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Immobilized Aldehydes And Olefins in the Solid Support Synthesis of Tetrahydroquinolines *via* a Three Component Condensation.

Alexander S. Kiselyov*†, Leon Smith II, Alex Virgilio, Robert W. Armstrong

Small Molecule Drug Discovery, Amgen Inc., 1840 DeHavilland Drive, Thousand Oaks, CA 91320-1789.

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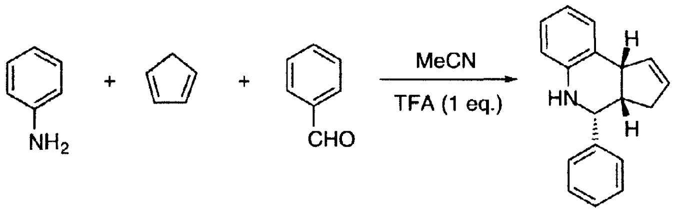
Abstract: Two novel and highly efficient solid support (SS) versions of tetrahydroquinoline synthesis based on the three component condensation reaction of aldehydes, anilines, and electron-rich olefins catalyzed by trifluoroacetic acid were described. In the first version, 4-carboxybenzaldehyde was immobilized on Acid sensitive **ME**thoxy **B**enz**A**ldehyde (**AMEBA**) resin as the solid-supported component of this reaction. The procedure provided tetrahydroquinolines in high yield (60-87%) and good purity (>80%). Further advancement of this solid-phase synthesis was achieved by using resin-bound olefins (prepared from immobilized 4-hydroxybenzaldehyde, and the corresponding Wittig reagents) with anilines, and aldehydes to afford the target products (61-85% yields, >85% purity). Both SS approaches allowed the use of novel alkene, aniline, and aldehyde entries, thereby yielding a diverse array of tetrahydroquinolines.

Keywords: solid-phase synthesis; condensations; aldehydes; olefins.

Multiple component condensation (MCC) reactions are powerful tools for the fast assembly of polysubstituted molecules, especially when applied to solid support synthesis.[1] Unlike linear libraries, the number of structural analogs generated is dependent only on the number, and availability of inputs in MCC reactions. MCC libraries are synthesized in a single chemical transformation, and thus, typically generated in a parallel fashion.

In our continuing effort toward the identification of new reaction templates on solid support,[2] we were interested in the versatile synthesis of polysubstituted tetrahydroquinolines (**1Aa**) described by Grieco, and others (Equation 1).[3]



(1)

This approach is based on the three-component condensation (3CC) of substituted anilines, electron-rich olefins, and aldehydes in the presence of an equimolar amount of trifluoroacetic acid (TFA) in acetonitrile.[3] Attempts have been made to expand the scope of this chemistry using heterocyclic amines, as well as various electron-rich olefins.[4] Of particular interest is the report by Kobayashi on the succesful application of polymer supported Sc, and Yb catalysts for this three-component condensation.[5]

We were interested in utilizing the condensation shown in equation 1 for the synthesis of tetrahydroquinolines on solid support.[6] Having the aromatic amine input as the anchoring site allowed us to tether the carboxylate directly to the resin, and successfully complete the first solid support version of this 3CC.[7] In order to further expand the scope of this solid support procedure, we decided to use a resin-bound aldehyde as an input. The use of an electron-deficient aldehyde allowed the introduction of new olefin, and aniline

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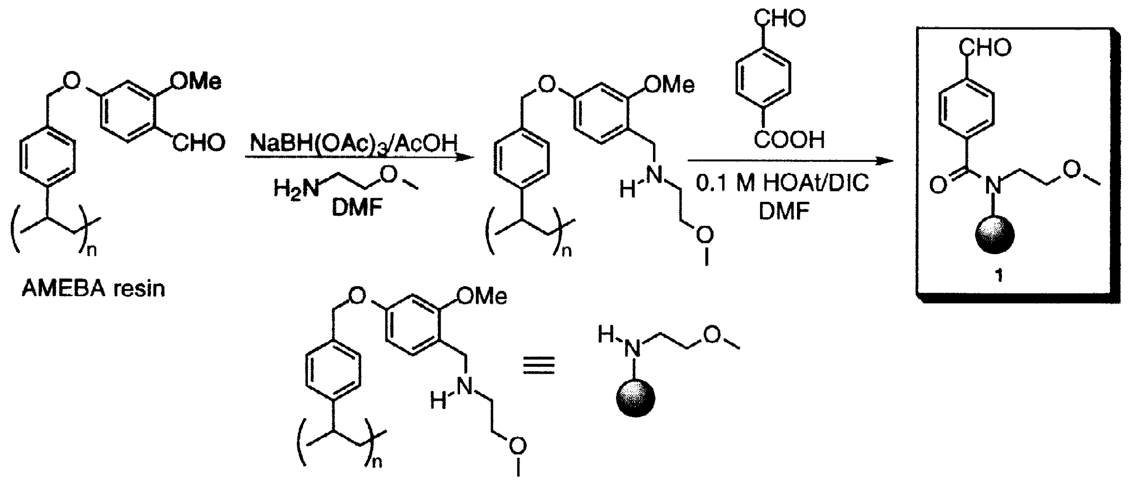
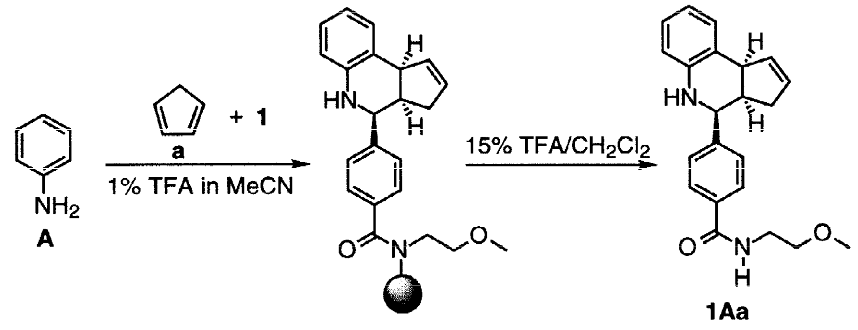
inputs.[6a] In order to maintain the diversity of the aldehyde site, we used the recently reported **Acid sensitive MEthoxy BenzAldehyde (AMEBA)** polystyrene resin which can be easily derivatized with amines.[8]

