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The Prins Cascade Cyclization Reaction for the Synthesis of Angularly-Fused Tetrahydropyran and Piperidine Derivatives

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2-Arylethylbut-3-en-1-ol is found to undergo smooth Prins cascade reactions with various aldehydes in the presence of $Sc(OTf)_3$ (10 mol-%) and a stoichiometric amount of TsOH to afford the corresponding *trans*-fused hexahydro-1*H*-benzo[*f*]isochromenes in good yields with excellent selectivity. Likewise, *N*-tosyl-2-phenethylbut-3-en-1-amine gives *trans*-fused octahydrobenzo[*f*]isoquinoline derivatives under similar conditions. This is the first example of the synthesis of hexahydro-1*H*-benzo[*f*]isochromene and octahydrobenzo[*f*]isoquinoline from 2-arylethylbut-3-en-1-ol and *N*-tosyl-2-phenethylbut-3-en-1-amine, respectively.

Introduction

The Prins cyclization reaction is a powerful synthetic route for the stereoselective construction of tetrahydropyran (THP) rings that are a core structural unit of many natural products.[1,2] It has been successfully applied to the total synthesis of THP-containing polyether antibiotics and other complex natural products.[3] In particular, the intramolecular Prins-cyclization reaction is very useful to construct bicyclic compounds such as bicyclo[3.3.1]nonane,[4a] azaspiro[4,4]nonane,[4b] and bicyclo[3,2,1]octane.[4c] Inspired by an intramolecular Prins reaction with tethered nucleophiles[5–7] we have successfully demonstrated the stereoselective synthesis of heterobicycles and tricycles.[8] However, the scope of these tandem processes has not been explored to construct benzo[*f*]isochromene and benzo[*f*]isoquinoline scaffolds from easily accessible 2-arylethylbut-3-en-1-ol and *N*-tosyl-2-phenethylbut-3-en-1-amine, respectively. Such skeletons are found in aromatized salvinorin A and dopamine congeners (Figure 1).[9]

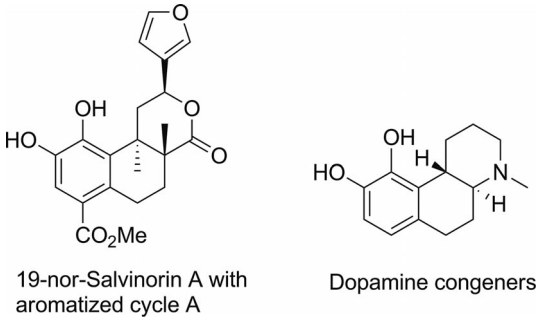
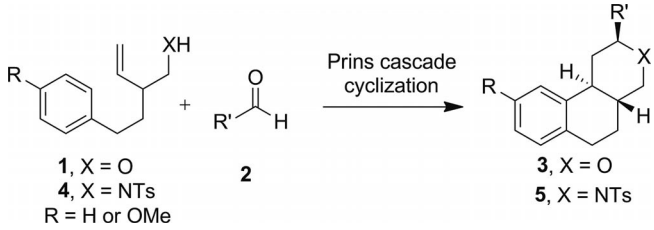


Figure 1. Biologically active benzo[*f*]isochromene and benzo[*f*]isoquinoline derivatives.

Results and Discussion

In continuation of our research on Prins-type cyclization reactions and its application to the total synthesis of natural products,[10] we herein report a new strategy for the stereoselective synthesis of hexahydro-1*H*-benzo[*f*]isochromene and octahydrobenzo[*f*]isoquinoline derivatives by means of Prins cascade cyclization reactions by using a combination of $Sc(OTf)_3$ (10 mol-%) and a stoichiometric amount of TsOH (Scheme 1).



Scheme 1. A tandem process for the hexahydro-1*H*-benzo[*f*]isochromene and octahydrobenzo-[*f*]isoquinoline motifs.

We first attempted the cyclization of 2-phenylethylbut-3-en-1-ol with 2-nitrobenzaldehyde by using various acid catalysts. To optimize the reaction conditions, several acid catalysts were screened and the results are presented in Table 1. Of the various catalysts, $InCl_3$ (20 mol-%) at 25 °C gave the desired product only in 25% yield (Table 1, Entry a) whereas no cyclization was observed with molecular iodine

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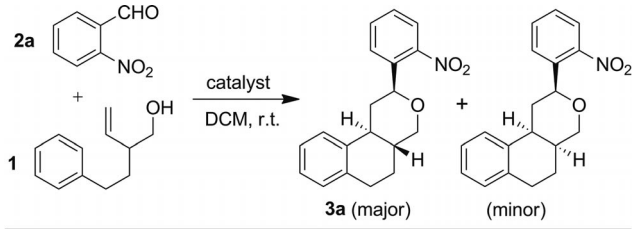
(20 mol-%; Table 1, Entry b). By using $Sc(OTf)_3$ (10 mol-%) the desired product was obtained only in 30% yield after a long reaction time (Table 1, Entry c). A stoichiometric amount of TsOH gave the required product in 55% yield. Interestingly, the combination of $Sc(OTf)_3$ (10 mol-%) and a stoichiometric amount of TsOH gave the product in 86% yield in a short reaction time (Table 1, Entry e). Under optimized conditions, the reaction requires $Sc(OTf)_3$ (10 mol-%) and TsOH (1.0 equiv.) in dichloromethane at room temperature. The high reactivity of the above reagent system may be attributed to synergistic/cooperative effects between the Lewis acid i.e. $Sc(OTf)_3$ and the Brønsted acid i.e. TsOH.[11] Therefore, a tandem process requires both Brønsted acid and Lewis acid to furnish good results. Under the above conditions, desired product **3a** was obtained in 86% yield with high *trans*-stereoselectivity (diastereomeric ratio: 90:10; Table 2, Entry a). The *trans*/*cis* ratio was determined from the ^{1}H NMR spectroscopic data of the crude product. The two diastereomers were inseparable by silica gel column chromatography.

