 49.4 (CH\(_2\)), 33.2 (CH\(_2\)), 24.8 (CH\(_2\)), 24.3 (CH\(_2\)), 23.9 (CH\(_2\)). HRMS (EI): calcd. for C\(_{22}\)H\(_{25}\)NO\(_2\): 335.1885, found 335.1885.

(2R*, 3S*, 6S*)-N-(4-hydroxybenzyl)-2-hydroxymethyl-3-methyl-6-phenylpiperidin-4-one (5da).
Prepared from the correspondent resin-bound imine (200 mg, 0.42 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5da as a brown oil (22 mg, 82%). \( R_f = 0.25 \) (DCM: MeOH, 20:1). \(^1\)H-NMR (CDCl\(_3\), 300 MHz): 7.59-7.00 (m; 7H), 6.82-6.67 (m; 2H), 4.22 (dd, \(^3\)J\(_{aa}=10.5, \)^3J\(_{ae}=4.6; 1H), 3.65 (d, \(^2\)J=13.1; 1H), 3.50 (d, \(^2\)J=13.1, 1H), 3.45-3.31 (m; 2H), 3.11-2.85 (m; 2H), 1.07 (d, \(^3\)J=6.8; 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): 210.2 (C), 155.8 (C), 142.7 (C), 130.7 (CH), 130.0 (C), 129.0 (CH), 127.9 (CH), 127.4 (CH), 115.7 (CH), 62.3 (CH\(_2\)), 62.0 (CH), 61.0 (CH), 24.8 (CH\(_2\)), 24.3 (CH\(_2\)), 23.9 (CH\(_2\)).
(2S*, 5S*)-N-benzyl-2-(4-hydroxyphenyl)-5-methylpiperidin-4-one (5’aa). Prepared from the correspondent resin-bound imine (120 mg, 1.7 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5’aa as a colourless oil (32 mg, 54%). \( R_f = 0.29 \) (DCM : MeOH, 20 : 1). \(^1\)H-NMR (CDCl\(_3\), 300 MHz): 7.45-7.22 (m; 7H), 6.87-6.81 (m; 2H), 3.83 (d, \(^2J=13.7\); 1H), 3.47 (dd, \(^3J_{aa}=11.4, ^3J_{ae}=3.2\); 1H), 3.19 (dd, \(^2J=11.3, ^3J_{ae}=6.0\); 1H), 2.89-2.62 (m; 3H), 2.49 (dd, \(^2J=14.2, ^3J_{ae}=3.2\); 1H), 2.10 (dd, \(^2J=11.5, ^3J_{ae}=11.5\); 1H), 0.95 (d; \(^3J=6.8\); 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): 210.6 (C), 155.4 (C), 128.8 (C), 128.5 (C), 128.4 (CH), 128.3 (CH), 127.0 (CH), 115.8 (CH), 115.5 (CH), 68.8 (CH), 59.4 (CH\(_2\)), 57.8 (CH\(_2\)), 50.6 (CH\(_2\)), 44.4 (CH), 11.2 (CH\(_3\)). HRMS (EI): calcd. for C\(_{19}\)H\(_{21}\)NO\(_2\): 295.1572, found 295.1568.

(2S*, 5S*)-N-allyl-2-(4-hydroxyphenyl)-5-methylpiperidin-4-one (5’ab). Prepared from the correspondent resin-bound imine (120 mg, 1.70 mmol/g). The aqueous HCl/THF method was used for the hydrolysis step. The cleavage step furnished compound 5’ab as a brown oil (33 mg, 66%). \( R_f = 0.26 \) (DCM : MeOH, 20 : 1). \(^1\)H-NMR (CDCl\(_3\), 300 MHz): 7.20 (d, \(^3J=8.5\); 2H), 5.85-5.75 (m; 1H), 5.15-4.70 (m; 2H), 3.22 (dd, \(^2J=13.9, ^3J=4.8, ^4J=1.2\); 1H), 2.91-2.79 (m; 1H), 2.68 (dd, \(^2J=13.9\); 1H), 2.56 (dd, \(^2J=14.1, ^3J=8.1\); 1H), 2.43 (dd, \(^2J=14.1, ^3J_{ae}=3.2\); 1H), 2.10 (dd, \(^2J=12.0, ^3J=6.6\); 3H). \(^{13}\)C-NMR (CDCl\(_3\), 75 MHz): 210.3 (C), 155.5 (C), 134.3 (CH), 133.5 (C), 128.6 (CH), 118.2 (CH), 115.6 (CH), 68.1 (CH), 59.4 (CH\(_2\)), 56.5 (CH\(_2\)), 50.2 (CH\(_2\)), 44.4 (CH), 11.3 (CH\(_3\)).