In the optimized protocol, the 4-carboxybenzaldehyde (0.1 mol.) was stirred for 10 min with 0.12 mol. of 1-hydroxy-7-azabenzotriazole (HOAt), and 0.11 mol. of 1,3-diisopropylcarbodiimide (DIC) in 100 mL of dry DMF. The AMEBA resin[8] was treated with the resulting solution for 12 hrs. to afford the desired immobilized aldehyde **1** (0.4 mM/g loading as determined by TFA cleavage, Scheme 1).



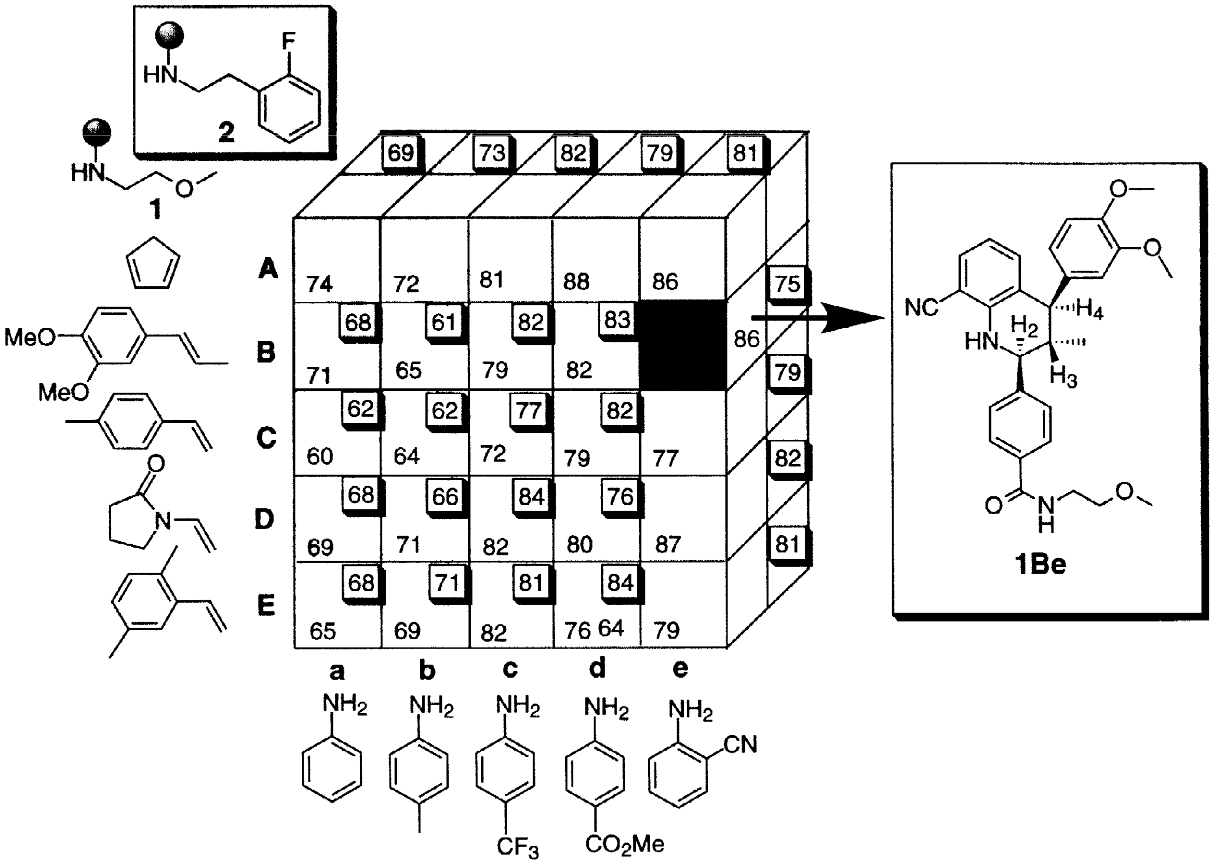
Scheme 1

The resulting resin **1** was reacted with aniline **A**, and cyclopentadiene **a** in MeCN in the presence of 1% TFA for 12 hrs to afford the targeted tetrahydroquinoline **1Aa** in 74% yield[9] (Scheme 2). Attempts to incubate the reaction mixtures for longer periods, or to resubject the resin to freshly prepared mixtures of (**A**), and (**a**) in 1 % TFA neither improved the yield of the reaction nor purity of the desired product **1Aa**. HPLC, and ^{1}H NMR analysis of the reaction mixtures revealed that the only impurity after the resin cleavage was the corresponding Schiff base (2-7% by HPLC). Increasing the concentration of TFA from 1 % to 3 % resulted in the premature cleavage of the nonreacted aldehyde. Several other solvents, including DMF, dioxane, THF, and MeOH, were inferior to MeCN as the reaction media. Furthermore, catalysis with Lewis acids, namely $LiBF_4$, $Yb(OTf)_3$, $TiCl_4$, $InCl_3$, or $FeCl_3$, afforded considerably lower yields of **1Aa**.