Table 1. Screening of various acid catalysts for the Prins cyclization reaction of 2-phenylethylbut-3-en-1-ol with 2-nitrobenzaldehyde.[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	*trans*/*cis* ratio[c]
a	20 mol-% $InCl_3$	12	25	95:5
b	20 mol-% I_2	12	0	–
c	10 mol-% $Sc(OTf)_3$	12	30	95:5
d	1 equiv. TsOH	12	55	92:8
e	10 mol-% $Sc(OTf)_3$ + 1 equiv.TsOH	2.5	86	92:8

[a] The reaction was performed on a 0.5 mmol scale. [b] Isolated yield. [c] *Trans*/*cis* ratio was determined from the ^{1}H NMR spectroscopic data of the crude product.

Under optimized conditions, thiophene-2-carbaldehyde also participated well in a tandem process to afford predominantly *trans*-fused product **3b** in 85% yield (*trans*/*cis* ratio = 90:10; Table 2, Entry b). The structure and stereochemistry of **3b** were established by means of double quantum filtered correlation spectroscopy (DQFCOSY). Proton 2-H shows a large coupling of 11.3 Hz with 1-H indicating an axial orientation of 2-H. Proton 4a-H shows a large coupling (J = 10.5 Hz) with 10b-H that also shows a large coupling with one of the 1-H protons indicating that 4a-H and 10b-H are in axial orientations. Thus, the fusion of two rings is *trans* as shown in Figure 2. Furthermore, the structure of **3b** was confirmed by X-ray crystallography (Figure 3).[12]

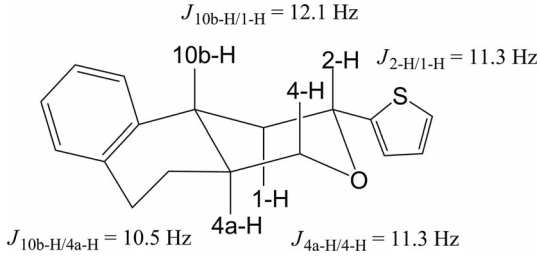


Figure 2. Characteristic coupling constants and chemical structure of **3b**.

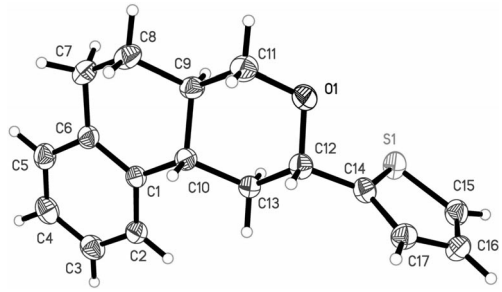
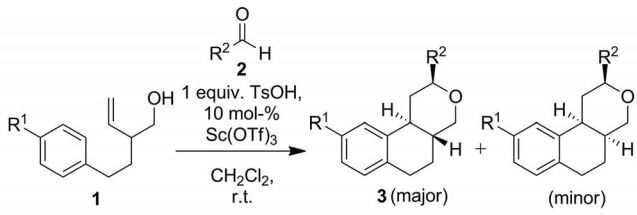


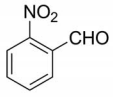
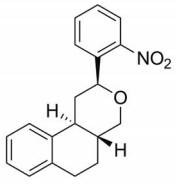
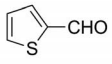
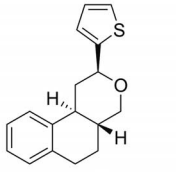
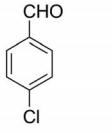
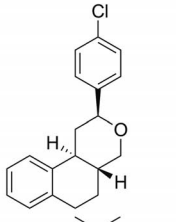
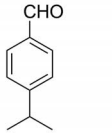
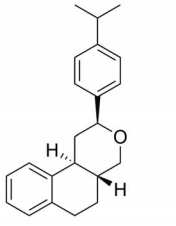
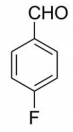
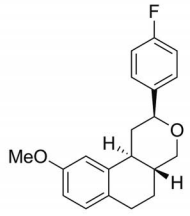
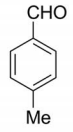
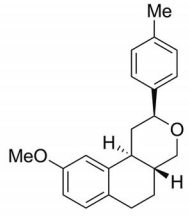
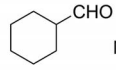
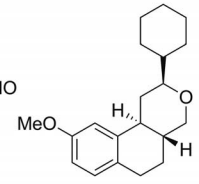
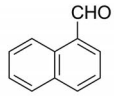
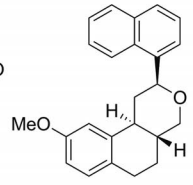
Figure 3. ORTEP diagram of **3b**.

