JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Tandem Prins/Friedel—Crafts Cyclization for Stereoselective Synthesis of Heterotricyclic Systems

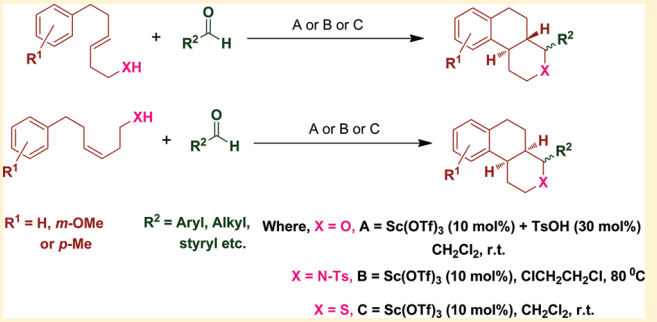
B. V. Subba Reddy,*[,†] Prashant Borkar,[†] J. S. Yadav,*[,†] B. Sridhar,[‡] and René Grée[§]

[†]Division of Organic Chemistry and [‡]Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India

[§]Université de Rennes 1, Laboratoire SCR, CNRS UMR 6226, Avenue du Général Leclerc, 35042 Rennes Cedex, France

Supporting Information

ABSTRACT: Homoallylic substrates such as (*E*)-6-arylhex-3-enyl alcohols, *N*-tosylamides, and thiols undergo smooth cross-coupling with various aldehydes in the presence of 10 mol % $Sc(OTf)_3$ and 30 mol % TsOH to afford the trans-fused hexahydro-1*H*-benzo[*f*]isochromenes, *N*-tosyloctahydrobenzo[*f*]-isoquinolines, and hexahydro-1*H*-benzo[*f*]isothiochromenes, respectively. However, the cross-coupling of (*Z*)-olefins such as 6-arylhex-3-enyl alcohols, *N*-tosylamides, and thiols with aldehydes affords the corresponding hexahydro-1*H*-benzo-[*f*]isochromenes, *N*-tosyloctahydrobenzo[*f*]isoquinolines, and hexahydro-1*H*-benzo[*f*]isothiochromenes with complete cis selectivity via intramolecular Prins-, aza-Prins-, and thia-Prins/Friedel—Crafts cyclizations, respectively. Though the Prins cyclization proceeds smoothly under the influence of $Sc(OTf)_3$, high conversions and enhanced reaction rates are achieved using a mixture of $Sc(OTf)_3$ and TsOH (1:3).



INTRODUCTION

The coupling of an olefin with a carbonyl compound in the presence of an acid catalyst is known as the 'Prins reaction', which normally provides a mixture of 1,3-diols, 1,3-dioxanes, and allylic alcohols.[1−4] In particular, the coupling of a homoallylic alcohol with a carbonyl compound in the presence of an acid catalyst is known as the 'Prins cyclization', which is a powerful synthetic tool for the stereoselective synthesis of tetrahydropyran scaffolds.[5] On the other hand, aza-Prins cyclization of homoallylic amides with carbonyl compounds is one of the most elegant approaches for the synthesis of piperidine derivatives.[5−8] In the same way, thia-Prins cyclization of homoallylic mercaptans with aldehydes under the influence of an acid catalyst provides the corresponding thia-tetrahydropyrans with high selectivity.[9,10] Subsequently, tandem Prins cyclizations, such as Prins/Ritter and Prins/Friedel—Crafts, have also been reported to produce 4-amido- and 4-aryltetrahydropyran derivatives, respectively.[5,11−18] Recently, a tandem ene/Prins cyclization has been reported to furnish annulated tetrahydropyran scaffolds.[19] Therefore, the Prins cyclization has emerged as a powerful method for stereoselective synthesis of a wide range of heterocycles such as tetrahydropyrans, thiapyrans, and piperidine scaffolds. In spite of its potential application in natural products synthesis,[20] the intramolecular versions of Prins and aza-Prins cyclizations are still unexplored.[5,14,21−24] To the best of our knowledge, until now, there have been no reports on the intramolecular versions of aza- and thia-Prins/Friedel—Crafts cyclizations.