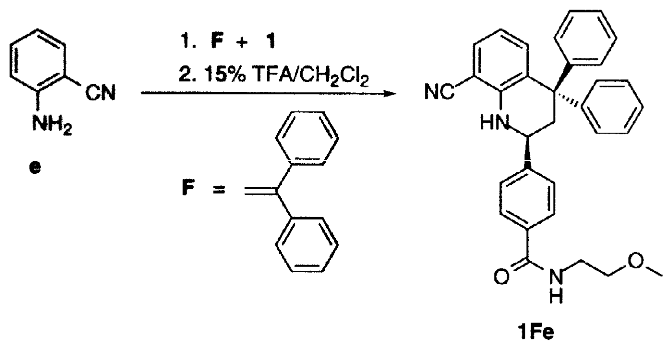
Scheme 2

Through the reaction conditions discussed above, we successfully synthesized a library of 50 members (Scheme 3). We found that several new olefins (C-E), along with previously reported A, and B^{3-5} are efficient entries for this 3CC reaction. The yields of the target tetrahydroquinolines varied from 60% to 87% (based upon 0.4 mM/g loading of the initial AMEBA resin 1). The best yields (72-87%) were achieved with the anilines containing electron-withdrawing substituents, and the olefinic entries A, B, and D. The nature of the amine immobilized on the AMEBA resin did not affect the yield or purity of the tetrahydroquinolines. Chemical yields[9] are given in Scheme 3. The single major impurity detected in the reaction mixtures (^{1}H NMR, HPLC) was the corresponding Schiff base (5-10% yield), the postulated intermediate in this 3CC.[3-5] The desired tetrahydroquinolines (>80% purity by HPLC) were isolated as single diastereomers after TFA cleavage. The relative stereochemistry of the products (ex. **1Be**, Scheme 3) was determined by ^{1}H NMR. The relative *trans* orientation of H_2, H_3, and H_4 was established from the large vicinal coupling constants $J_{2,3}$, and $J_{3,4}$ = 9.0 Hz .



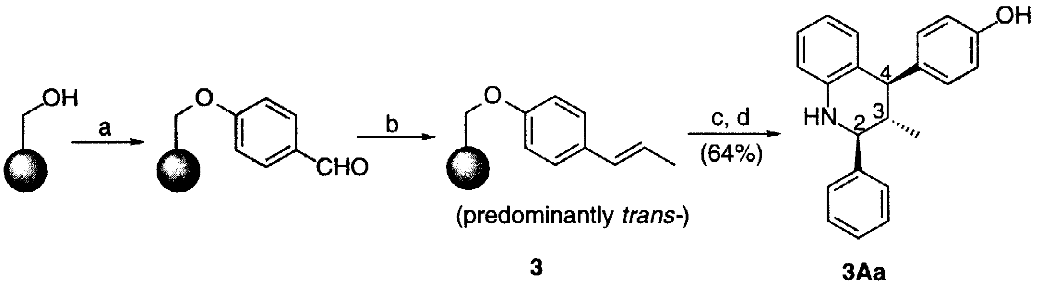
Scheme 3. The library of tetrahydroquinolines synthesized by three-component condensation of the resin-bound 4-carboxybenzaldehyde with olefins A-E, and anilines a-e. Chemical yields corresponding to the reaction with resin 2 are given in boxes.

1,1-Diphenylethylene (F) was found to react with the anilines bearing strong electron-withdrawing groups (d, e), and AMEBA resin 1 to afford the products of the 3CC (Equation 2) in 69%, and 76% yields respectively. Reactions between F, and anilines a, and b did not afford the desired tetrahydroquinolines, whereas 3CC with c afforded the Schiff base as the major product (*ca.* 70% GCMS yield) along with a small amount of tetrahydroquinoline (10%), and the nonreacted aldehyde.



(2)