Other aromatic aldehydes such as 4-chloro- and 4-isopropylbenzaldehydes are also found to be effective in providing the desired products in good yields (Table 2, Entries c and d). Next, we extended this cascade process to other aryl-tethered homoallylic alcohols i.e. 2-(4-methoxyphenethyl)but-3-en-1-ol (**1**, R = OMe). Interestingly, various aromatic aldehydes like 4-fluorobenzaldehyde, 4-methylbenzaldehyde and 1-naphthaldehyde underwent smooth cyclization reactions with 4-methoxyphenyl-tethered homoallyl alcohol to furnish the corresponding *trans*-fused hexahydro-1*H*-benzo[*f*]isochromenes in good yields (Table 2, Entries e, f and h). The present method works not only with aromatic aldehydes but also with aliphatic aldehydes such as cyclohexanecarboxaldehyde to afford the alkyl-substituted hexahydro-1*H*-benzo[*f*]isochromene (Table 2, Entry g). In all cases, the reaction afforded *trans*-fused products with good to excellent diastereoselectivity. The formation of the minor *cis*-fused product might occur through trapping of the secondary carbenium ion from the same face as the dihydrostyryl substituent. Unlike electron-rich aryl-tethered homoallylic substrates, the electron-deficient homoallylic alcohols are not so effective for this cyclization. For example, treatment of 2-[4-(trifluoromethyl)phenethyl]-but-3-en-1-ol with benzaldehyde gave the desired product in very low yield (< 10%) under similar conditions. Unlike the reported method, no dihydropyran was formed under our reaction conditions.[3j]

Inspired by the results obtained with aryl-tethered homoallylic alcohol, we extended our efforts to examine this tandem process with phenyl-tethered homoallyl *N*-tosylamide. Accordingly, *N*-tosyl-2-phenethylbut-3-en-1-amine (**4**) was treated with isobutyraldehyde in the presence of $Sc(OTf)_3$ (10 mol-%) and a stoichiometric amount of TsOH in 1,2-dichloroethane (DCE). No reaction was observed at room

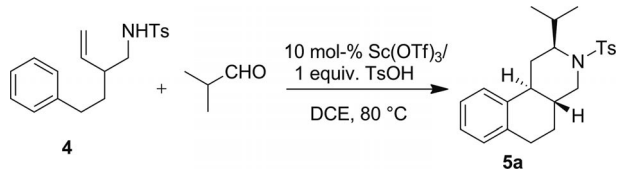
Table 2. Synthesis of hexahydro-1*H*-benzo[*f*]isochromene derivatives through Prins cascade cyclization reactions.[a]



Entry	R^1	Aldehyde	Product (**3**)[b]	Time (h)	Yield (%)[c]	*trans*/*cis* ratio[d]
a	H			3.5	86	92:8
b	H			4	85	90:10
c	H			4	80	90:10
d	H			5	82	84:14
e	MeO			3	88	95:5
f	MeO			4	78	95:5
g	MeO			5	75	95:5
h	MeO			5	85	95:5

[a] The reactions were performed on a 0.5 mmol scale. [b] All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy, IR and mass spectroscopy. [c] Yield refers to pure products after column chromatography. [d] Diastereomeric ratio was determined from the ^{1}H NMR spectra of the crude product.

temperature, however, by increasing the reaction temperature to 80 °C, corresponding product isopropyl-substituted octahydrobenzo[*f*]isoquinoline **5a** was obtained in 78% yield with exclusive *trans*-selectivity (Scheme 2, Table 3, Entry a).

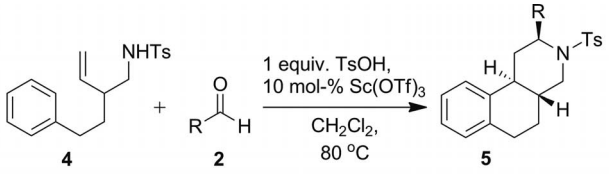


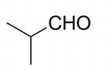
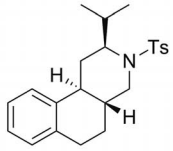
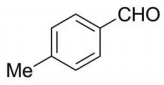
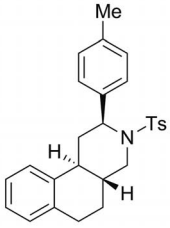
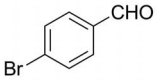
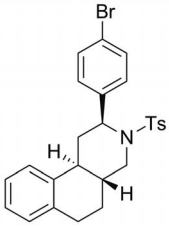
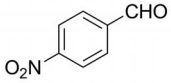
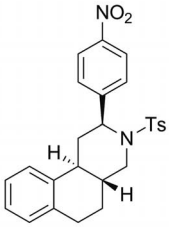
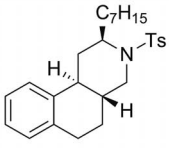
Scheme 2. Synthesis of octahydrobenzo[*f*]isoquinoline by aza-Prins cascade cyclization reaction.