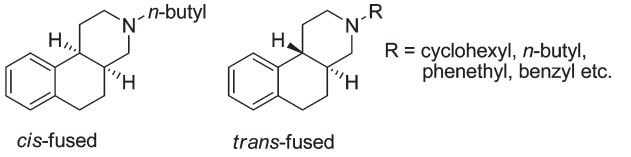
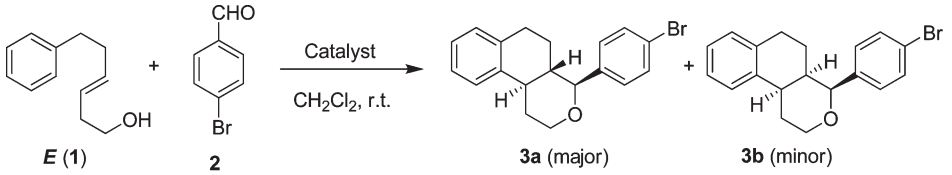


Figure 1. Examples of bioactive octahydrobenzo[*f*]isoquinoline analogues.

The saturated form of the hexahydro-1*H*-benzo[*f*]isochromene skeleton is typically found in some biologically active natural products such as alpindenosides C and D and curcumanggoside.[25,26] Alpindenosides C and D are a novel class of labdane diterpene glycosides isolated from the stems of *Alpinia densespicata* which exhibit moderate NO inhibitory activities, whereas they are noncytotoxic at 20 μM against several human tumor cell lines. Curcumanggoside is also a labdane diterpene glycoside isolated from the rhizomes of *Curcuma mangga*. Some of the trans- and cis-fused octahydrobenzo[*f*]isoquinoline analogues (Figure 1) show a high affinity toward σ receptors with regard to psychotomimetic effects[27−29] or as potential calcium channel blockers.[30] Thiapyrans are rarely available in Nature. The thiapyran motif occupies a key role in a number of pharmaceutical agents such as cephalosporins and dithiathromboxane A_2.[31,32] Furthermore, thiacyclohexane derivatives can be transformed into a variety of

Received: January 28, 2011
Published: August 15, 2011

Table 1. Catalyst Optimization for Intramolecular Prins/Friedel−Crafts Cyclization of (*E*)-6-Phenylhex-3-en-1-ol with 4-Bromobenzaldehyde[a]



entry	$Sc(OTf)_3$(mol %)	TsOH(mol %)	TfOH(mol %)	time (h)	yield (%)[b]
a	10			30	75
b	30			24	80
c		10		36	49
d		30		30	57
e	30	10		16	84
f	10	10		18	80
g	10	20		11	85
h	10	30		7	92
i			30	24	65
j	10		30	8	86

[a] Reaction was performed at 0.5 mmol scale with respect to olefin in dichloromethane at room temperature. [b] Combined yield of trans- and cis-fused product (diastereomeric ratio = 9:1) after column chromatography.

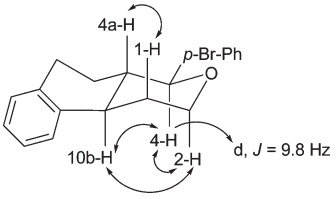


Figure 2. Characteristic NOEs and chemical structure of (4*S**,4a*S**,10b*R**)-4-(4-bromophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (**3a**).

structures through simple reactions such as hydrogenolysis, oxidation, and olefination.[33,34]