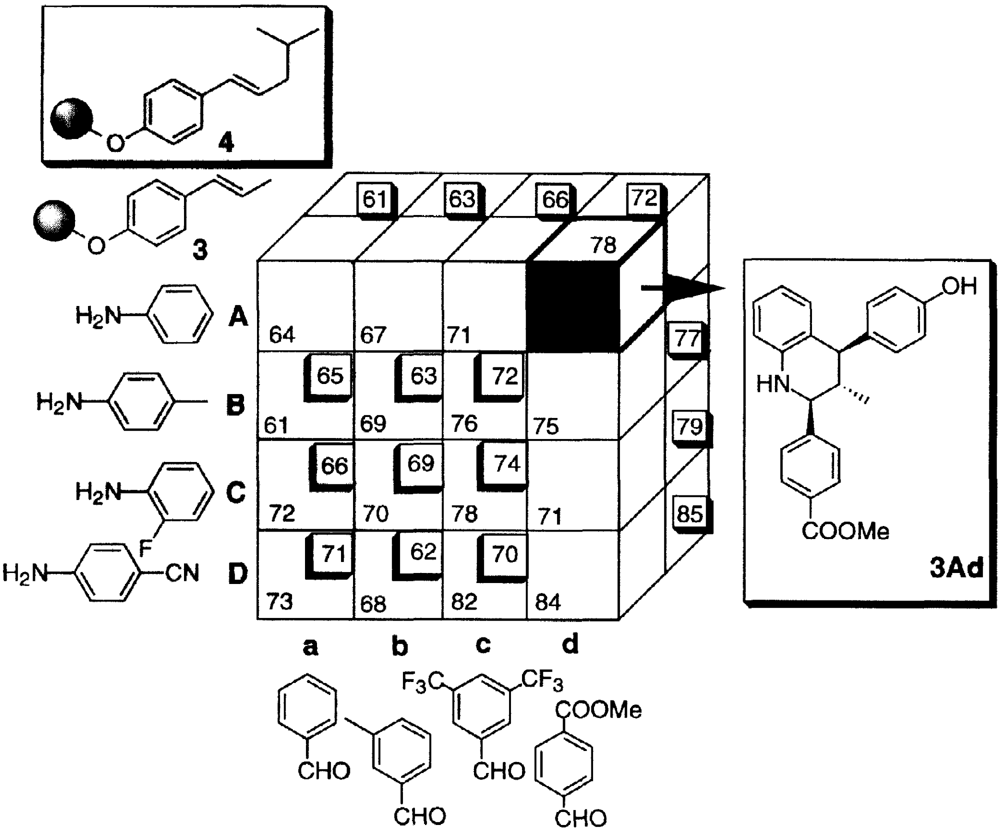
To expand the utility of this solid support procedure, we used resin-bound olefins as inputs. Application of the immobilized electron-rich olefin allowed the introduction of new aldehyde, and aniline inputs. In order to maintain the diversity on the olefin site, we modified the Wang-resin bound 4-hydroxybenzaldehyde with Wittig reagents (Scheme 4). In the optimized protocol, the Wang resin was added to a mixture of 4-hydroxybenzaldehyde, PPh_3, and DIAD in *N*-methylmorpholine to afford the target immobilized aldehyde (0.35 mM/g loading as determined by TFA cleavage). The aldehyde resin[10] was added to a solution of Wittig reagent (prepared from the corresponding phosphonium salt, and *n*-BuLi) in THF to yield the desired polymer-bound styrene **3** (0.30 mM/g loading, ratio *trans-/cis-* = 90/10 according to ^1H NMR). Resin **3** was further reacted with aniline **a**, and benzaldehyde **A** in acetonitrile in the presence of 1% TFA for 12 hrs, and cleaved to afford the targeted tetrahydroquinoline **3Aa** in 64% yield (determined by the cleavage of resin with 15% TFA/CH_2Cl_2) as a single diastereomer (HPLC).[3,7,8] The relative stereochemistry of **3Aa** was determined by ^1H NMR (the large vicinal coupling constants $J_{2,3}$ and $J_{3,4}$ = 9.0 Hz indicated the relative *trans* orientation of H2, H3, and H4).



Conditions: a) PPh_3, DIAD, NMM, 12 hrs.; b) $Ph_3P{=}CHMe$, dry THF, -20°C - R.T., 12 hrs.; c) $PhNH_2$(**a**), PhCHO (**A**),1% TFA in MeCN, 24 hrs.; d) 20% TFA in CH_2Cl_2, 45 min.

Scheme 4.

A library of 32 members (Scheme 5) was synthesized in parallel using the following optimized protocol; the polymer bound olefins **3**, and **4** were treated with anilines, and aldehydes in the $MeCN/CH_2Cl_2$ system (9:1) (CH_2Cl_2 was added to increase the solubility of the intermediate Schiff bases), and 1% TFA in MeCN to afford the desired tetrahydroquinoline products (85-95% purity by HPLC, and ^1H NMR analysis). The yields of the tetrahydroquinolines varied from 61% to 85% (based upon 0.30 mM/g loading). The best yields (about 80-85%) were achieved with the anilines, and aldehydes containing electron-withdrawing groups (entries **C**, **D**, **c**, **d**). We found that several new anilines (**B-D**), along with the previously reported **A**, are efficient entries for this 3CC reaction. The nature of the immobilized styrenes (**3** *vs* **4**) affected neither the yield,nor the purity of tetrahy-



Scheme 5. The library of tetrahydroquinolines synthesized by three-component condensation of the resin-bound olefins **1** and **2** with anilines **A**-**E** and aldehydes **a**-**e**. Chemical yields corresponding to the reactions with resin **2** are given in boxes.

droquinolines. Chemical yields are provided in Scheme 5. The single major impurity detected in the reaction mixtures (^{1}H NMR, HPLC) was the corresponding nonreacted styrene (5-10% yield).[11] The purity of the desired tetrahydroquinolines (>85% by HPLC) synthesized *via* this protocol was superior to that of similar structures previously prepared by us[7] (by approximately 5-15%, HPLC analysis).