The structure and stereochemistry of **5a** was characterized by using DQFCOSY techniques. Proton 2-H shows a large coupling of 10 Hz with 1-H indicating an axial orientation of 2-H. Also 4a-H shows a large coupling (J = 11 Hz) with 10b-H that further shows a large coupling with one of the 1-H protons indicating that 4a-H and 10b-H are in an axial position. Thus, the fusion of two rings is *trans* as shown in Figure 4.

The scope of the aza-Prins cascade reaction was studied with *N*-tosyl-2-phenethylbut-3-en-1-amine (**4**) and various aldehydes and the results are summarized in Table 3. Similarly, *n*-octanal reacted well to afford corresponding product **5e** under identical reaction conditions (Table 3, Entry e). Aromatic aldehydes such as 4-methyl-, 4-bromo- and 4-nitro-benzaldehydes also reacted smoothly with **4** affording aryl-substituted *trans*-fused octahydrobenzo[*f*]isoquinolines in good yields (Table 3, Entries b, c and d). In most cases, aromatic aldehydes gave products in higher yields

Table 3. Synthesis of octahydrobenzo[*f*]isoquinolines derivatives by aza-Prins cascade cyclization reaction.[a]



Entry	Aldehyde	Product (**5**)[b]	Time (h)	Yield (%)[c]
a			4	78
b			8	75
c			7	88
d			8	80
e	n-C_7H_{15}-CHO		4	78

[a] The reactions were performed on a 0.5 mmol scale. [b] All the products were characterized by ^1H and ^{13}C NMR spectroscopy, IR and mass spectroscopy. [c] Yield refers to pure products after column chromatography.

than aliphatic counterparts. In the case of the aza-Prins cyclization reaction, a tethered aryl nucleophile attacks the six-membered cyclic carbocation selectively from the equatorial side resulting in the exclusive formation of the *trans*-isomer.

Next, we attempted the deprotection of the *N*-tosyl group of **5a** by using lithium naphthalide at –40 °C to generate free amine **6** to be evaluated as a dopamine congener (Scheme 3).

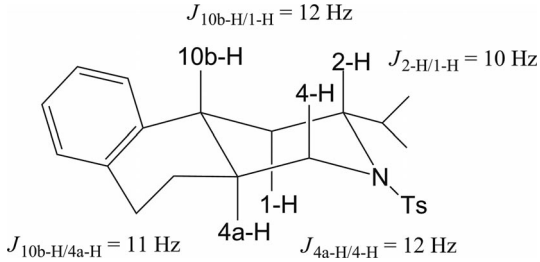
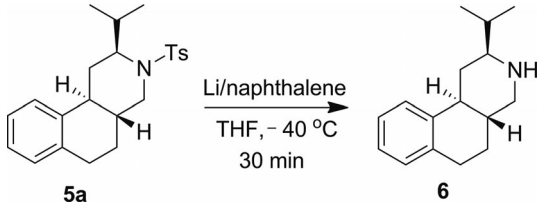


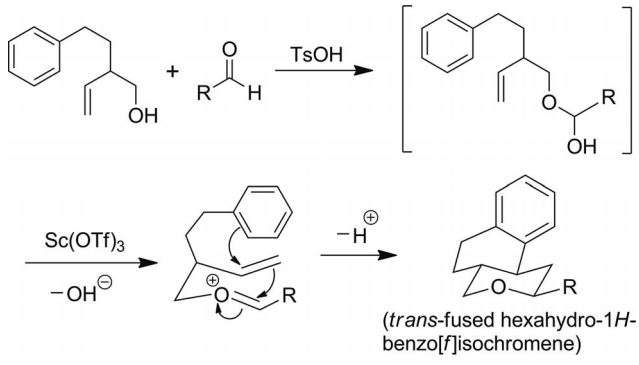
Figure 4. Characteristic coupling constants and chemical structure of **5a**.



Scheme 3. Deprotection of **5a**.

Although various acids were studied for this conversion (Table 1), the combination of $Sc(OTf)_3$ (10 mol-%) and a stoichiometric amount of TsOH was found to give the best results in both Prins and aza-Prins cascade reactions. Next, we examined the effect of various solvents such as dichloromethane, DCE and toluene. Dichloromethane appeared to give the best results for the Prins cyclization reaction, and DCE was found to give high conversions in the aza-Prins cyclization reaction. This method is simple and convenient and provides the desired products in good yields with good to excellent stereoselectivity.

A plausible mechanism for a tandem Prins process is proposed in Scheme 4. The reaction was assumed to proceed through the formation of an oxocarbenium ion generated in situ from the hemi-acetal that is in turn formed by the reaction of a homoallylic alcohol with an aldehyde under acidic conditions. This is followed by attack of the olefin generating a carbocation that is simultaneously trapped by a tethered aryl nucleophile to give the desired hexahydro-1*H*-benzo[*f*]isochromene. In this reaction, the Brønsted acid activates the aldehyde to generate the hemi-acetal from the aldehyde and a homoallylic alcohol whereas the Lewis acid



Scheme 4. A plausible reaction pathway for a tandem Prins reaction.

facilitates the olefin cyclization as well as a Friedel–Crafts reaction. Therefore, both the Brønsted acid and Lewis acid are essential to facilitate the reaction.