RESULTS AND DISCUSSION

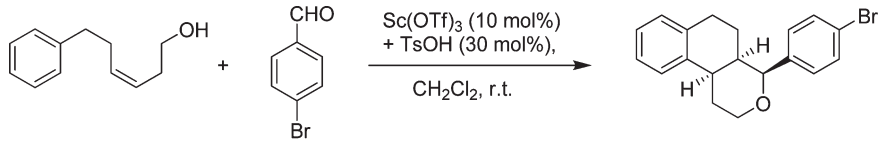
In a continuation of our research program on Prins-type cyclizations and its application to the total synthesis of natural products,[35−37] we herein report a versatile method for stereoselective synthesis of heterotricycles, namely, hexahydro-1*H*-benzo[*f*]isochromene, octahydrobenzo[*f*]isoquinoline, and hexahydro-1*H*-benzo[*f*]isothiochromene, via intramolecular Prins-, aza-Prins-, and thia-Prins/Friedel−Crafts cyclizations, respectively.

As a model reaction, we first attempted the cross-coupling of 4-bromobenzaldehyde (**2**) with (*E*)-6-phenylhex-3-en-1-ol (**1**) in the presence of 10 mol % $Sc(OTf)_3$ and 30 mol % TsOH in dichloromethane. The reaction proceeded smoothly at room temperature to furnish the corresponding product **3a** in 92% yield with a high trans selectivity (90:10, Table 1, entry **h**). The ratio of trans/cis isomers was determined by ^{1}H NMR spectra of a crude product. The two diastereomers could easily be separated by silica gel column chromatography. The combination of $Sc(OTf)_3$ and TsOH (1:3) works more effective than either $Sc(OTf)_3$ or TsOH alone in terms of reaction time and yield (Table 1). The high catalytic activity of the above reagent system may be explained by means of a cooperative catalysis[38] between $Sc(OTf)_3$ and an organic cocatalyst (TsOH) or by in situ formation of $Sc(OTs)_3$. However, no $Sc(OTs)_3$ was formed in situ from $Sc(OTf)_3$ and TsOH, which was later confirmed by running a simple ^{1}H NMR experiment of the catalyst. Indeed, no significant change in chemical shift (δ) values of the *p*-tolyl group of TsOH was observed in the ^{1}H NMR spectrum. Formation of $Sc(OTs)_3$ may be ruled out further as there was no characteristic m/z peak for $Sc(OTs)_3$ in the mass spetrum. Moreover, it was supported by performing the reaction in the presence of $Sc(OTf)_3$ and TfOH wherein similar enhanced catalytic activity was observed (entry **j**, Table 1).

The structure and stereochemistry of (4*S**,4a*S**,10b*R**)-4-(4-bromophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene **3a** was established by NOE experiments. The proton 4-H shows a large coupling of 9.8 Hz with 4a-H indicating the axial orientation of 4-H. Also, 4a-H shows a large coupling (12.1 Hz) with 10b-H, which further shows a large coupling with one of the 1-H protons, indicating that 4a-H and 10b-H are in axial positions. In addition to the couplings, the presence of NOE cross-peaks between 4-H, 10b-H, and 2-H as well as cross-peaks between 4a-H and 1-H confirmed that the fusion between the two rings is trans (Figure 2). The double-edged arrows show characteristic NOE correlations. Furthermore, the structure of **3a** was confirmed by X-ray crystallography.[39]

However, the cross-coupling of (*Z*)-6-phenylhex-3-en-1-ol with 4-bromobenzaldehyde in the presence of 10 mol % $Sc(OTf)_3$ and 30 mol % TsOH in dichloromethane at room temperature gave the product **3b** in 88% yield with complete cis selectivity (Scheme 1, Table 2, entry **b**). The above results provided a gateway to extend this process to a variety of other interesting substrates like (*E*)- and (*Z*)-6-(3-methoxyphenyl)hex-3-en-1-ol and (*E*)- and (*Z*)-6-*p*-tolylhex-3-en-1-ol. The scope of the reaction is illustrated with respect to various aldehydes like