In summary, we have described two novel, and highly efficient SS versions of the tetrahydroquinoline synthesis based on the 3CC reaction of aldehydes, anilines, and electron-rich olefins catalyzed by TFA. In the first version, 4-carboxybenzaldehyde, immobilized on AMEBA resin was a solid-supported component of the 3CC. This approach was found to provide tetrahydroquinolines in high yield (60-87%), and good purity (>80%). In the second version, further advancement was achieved by using resin-bound olefins, prepared from immobilized 4-hydroxybenzaldehyde, and the corresponding Wittig reagents. The targeted products were also obtained in comparable yields (61-85%), and excellent purity (>85%). In both strategies, the yield of the product was found to be directly related to the nature of the components in this 3CC. For example, the best yields of tetrahydroquinolines were achieved with the aniline, or aldehyde inputs containing electron-withdrawing substituents. In addition, the latest approach allowed the elimination of the imine impurity from the final product. In both SS strategies the scope of alkene, aniline, and aldehyde entries was dramatically expanded, providing a diverse array of the target compounds, superior to that reported previously for the solid support synthesis of tetrahydroquinolines.[7]

Experimental Section.

Materials. All solid phase reactions were carried out at room temperature. Reagents were purchased from Aldrich, and Acros, and used without further purification. Wang resin (loading 0.6 mmol/g) was purchased from Novabiochem, and washed with DMF, MeOH, CH_2Cl_2, and MeCN prior to use.

General Methods. All reactions were carried out in Alltech® vessels (100 mg of resin per reaction vessel). Concentration of solutions after workup was performed by reduced pressure rotary evaporation. ^1H NMR spectra were obtained on a Bruker 500 instrument with $CDCl_3$ as the solvent. MS analysis (ES and CI modes) was performed on a Perkin Elmer API 165 instrument. HPLC analysis was performed on a Beckman Gold Analytic 126 apparatus with a diode array detector model 168 at the wavelengths of 220 nm and 254 nm. The column employed was an Ultrasphere C18 cartridge 250mm x 4.6 mm. The solvent system was $MeCN/H_2O$ (.1% TFA added), flow rate 1 mL/min.

General Procedure for Preparing 4-Carboxybenzaldehyde on AMEBA Solid Support. In the optimized protocol, 4-carboxybenzaldehyde (0.1 mol) was stirred for 10 min with 0.12 mol of HOAt, and 0.11 mol of DIC in 1L of dry DMF. AMEBA resin[8] (100 g) was added. The resulting slurry was agitated for 12 hrs on a Lab-Line orbit shaker, filtered, washed with DMF, MeOH, CH_2Cl_2, and dried *in vacuo* to afford the targeted immobilized aldehyde **1** (0.4 mM/g loading as determined by TFA cleavage).

General Procedure For Synthesis of Tetrahydroquinolines *via* Three-Component Condensation on AMEBA Resin. This library was synthesized in parallel under the following reaction conditions: the polymer bound 4-carboxybenzaldehyde **1** (250 mg of resin per reaction vessel, 0.4 mM/g loading) was treated with 300 μL of a 0.5 M solution of aniline, and 300 μL of a 0.5 M solution of alkene in MeCN. 400 μL of a 2% solution of TFA in MeCN was introduced, and the mixture was agitated by bubbling N_2. After 24 hrs., the resulting resin was filtered, washed with DMF, MeOH, CH_2Cl_2, dried in the vacuum oven, and treated with a 15% TFA/CH_2Cl_2 solution (2 mL per reaction vessel) to cleave the target tetrahydroquinoline product. The resulting solution was collected, concentrated under reduced pressure (**attention! efficient liquid N_2 trap**), and the oily residue was triturated with Et_2O to afford the desired product as a solid.

General Procedure for Preparing Immobilized Styrenes on Solid Support. In the optimized protocol, Wang resin (105 g, 0.58 mM/g loading) was added at 0°C to a gently stirred mixture of 4-hydroxybenzaldehyde, PPh_3, DIAD (all reagents were 0.4 M in dry N-methylmorpholine, 1L overall volume). The resulting slurry was stirred for 8 hrs. at 0°C, and 16 hrs. at RT, filtered, washed with DMF, MeOH, CH_2Cl_2, and dried *in vacuo* to afford the targeted immobilized aldehyde (0.35 mM/g loading as determined by TFA cleavage). The aldehyde resin (20 g) was dried several times by coevaporation with dry toluene immediately prior to use.[10] The dried resin was added to a gently stirred solution of Wittig reagent (0.2 M solution in dry THF, 200 mL, prepared from the corresponding phosphonium salt, and *n*-BuLi) at -20°C (water-ethyleneglycol bath) under Ar. The resulting slurry was stirred at this temperature for 6 hrs., and for an additional 18 hrs. at RT, filtered, washed with 2% AcOH in DMF, DMF, MeOH, CH_2Cl_2, dried *in vacuo*, treated again with Wittig reagent , washed, and dried to afford the desired polymer-bound styrene **3** (0.30 mM/g loading, ratio *trans-/cis-* = 90/10 according to ^1H NMR).