The cyclization reaction could also proceed through a 3,3-sigmatropic rearrangement as proposed by Overmann et al., but the product is as same as the Prins cyclization reaction.[13]

Conclusions

In summary, we have demonstrated a new Prins cascade reaction process for the stereoselective synthesis of a wide range of *trans*-fused hexahydro-1*H*-benzo[*f*]isochromene and octahydrobenzo[*f*]isoquinoline derivatives in good yields with high selectivity. This cascade process provides easy access to angularly-fused oxa- and aza-tricycles in a single-step process. Thus, newly prepared octahydrobenzo-[*f*]isoquinoline derivatives can be evaluated as dopamine congeners.

Experimental Section

General: Dichloromethane was dried according to a standard literature procedure. The reactions were performed in oven-dried two-necked round-bottomed flasks under an argon atmosphere. Glass syringes were used to transfer solvent. Products were purified by column chromatography on silica gel of 60–120 or 100–200 mesh. Thin-layer chromatography plates were visualized by using ultraviolet light and/or exposure to iodine vapours and/or exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (–250 °C). Organic solutions were concentrated on a rotary evaporator at 35–40 °C. IR spectra were recorded on FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a 300, 400, 500 or 600 MHz NMR spectrometers with TMS as an internal standard. Mass spectra were recorded with a mass spectrometer by using the electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) techniques.

Typical Procedure for Prins Cascade Cyclization Reaction: To a stirred solution of 2-arylethylbut-3-en-1-ol (**1**; 0.5 mmol) and aldehyde (0.6 mmol) in dry dichloromethane (5 mL) was added Sc(OTf)$_3$ (10 mol-%) and TsOH (0.5 mmol, 1 equiv.). The resulting mixture was stirred at room temperature under an nitrogen atmosphere for the specified time (Table 2). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (1.0 mL) and extracted with dichloromethane (2× 5 mL). The organic layers were combined, washed with brine (3× 5 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) with ethyl acetate/hexane as eluent to afford the pure product.

(2*S,4a*R**,10b*S**)-2-(2-Nitrophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3a):** (Table 2, Entry a). Yield 86% as a brown solid, m.p. 110–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 9.0 Hz, 1 H), 7.84 (d, J = 7.5 Hz, 1 H), 7.64 (t, J = 6.8 Hz, 1 H), 7.46–7.40 (m, 1 H), 7.21–7.10 (m, 4 H), 5.15–5.12 (m, 1 H), 4.15 (dd, J = 11.3, 3.7 Hz, 1 H), 3.47 (t, J = 11.3 Hz, 1 H), 2.98–2.91 (m, 1 H), 2.88–2.77 (m, 2 H), 1.86–1.69 (m, 2 H), 1.61–1.37 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6, 138.4, 138.1, 136.3, 133.4, 129.0, 128.2, 128.0, 126.1, 125.7, 125.5, 124.1, 75.7, 73.4, 41.4, 38.7, 37.6, 28.7, 24.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3064, 3017, 2921, 2853, 1609, 1577, 1525, 1456, 1346, 1305, 1142, 1071, 767, 741, 705, 567 cm^{-1}. HRMS (APCI): calcd. for $C_{19}H_{19}NO_3$ $[M]^+$ 310.14377; found 310.14394.

(2*S,4a*R**,10b*S**)-2-(Thiophen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3b):** (Table 2, Entry b). Yield 85% as a white solid, m.p. 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 3 H), 7.18–7.10 (m, 4 H), 4.53 (dd, J = 11.3, 2.2 Hz, 1 H), 4.14 (dd, J = 3.7, 10.5 Hz, 1 H), 3.45 (dd, J = 10.5, 11.3 Hz, 1 H), 2.97–2.86 (m, 2 H), 2.73–2.66 (m, 1 H), 2.56–2.50 (m, 1 H), 1.88–1.69 (m, 2 H), 1.61–1.38 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 138.6, 136.5, 133.1, 129.2, 128.5, 127.4, 126.2, 125.8, 124.5, 79.7, 73.5, 41.6, 38.6, 38.3, 28.8, 24.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2921, 2851, 1484, 1453, 1358, 1255, 1089, 1039, 763, 738, 701, 546 cm^{-1}. HRMS (APCI): calcd. for $C_{17}H_{18}OS$ $[M]^+$ 270.10729; found 270.10750.

(2*S,4a*R**,10b*S**)-2-(4-Chlorophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3c):** (Table 2, Entry c). Yield 80% as a semi solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.28 (m, 2 H), 7.20–7.10 (m, 4 H), 7.12–7.06 (m, 1 H), 7.08–6.90 (m, 1 H), 4.83 (dd, J = 11.3, 1.5 Hz, 1 H), 4.13 (dd, J = 11.3, 3.7 Hz, 1 H), 3.48 (dd, J = 11.3, 10.5 Hz, 1 H), 2.96–2.88 (m, 2 H), 2.74–2.69 (m, 1 H), 1.84–1.70 (m, 4 H), 1.51–1.37 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9, 138.3, 136.4, 129.1, 126.4, 126.1, 125.7, 124.5, 123.5, 76.0, 41.4, 38.4, 38.1, 28.7, 24.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2923, 2853, 1490, 1455, 1364, 1273, 1218, 1089, 1037, 1014, 825, 768, 740, 562 cm^{-1}. HRMS (APCI): calcd. for $C_{19}H_{19}ClO$ $[M]^+$ 298.11189; found 298.11197.