Scheme 1. Reaction of (*Z*)-6-Phenylhex-3-en-1-ol with 4-Bromobenzaldehyde



***Z* (1)** **2** **3b**

cyclohexanecarboxaldehyde, thiophene-2-carbaldehyde, 3-methylbutanal, 4-nitrobenzaldehyde, and cinnamaldehyde, and the results are presented in Table 2 (entries **c**−**h**, **k**−**n**). In all cases, the corresponding hexahydro-1*H*-benzo[*f*]isochromenes (entries **g**, **h**, **k**−**n**, Table 2) were obtained in good yields with high selectivity. The geometry of the olefin controls the stereoselectivity of the reaction. It is known that cis olefin gives cis-fused product exclusively, whereas trans olefin provides trans-fused product predominantly. This method works well not only with aldehydes but also with ketones. For instance, cyclohexanone affords the spiropyrans under identical conditions (entries **i** and **j**). In the case of the meta-substituted aryl group, for example, 6-(3-methoxyphenyl)hex-3-en-1-ol, the corresponding product was obtained as a 3:1 mixture of para/ortho isomers (entries **g**−**j**, Table 2). The ratio of para/ortho isomers was determined by ^{1}H NMR spectra of the crude product. The two regioisomers could easily be separated by silica gel column chromatography. In the case of entry **a**, formation of minor cis-fused product (10%) may be due to some nonconcertedness during the process of cyclization with 4-bromobenzaldehyde in which a minor amount of trapping of the secondary carbenium ion may occur from the same face as the dihydrostyryl substituent.

Next, we examined the aza-Prins/Friedel−Crafts cyclization of 4-methyl-*N*-(6-arylhex-3-enyl)benzenesulfonamide (**4**) with aldehydes. Accordingly, 3-methylbutanal was treated with (*E*)-4-methyl-*N*-(6-phenylhex-3-enyl)benzenesulfonamide (**4**) in the presence of 10 mol % Sc(OTf)$_3$ in 1,2-dichloroethane. To our surprize, aza-Prins cyclization proceeded at 80 °C to afford the corresponding trans-fused *N*-tosyl-octahydrobenzo[*f*]isoquinoline **5e** in 78% yield as a sole product (Table 3, entry **e**). Likewise, coupling of (*Z*)-4-methyl-*N*-(6-phenylhex-3-enyl)benzenesulfonamide with 3-methylbutanal gave the cis-fused *N*-tosyl-octahydrobenzo[*f*]isoquinoline **5f** in 80% yield exclusively (Table 3, entry **f**). The structure and stereochemistry of (4*S**,4a*R**,10b*R**)-4-isobutyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline **5f** was established by NOE experiments. The coupling between 4-H and 4a-H protons is 1 Hz. This indicates that 4-H and 4a-H are in equatorial positions. This is further confirmed by a small coupling between 4a-H and 10b-H (4.9 Hz) and absence of NOE cross-peaks between 4-H/10b-H, 4-H/2-H, 4a-H/1-H. The proton 10b-H is in the axial position since it shows a large coupling (11.7 Hz) with one of the 1-H protons and NOE with one of the 2-H protons. From these observations, it is confirmed that the cis fusion takes place between the two rings (Figure 3). The coupling values and NOEs are consistent with the structure as shown in Figure 3. The double-edged arrows show characteristic NOE correlations. Furthermore, the structure of **5f** was confirmed by X-ray crystallography.[39]

The scope of the reaction is illustrated with regard to substrates such as (*E*)- and (*Z*)-4-methyl-*N*-(6-(3-methoxyphenyl)hex-3-enyl)benzenesulfonamide and (*E*)- and (*Z*)-4-methyl-*N*-(6-*p*-tolylhex-3-enyl)benzenesulfonamide and various aldehydes, and the results are summarized in Table 3. Notably, paraformaldehyde[40] also

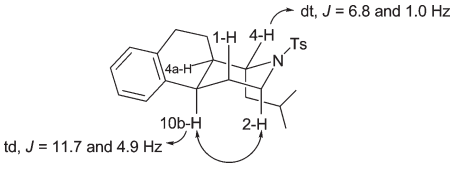


Figure 3. Coupling constants and characteristic NOEs of (4*S**,4a*R**,10b*R**)-4-isobutyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (**5f**).