General Procedure For Solid Support Synthesis of Tetrahydroquinolines *via* Three-Component Condensation. This library was synthesized in parallel under the following reaction conditions:

the polymer bound olefin **3** (250 mg of resin per reaction vessel, standard loading 0.30 mM/g) was treated with 500 μL of a 0.5M solution of aniline, and 500 μL of a 0.5M solution of aldehyde in a (9:1) $MeCN/CH_2Cl_2$ system (CH_2Cl_2 was added for better solubility of the intermediate Schiff bases). 50mL of 1% TFA in MeCN was introduced, and the mixture was agitated by bubbling N_2. After 12 hrs., the resulting resin was filtered, washed with DMF, MeOH, CH_2Cl_2, dried and treated with 15% TFA (2 mL per vessel) to cleave the targeted tetrahydroquinoline product. The resulting solution was collected, concentrated under reduced pressure (**CAUTION! efficient liquid N_2 trap**), and the residue was triturated with Et_2O to afford the desired solid product (85-95% purity by HPLC, and ^1H NMR analysis).

Selected Analytical Data:

(2*R,3*S**,4*R**)-4-(4-(2-Methoxyethyl)amidophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (1Aa)**: 25.8 mg (74%); HPLC t_R = 5.88; ^1H NMR (CD_3OD): δ 2.02 (m, 1H), 2.43 (m, 2H), 2.52 (m, 1H), 3.05 (m, 2H), 3.11 (m, 1H), 3.18 (m, 1H), 3.31 (d, *J* = 3.5 Hz, 1H), 3.54 (s, 3H), 5.52 (d, *J* = 3.5 Hz, 1H), 5.74 (d, *J* = 3.5 Hz, 1H), 6.89-7.21 (m, 4H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H); ESI MS *m/z* 349 ($M + H^+$); 347 ($M-H^+$).

(2*R,3*S**,4*R**)-8-Methyl-4-(4-(2-methoxyethyl)amidophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (1Ab)**: 26.1 mg (72%); HPLC t_R = 5.95; ^1H NMR: δ 2.03 (m, 1H), 2.14 (s, 3H), 2.45 (m, 2H), 2.58 (m, 1H), 3.08 (m, 2H), 3.12 (m, 1H), 3.19 (m, 1H), 3.30 (d, *J* = 3.5 Hz, 1H), 3.56 (s, 3H), 5.54 (d, *J* = 3.5 Hz, 1H), 5.78 (d, *J* = 3.5 Hz, 1H), 6.84 (d, *J* = 8.0Hz, 1H), 6.98 (s, 1H), 7.11 (d, *J* = 8.0HZ, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H); ESI MS *m/z* 363 ($M + H^+$); 361 ($M-H^+$).

(2*R,3*S**,4*R**)-8-Trifluoromethyl-4-(4-(2-methoxyethyl)amidophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (1Ac)**: 33.7 mg (81%); HPLC t_R = 6.73; ^1H NMR: δ 2.00 (m, 1H), 2.41 (m, 2H), 2.58 (m, 1H), 3.04 (m, 2H), 3.07 (m, 1H), 3.17 (m, 1H), 3.29 (d, *J* = 3.5 Hz, 1H), 3.55 (s, 3H), 5.52 (d, *J* = 3.5 Hz, 1H), 5.75 (d, *J* = 3.5 Hz, 1H), 7.31 (d, *J* = 8.5Hz, 1H), 7.48 (s, 1H), 7.61 (d, *J* = 8.5Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H) ESI MS *m/z* 417 ($M + H^+$); 415 ($M-H^+$).

(2*R,3*S**,4*R**)-8-Carbmethoxy-4-(4-(2-methoxyethyl)amidophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (1Ad)**: 35.7mg (88%); HPLC t_R = 5.64; ^1H NMR: δ 2.06 (m, 1H), 2.42 (m, 2H), 2.61 (m, 1H), 3.06 (m, 2H), 3.18 (m, 1H), 3.25 (m, 1H), 3.31 (d, *J* = 3.5 Hz, 1H), 3.56 (s, 3H), 3.98 (s, 3H), 5.51 (d, *J* = 3.5 Hz, 1H), 5.73 (d, *J* = 3.5 Hz, 1H), 7.38 (d, *J* = 8.5Hz, 1H), 7.51 (s, 1H), 7.63 (d, *J* = 8.5Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H); ESI MS *m/z* 407 ($M + H^+$); 405 ($M-H^+$).

(2*R,3*S**,4*R**)-8-Cyano-4-(4-(2-methoxyethyl)amidophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (1Ae)**: 32.1 mg (86%); HPLC t_R = 5.72; ^1H NMR: δ 2.03 (m, 1H), 2.42 (m, 2H), 2.59 (m, 1H), 3.08 (m, 2H), 3.12 (m, 1H), 3.18 (m, 1H), 3.29 (d, *J* = 3.5 Hz, 1H), 3.57 (s, 3H), 5.56 (d, *J* = 3.5 Hz, 1H), 5.76 (d, *J* = 3.5 Hz, 1H), 7.28 (d, *J* = 8.5Hz, 1H), 7.35 (s, 1H), 7.58 (d, *J* = 8.5Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H); ESI MS *m/z* 374 ($M + H^+$); 372 ($M-H^+$).

(2*R,3*R**,4*S**)-2-(4-(2-Methoxyethyl)amidophenyl)-4(3,4-dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (1Ba)**: 32.7 mg (71%); HPLC t_R = 6.76; ^1H NMR: δ 0.85 (d, *J* = 8.0 Hz, 3H), 2.05 (m, 1H), 2.38 (m, 2H), 2.53 (d, *J* = 9.0Hz, 1H), 3.05 (m, 2H), 3.35 (d, *J* = 9.0Hz, 1H), 3.54 (s, 1H), 3.64 (s, 3H), 3.72 (s, 3H), 6.65-7.19 (m, 7H), 7.58 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 461 (M + H$^+$); 459 (M-H$^+$).