(2*S,4a*R**,10b*S**)-2-(4-Isopropylphenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3d):** (Table 2, Entry d). Yield 82% as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, J = 7.9 Hz, 2 H), 7.24–7.19 (m, 2 H), 7.17–7.09 (m, 4 H), 4.52 (d, J = 10.8 Hz, 1 H), 4.13 (dd, J = 10.8, 3.9 Hz, 1 H), 3.44 (t, J = 10.8 Hz, 1 H), 3.00–2.83 (m, 2 H), 2.72–2.67 (m, 1 H), 2.59 (m, 1 H), 1.95–1.72 (m, 3 H), 1.65 (q, J = 11.8 Hz, 1 H), 1.49–1.41 (m, 1 H), 1.24 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.2, 138.9, 136.6, 129.1, 128.7, 126.5, 126.4, 126.2, 126.1, 126.0, 125.8, 124.6, 80.5, 73.6, 41.8, 38.7, 38.0, 33.9, 31.5, 30.2, 28.9, 24.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2956, 2924, 2863, 1490, 1457, 1363, 1093, 963, 828, 768, 739, 574 cm^{-1}. HRMS (APCI): calcd. for $C_{22}H_{26}O$ $[M]^+$ 306.19782; found 306.19567.

(2*S,4a*R**,10b*S**)-2-(4-Fluorophenyl)-9-methoxy-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3e):** (Table 2, Entry e). Yield 88% as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (dd, J = 8.3, 3.0 Hz, 1 H), 7.07–7.02 (m, 3 H), 6.79–6.69 (m, 2 H), 4.52 (dd, J = 11.3, 2.2 Hz, 1 H), 4.15 (dd, J = 11.3, 3.7 Hz, 1 H), 3.75 (s, 3 H), 3.43 (dd, J = 11.3, 10.5 Hz, 1 H), 2.89–2.83 (m, 1 H), 2.67 (td, J = 11.3, 3.0 Hz, 1 H), 2.51–2.45 (m, 1 H), 1.83–1.39 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 157.9, 139.8, 138.7, 130.0, 128.6, 127.8, 127.7, 115.4, 115.1, 111.7, 110.2, 79.8, 73.5, 65.3, 41.9, 38.7, 29.7, 28.0, 24.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2956, 2924, 2863, 1490, 1457, 1363, 1093, 963, 828, 768, 739, 574 cm^{-1}. HRMS (APCI): calcd. for $C_{20}H_{21}FO_2$ $[M]^+$ 312.15201; found 312.15047.

(2*S,4a*R**,10b*S**)-9-Methoxy-2-*p*-tolyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3f):** (Table 2, Entry f) Yield 78% as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, J = 7.5 Hz, 2 H), 7.16 (d, J = 7.5 Hz, 2 H), 7.01 (d, J = 7.5 Hz, 1 H), 6.73–6.69 (m, 2 H), 4.50 (dd, J = 11.3, 2.6 Hz, 1 H), 4.14 (dd, J = 11.3, 3.7 Hz, 1 H), 3.74 (s, 3 H), 3.45 (dd, J = 11.3, 10.5 Hz, 1 H), 2.89–2.83 (m, 1 H), 2.65 (td, J = 11.3, 3.0 Hz, 1 H), 2.48 (dt, J = 6.0, 3.0 Hz, 1 H), 2.35 (s, 3 H), 1.83–1.56 (m, 4 H), 1.49–1.39 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 139.6, 137.2,

129.8, 129.0, 128.4, 125.9, 111.8, 109.9, 80.3, 73.4, 55.2, 41.9, 38.6, 38.1, 27.9, 24.7, 21.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2922, 2852, 1609, 1577, 1498, 1460, 1280, 1248, 1223, 1157, 1146, 1094, 1073, 1039, 815, 712, 561 cm^{-1}. HRMS (APCI): calcd. for $C_{21}H_{24}O_2$ $[M]^+$ 308.17708; found 308.17709.

(2*S,4a*R**,10b*S**)-2-Cyclohexyl-9-methoxy-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3g):** (Table 2, Entry g). Yield 75% as a semi solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.3 Hz, 1 H), 6.80–6.68 (m, 3 H), 5.03–4.9 (m, 1 H), 4.20 (dd, J = 11.3, 3.7 Hz, 1 H), 3.79 (s, 3 H), 3.22 (dd, J = 11.3, 10.5 Hz, 1 H), 2.85–2.80 (m, 1 H), 2.48–2.39 (m, 1 H), 2.32–2.24 (m, 1 H), 2.07–2.0 (m, 1 H), 1.92 (d, J = 12.0 Hz, 1 H), 1.78–1.54 (m, 6 H), 1.48–1.25 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.6, 129.8, 128.7, 111.0, 110.6, 82.4, 73.2, 55.3, 43.2, 41.6, 39.1, 29.6, 29.1, 28.9, 27.9, 26.6, 26.2, 24.8, 14.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2924, 2853, 1610, 1498, 1451, 1279, 1246, 1145, 1100, 772 cm^{-1}. HRMS (APCI): calcd. for $C_{20}H_{28}O_2$ $[M + H]^+$ 301.21514; found 301.21621.