(2S*, 5S*, 6S*)-N-benzyl-2-(4-hydroxyphenyl)octahidroquinolin-4-one (5’ca). Prepared from the correspondent resin-bound imine (120 mg, 1.83 mmol/g). The TFA/DCM method was used for the hydrolysis step. The cleavage step furnished compound 5’ca as a bright red oil (43 mg, 59%). \( R_f = 0.48 \) (DCM : MeOH, 20 : 1). \(^1\)H-NMR (CDCl\(_3\), 200 MHz): 7.32-7.12 (m; 7H), 6.79-6.65 (m; 2H), 3.93 (d, \(^2J=15.9\); 1H), 3.78 (dd, \(^3J_{ae}=11.5, ^3J_{ae}=3.3\); 1H), 3.50 (d, \(^2J=15.9\); 1H), 2.87-2.75 (m; 2H), 2.55-2.44 (m; 3H), 2.11-1.98 (m; 2H), 1.80-1.63 (m; 2H), 1.30-1.10 (m; 3H). \(^{13}\)C-NMR (CDCl\(_3\), 50 MHz): 210.3 (C), 155.3 (C), 141.0 (C), 134.4 (C), 128.5 (CH), 127.8 (CH), 127.4 (CH), 126.0 (CH), 115.5 (CH), 68.2 (CH), 67.5 (CH), 53.3 (CH), 53.2 (CH\(_2\)), 49.7 (CH\(_2\)), 33.6 (CH\(_2\)), 25.1 (CH\(_2\)), 24.5 (CH\(_2\)), 24.1 (CH\(_2\)).
Procedure for the reduction of the enaminic-adduct 5aa. Synthesis of solid-supported 4-aminopiperidine 6: The enaminic resin 3aa (200 mg) was suspended in dry THF (10 mL) in a schlenk flask under nitrogen atmosphere and stirred for 5 min. Then, NaBH₄ (80 mg, 2 mmol) was added and the reaction mixture was gently stirred for 30 min. Thereafter, dry AcOH (1 mL) was added dropwise and the suspension was heated to reflux overnight. After cooling, the resin was filtered and washed with water, THF, DCM, MeOH, DMF and DCM, affording the immobilized 4-aminopiperidine 6.


The cleavage procedure is identical to that described above for the synthesis of piperidones 5 and 5'.

(2S*, 4S*, 5S*)-N-(4-hydroxyphenyl)-5-methyl-4-(N,N-methylphenyl)-2-phenylpiperidine (7).

Prepared from the correspondent resin-bound imine 2a (200 mg, 0.42 mmol/g). The enaminic Diels-Alder adduct was reduced as described above. The cleavage step furnished a residue which was purified by flash chromatography (gradient hexanes:AcOEt 15:1 to 5:1) to afford piperidine 7 as a colourless oil (15 mg, 46%). Rₜ= 0.51 (DCM : MeOH, 20 : 1). ¹H-NMR (CDCl₃, 300 MHz): 7.55-7.09 (m; 9H), 6.82-6.65 (m; 5H), 3.94-3.83 (m; 1H), 3.71 (d, ²J=13.2; 1H), 3.31-3.24 (m; 1H), 2.82-2.76 (m; 4H), 2.74 (d; ²J=13.2; 1H), 2.31-2.22 (m; 3H), 1.79-1.58 (m; 1H), 1.11 (d, ³J=6.3; 3H). ¹³C-NMR (CDCl₃, 75 MHz): 154.2 (C), 149.5 (C), 144.8 (C), 131.8 (C), 129.4 (CH), 128.7 (CH), 127.2 (CH), 116.1 (CH), 115.3 (CH), 114.9 (CH), 112.5 (CH), 112.4 (CH), 69.3 (CH), 58.7 (CH₃), 58.1 (CH₂), 56.0 (CH₂), 36.3 (CH₂), 33.3 (CH₃), 32.2 (CH), 12.8 (CH₃). HRMS (FAB): calcd. for C₂₆H₃₀N₂O + H: 387.2436, found 387.2420.