(2R^*,3R^*,4S^*)-6-Methyl-2-(4-(2-methoxyethyl)amidophenyl)-4(3,4-dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (1Bb): 30.9 mg (65%); HPLC t_R = 6.81; ^{1}H NMR: δ 0.88 (d, J = 8.0 Hz, 3H), 2.06 (m, 1H), 2.11 (s, 3H), 2.36 (m, 2H), 2.54 (d, J = 9.0Hz, 1H), 3.06 (m, 2H), 3.38 (d, J = 9.0Hz, 1H), 3.58 (s, 1H), 3.65 (s, 3H), 3.74 (s, 3H), 6.68-7.20 (m, 6H), 7.54 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 475 (M + H$^+$); 473 (M-H$^+$).

(2R^*,3R^*,4S^*)-6-Trifluoromethyl-2-(4-(2-fluorophenethyl)amidophenyl)-4(3,4-dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (2Bc): 48.5 mg (82%); HPLC t_R = 6.76; ^{1}H NMR: δ 0.92 (d, J = 8.0 Hz, 3H), 2.03 (m, 1H), 2.35 (m, 2H), 2.51 (d, J = 9.0Hz, 1H), 3.02 (m, 2H), 3.34 (d, J = 9.0Hz, 1H), 3.66 (s, 3H), 3.75 (s, 3H), 6.72-7.28 (m, 8H), 7.35 (s, 1H), 7. 47 (d, J = 8.5Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 593 (M + H$^+$); 591 (M-H$^+$).

***cis*-2-(4-(2-Methoxyethyl)amidophenyl)-4-(4-methylphenyl)-1,2,3,4-tetrahydroquinoline (1Ca)**: 24.0 mg (60%); HPLC t_R = 6.02; ^{1}H NMR: δ 2.03 (m, 2H), 2.12 (s, 3H), 2.39 (m, 2H), 2.68 (m, 1H), 3.07 (m, 2H), 3.37 (m, 1H), 3.52 (s, 3H), 6.81-7.23 (m, 8H), 7.49(d, J = 8.0Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 401 (M + H$^+$); 399 (M-H$^+$).

***cis*-2-(4-(2-Fluorophenethyl)amidophenyl)-4-(4-methylphenyl)-1,2,3,4-tetrahydroquinoline (2Ca)**: 28.8 mg (62%); HPLC t_R = 6.14; ^{1}H NMR: δ 2.05 (m, 2H), 2.14 (s, 3H), 2.35 (m, 2H), 2.64 (m, 1H), 3.11 (m, 2H), 3.35 (m, 1H), 6.78-7.38 (m, 12H), 7.53 (d, J = 8.0Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 465 (M + H$^+$); 463 (M-H$^+$).

***cis*-2-(4-(2-Methoxyethyl)amidophenyl)-4-*N*(2-pyrrolidino)-1,2,3,4-tetrahydroquinoline (1Da)**: 27.1 mg (69%); HPLC t_R = 5.23; ^{1}H NMR: δ 1.86-2.39 (m, 6H), 2.48-2.64 (m, 3H), 3.02 (m, 2H), 3.24-3.32 (m, 3H), 3.57 (s, 3H), 7.05-7.26 (m, 4H), 7.52 (d, J = 8.0Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 394 (M + H$^+$); 392 (M-H$^+$).

***cis*-2-(4-(2-Methoxyethyl)amidophenyl)-4-(2,5-dimethylphenyl)-1,2,3,4-tetrahydroquinoline (1Eb)**: 29.5 mg (69%); HPLC t_R = 6.02; ^{1}H NMR: δ 2.01 (m, 2H), 2.08-2.14 (m, 9H), 2.28 (m, 2H), 2.56 (m, 1H), 3.01 (m, 2H), 3.26 (m, 1H), 3.47 (s, 3H), 6.83-7.21 (m, 6H), 7.54 (d, J = 8.0Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 429 (M + H$^+$); 427 (M-H$^+$).

***cis*-2-(4-(2-Fluorophenethyl)amidophenyl)-4-(2,5-dimethylphenyl)-1,2,3,4-tetrahydroquinoline (2Ea)**: 32.5 mg (68%); HPLC t_R = 6.25; ^{1}H NMR: δ 2.06 (m, 2H), 2.10 (s, 3H), 2.14 (s, 3H), 2.41(m, 2H), 2.71 (m, 1H), 3.12 (m, 2H), 3.42 (m, 1H), 6.75-7.38 (m, 11H), 7.46 (d, J = 8.0Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 479 (M + H$^+$); 477 (M-H$^+$).

8-Cyano-2-(4-(2-methoxyethyl)amidophenyl)-4,4-diphenyl-1,2,3,4-tetrhydroquinoline (1Fe): 37.0 mg (76%); HPLC t_R = 7.32; ^{1}H NMR: δ 1.99 (m, 2H), 2.44 (m, 2H), 3.16 (m, 2H), 3.38 (m, 1H), 6.89-7.28 (m, 11H), 7.33 (d, J = 8.0Hz, 1H), 7.43 (d, J = 8.0Hz, 2H), 7.54 (d, J = 8.0Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H); ESI MS *m/z* 488 (M + H$^+$); 486 (M-H$^+$).