(2*S,4a*R**,10b*S**)-9-Methoxy-2-(naphthalen-1-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3h):** (Table 2, Entry h). Yield 76% as a white liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.3 Hz, 1 H), 7.68 (d, J = 6.7 Hz, 1 H), 7.56–7.42 (m, 4 H), 7.05 (d, J = 9.0 Hz, 1 H), 6.73–6.70 (m, 3 H), 5.27 (dd, J = 11.3 and 2.2 Hz, 1 H), 4.26 (dd, J = 11.3, 3.7 Hz, 1 H), 3.70 (s, 3 H), 3.61 (dd, J = 11.3, 10.5 Hz, 1 H), 2.95–2.78 (m, 2 H), 2.73–2.67 (m, 1 H), 1.85 (m, 3 H), 1.56–1.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 133.4, 130.0, 129.5, 128.4, 128.1, 127.6, 125.5, 125.1, 125.0, 123.0, 122.9, 111.4, 109.7, 76.1, 73.4, 54.8, 41.7, 38.4, 36.7, 27.5, 24.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2923, 2853, 1610, 1498, 1460, 1245, 1222, 1141, 773 cm^{-1}. HRMS (APCI): calcd. for $C_{24}H_{24}O_2$ $[M]^+$ 344.17708; found 344.17700.

Typical Procedure for Aza-Prins Cascade Cyclization Reaction: To a stirred solution of 4-methyl-*N*-(6-arylhex-3-enyl)benzenesulfonamide (**4**; 0.5 mmol) and aldehyde (0.6 mmol) in dry DCE (5 mL) was added $Sc(OTf)_3$ (10 mol-%) and TsOH (0.5 mmol). The resulting mixture was heated at 80 °C under a nitrogen atmosphere for the specified time (Table 3). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (0.5 mL) and extracted with dichloromethane (2 × 5 mL). The organic phases were combined, washed with brine (3 × 2 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (60–120 mesh) with ethyl acetate/hexane as eluent to afford the pure product.

(2*S,4a*R**,10b*S**)-2-Isopropyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5a):** (Table 3, Entry a). Yield 78% as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 7.9 Hz, 2 H), 7.21 (d, J = 7.9 Hz, 2 H), 7.15–7.08 (m, 3 H), 7.05–7.03 (m, 1 H), 3.86 (dd, J = 13.9, 3.9 Hz, 1 H), 3.80 (dd, J = 9.9, 4.9 Hz, 1 H), 2.57–2.53 (m, 1 H), 2.42 (d, J = 13.9 Hz, 1 H), 2.37 (s, 3 H), 2.15–2.09 (m, 1 H), 1.74–1.55 (m, 3 H), 1.40–1.32 (m, 1 H), 1.01 (dd, J = 9.9, 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 138.9, 138.5, 136.7, 129.7, 129.1, 126.8, 126.0, 125.7, 124.6, 60.1, 46.9, 37.5, 36.3, 29.5, 28.7, 26.7, 26.3, 21.5, 20.4, 20.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2963, 2922, 2871, 1598, 1452, 1335, 1156, 1091, 1053, 1019, 971, 814, 764, 668, 594, 550 cm^{-1}. HRMS (APCI): calcd. for $C_{23}H_{29}NO_2S$ $[M]^+$ 383.19135; found 383.19180.

(2*S,4a*R**,10b*S**)-2-*p*-Tolyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5b):** (Table 3, Entry b). Yield 75% as a semi solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.1 Hz, 2 H), 7.23 (m, 6 H), 7.12–7.02 (m, 4 H), 6.99–6.98 (m, 1 H), 5.40 (d, J = 3.5 Hz, 1 H), 3.88 (dd, J = 13.7, 3.5 Hz, 1 H), 2.91–2.16 (m, 4 H), 2.32 (s, 3 H), 2.26 (s, 3 H), 1.75–1.48 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 136.7, 136.6, 135.6, 129.8, 129.5, 129.1, 126.8, 126.6, 126.1, 125.8, 25.7, 55.5, 47.4, 38.0, 36.6, 31.9, 28.7, 26.2, 21.5, 20.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2920, 2851, 1449, 1335, 1219, 1159, 1092, 919, 772, 670, 556 cm^{-1}. HRMS (APCI): calcd. for $C_{27}H_{37}NO_2S$ $[M + H]^+$ 440.26178; found 440.26117.

(2*S,4a*R**,10b*S**)-2-(4-Bromophenyl)-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5c):** (Table 3, Entry c). Yield 88% as a white solid, m.p. 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 7.9 Hz, 2 H), 7.45 (d, J = 7.9 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 7.24 (d, J = 6.9 Hz, 1 H), 7.18 (d, J = 6.9 Hz, 1 H), 7.02–7.15 (m, 3 H), 5.45 (d, J = 3.9 Hz, 1 H), 3.94 (dd, J = 13.9, 3.9 Hz, 1 H), 2.90–2.75 (m, 4 H), 2.39 (s, 3 H), 1.78–1.52 (m, 4 H), 1.42–1.30 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 138.2, 137.9, 136.7, 131.9, 129.8, 129.3, 128.5, 126.8, 126.2, 125.9, 124.6, 55.3, 47.5, 37.9, 36.5, 31.8, 28.6, 26.1, 21.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2922, 2854, 1596, 1488, 1452, 1335, 1159, 1092, 1010, 943, 919, 812, 741, 674, 544 cm^{-1}. HRMS (APCI): calcd. for $C_{26}H_{26}BrNO_2S$ $[M + H]^+$ 496.09404; found 496.09743.

(2*S,4a*R**,10b*S**)-2-(4-Nitrophenyl)-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5d):** (Table 3, Entry d). Yield 80% as a brown solid, m.p. 140–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 9.0 Hz, 2 H), 7.69–7.62 (m, 3 H), 7.54 (d, J = 8.3 Hz, 2 H), 7.20–7.18 (m, 3 H), 7.15–6.96 (m, 2 H), 5.50 (d, J = 4.5 Hz, 1 H), 3.95 (dd, J = 12.8, 4.5 Hz, 1 H), 2.91–2.86 (m, 1 H), 2.83–2.79 (m, 1 H), 2.75–2.68 (m, 2 H), 2.34 (s, 3 H), 2.25 (t, J = 11.3 Hz, 1 H), 1.69–1.57 (m, 1 H), 1.56–1.36 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 137.3, 136.7, 136.2, 130.0, 129.7, 129.3, 127.7, 127.1, 126.8, 126, 125.9, 125.8, 124.6, 55.7, 47.8, 37.9, 36.7, 32.2, 28.6, 26.2, 21.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2924, 2851, 1599, 1519, 1492, 1452, 1344, 1219, 1159, 1092, 920, 855, 712, 671, 550 cm^{-1}. HRMS (APCI): calcd. for $C_{26}H_{26}N_2O_4S$ $[M + H]^+$ 496.16874; found 463.16874.

(2*R,4a*R**,10b*S**)-2-Heptyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5e):** (Table 3, Entry e). Yield 78% as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.5 Hz, 2 H), 7.20 (d, J = 8.3 Hz, 2 H), 7.13–7.04 (m, 4 H), 4.27–4.20 (m, 1 H), 3.80 (dd, J = 14.3, 3.7 Hz, 1 H), 2.90–2.79 (m, 3 H), 2.66–2.56 (m, 1 H), 2.38 (s, 3 H), 2.30–2.23 (m, 1 H), 1.81–1.72 (m, 1 H), 1.68–1.49 (m, 3 H), 1.46–1.21 (m, 13 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 138.5, 136.7, 129.7, 129.1, 126.9, 126.1, 125.8, 124.7, 53.7, 46.4, 38.2, 36.2, 32.1, 31.9, 30.3, 29.4, 29.2, 28.8, 26.7, 26.5, 22.7, 21.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2953, 2856, 1490, 1456, 1334, 1157, 1091, 1024, 987, 920, 814, 740, 667, 595, 551 cm^{-1}. HRMS (APCI): calcd. for $C_{27}H_{37}NO_2S$ $[M + H]^+$ 440.26178; found 440.26117.

Procedure for Synthesis of Free Amine 6 from 5a (*N*-Tosyl Deprotection): To a stirred solution of (2*S**,4a*R**,10b*R**)-2-isopropyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (**5a**; 0.1 mmol) in anhydrous THF (2 mL) was added a Li-naphthalide solution (prepared by using 4 equiv. lithium and 8 equiv. naphthalene in 2 mL THF) at –40 °C dropwise. The reaction mixture was stirred at the same temperature for 20 to 30 min and then quenched with saturated NH_4Cl solution (0.5 mL), diluted with water (2 mL) and extracted with ethyl acetate (2 × 2 mL). The organic phases were combined, washed with brine (2 × 1 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (60–120 mesh) with methanol/chloroform as eluent to afford pure product **6**.

(2*S,4a*R**,10b*S**)-2-Isopropyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-isoquinoline (6):** (Scheme 3). Yield 82% as a semi solid. ^{1}H NMR

(500 MHz, $CDCl_3$): δ = 8.60 (br. s, 1 H), 7.15–6.99 (m, 4 H), 3.46–3.35 (m, 1 H), 3.33–3.22 (m, 1 H), 2.96–2.69 (m, 2 H), 2.66–2.49 (m, 2 H), 2.22–1.75 (m, 5 H), 1.49–1.37 (m, 1 H), 1.20 (d, J = 5.8 Hz, 3 H), 1.03 (d, J = 5.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.7, 136.3, 129.3, 126.5, 126.0, 124.6, 59.6, 44.6, 36.1, 35.2, 28.6, 28.5, 26.5, 25.5, 20.4, 19.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3417, 2925, 2851, 1587, 1454, 1380, 1218, 771, 743 cm^{-1}. MS (ESI): m/z = 230 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{23}N$ $[M + H]^+$ 230.1903; found 230.1908.

Supporting Information (see footnote on the first page of this article): Preparation of starting materials, copies of ^1H and ^{13}C NMR spectra of products, copies of ^1H and ^{13}C NMR spectra of starting materials.

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[12] CCDC-887311 contains supplementary crystallographic data for compound **3c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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