(2R^*,3R^*,4S^*)-2-Phenyl-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (3Aa): yield 15.1 mg (64%); HPLC t_R = 8.14; ^{1}H NMR: δ 1.02 (d, J = 8.5 Hz, 3H), 2.09 (m, 1H), 2.42 (d, J = 9.0 Hz, 1H), 3.57 (d, J = 9.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 6.96-7.44 (m, 9H); ESI MS *m/z* 316 (M + H$^+$), 314 (M - H$^+$).

(2*R,3*R**,4*S**)-2-(3-Methylphenyl)-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (3Ab)**: yield 16.5 mg (67%); HPLC t_R = 6.96; ^{1}H NMR: δ 1.03 (d, *J* = 8.5 Hz, 3H), 2.10 (m, 1H), 2.13 (s, 3H), 2.42 (d, *J* = 9.0 Hz, 1H), 3.57 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.96-7.34 (m, 8H); ESI MS *m/z* 330 (M + H$^+$), 328 (M - H$^+$).

(2*R,3*R**,4*S**)-2-(3,5-bistrifluoromethylphenyl)-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (3Ac)**: yield 24.0 mg (71%); HPLC t_R = 8.23; ^{1}H NMR: δ 1.00 (d, *J* = 8.5 Hz, 3H), 2.08 (m, 1H), 2.45 (d, *J* = 9.0 Hz, 1H), 3.63 (d, *J* = 9.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.96-7.23 (m, 4H); 7.47 (s, 2H), 7.59 (s, 1H); ESI MS *m/z* 452 (M + H$^+$), 450 (M - H$^+$).

(2*R,3*R**,4*S**)-2-Phenyl-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (3Ad)**: yield 21.8 mg (78%); HPLC t_R = 6.96; ^{1}H NMR: δ 1.05 (d, *J* = 8.5 Hz, 3H), 2.14 (m, 1H), 2.43 (d, *J* = 9.0 Hz, 1H), 3.69 (d, *J* = 9.0 Hz, 1H), 3.98 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.95-7.30 (m, 4H); 7.71 (d, *J* = 8.0Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H); ESI MS *m/z* 374 (M + H$^+$), 372 (M - H$^+$).

(2*R,3*R**,4*S**)-6-Methyl-2-phenyl-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (3Ba)**: yield 15.1 mg (61%); HPLC t_R = 6.45; ^{1}H NMR: δ 1.04 (d, *J* = 8.5 Hz, 3H), 1.95 (m, 1H), 2.11 (s, 3H), 2.32 (d, *J* = 9.0 Hz, 1H), 3.58 (d, *J* = 9.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.99-7.38 (m, 6H); ESI MS *m/z* 330 (M + H$^+$), 328 (M - H$^+$).

(2*R,3*R**,4*S**)-8-Trifluoromethyl-2-(3-methylphenyl)-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline (3Cb)**: yield 20.8 mg (70%); HPLC t_R = 6.76; ^{1}H NMR: δ 0.98 (d, *J* = 8.5 Hz, 3H), 2.10 (m, 1H), 2.44 (d, *J* = 9.0 Hz, 1H), 3.87 (d, *J* = 9.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.89 (s, 1H), 6.94-7.25 (m, 4H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 1H); ESI MS *m/z* 398 (M + H$^+$), 396 (M-H$^+$).

(2*R,3*R**,4*S**)-2-Phenyl-4-(4-hydroxyphenyl)-3-isobutyl-1,2,3,4-tetrahydroquinoline (4Aa)**: yield 16.3 mg (61%); HPLC t_R = 8.11; ^{1}H NMR: δ 0.81-1.37 (m, 9H), 1.95 (m, 1H), 2.24 (d, *J* = 9.0 Hz, 1H), 3.60 (d, *J* = 9.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.96-7.29 (m, 9H); ESI MS *m/z* 358 (M + H$^+$), 356 (M - H$^+$).

(2*R,3*R**,4*S**)-6-Methyl-2-(4-carbmethoxyphenyl)-4-(4-hydroxyphenyl)-3-isobutyl-1,2,3,4-tetrahydroquinoline (4Bd)**: yield 24.8 mg (77%); HPLC t_R = 7.15; ^{1}H NMR: δ 0.82-1.45 (m, 9H), 1.95 (m, 1H), 2.08 (s, 3H), 2.29 (d, *J* = 9.0 Hz, 1H), 3.63 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.96 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H); ESI MS *m/z* 430 (M + H$^+$), 428 (M - H$^+$).

References and Notes.

†This paper is dedicated to my daughter Alexandra.

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(9) Determined by the yield of the resulting amidoaldehyde after cleavage of AMEBA resin with 15% TFA/CH_2Cl_2. All compounds were characterized by ^1H NMR, ESIMS, and HPLC.

(10) Hird, N.W.; Irie, K.; Nagai, K. *Tetrahedron Lett.* **1997**, *38*, 7111; similar to the observations described in this paper, we found that efficient preparation of the target olefin resin **3** or **4** required rigorously dried aldehyde resin.

(11) The nonreacted Schiff base, the common impurity in the synthesis of tetrahydroquinolines using resin-bound aniline, was not detected.