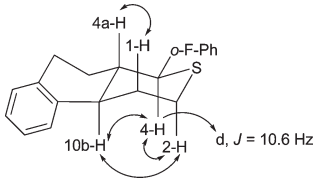


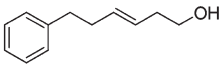
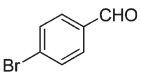
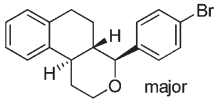
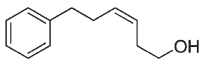
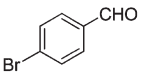
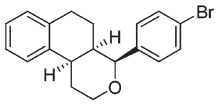
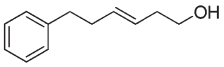
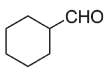
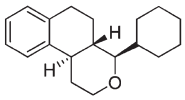
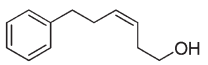
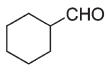
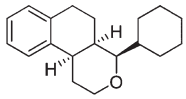
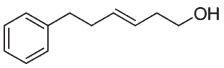
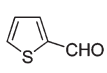
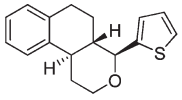
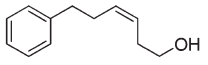
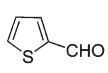
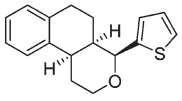
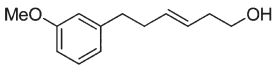
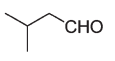
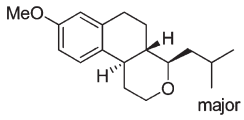
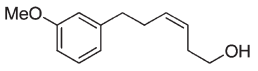
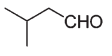
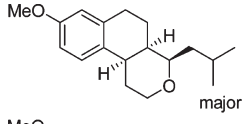
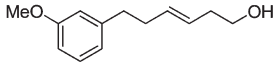
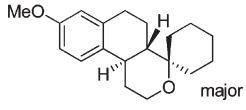
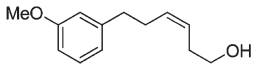
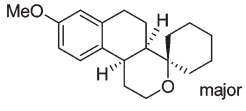
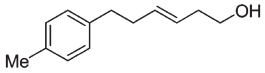
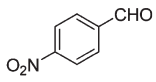
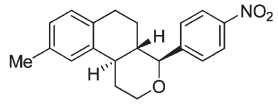
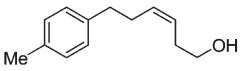
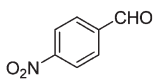
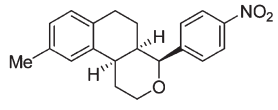
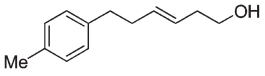
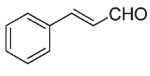
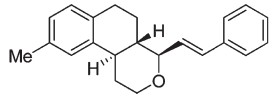
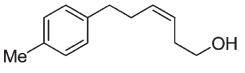
Figure 4. Characteristic NOEs and chemical structure of (4*S**,4a*S**,10b*R**)-4-(2-fluorophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (**7a**).

participated well in this cyclization (entries **g** and **h**, Table 3). As shown in Table 3, aromatic aldehydes gave slightly lower yields than aliphatic counterparts (entries **c**, **d**, **m** and **n**). In the case of 4-methyl-*N*-(6-(3-methoxyphenyl)hex-3-enyl)benzenesulfonamide, products **5i**−**l** were obtained as a 2:1 mixture of para/ortho-substituted products (entries **i**−**l**, Table 3). The two regioisomers could easily be separated by silica gel column chromatography.

Encouraged by the results obtained with aryl-tethered homoallylic alcohols (**1**) and tosylamides (**4**), we turned our attention to extend this process for the thia-Prins/Friedel−Crafts cyclization. Accordingly, 2-fluorobenzaldehyde was treated with (*E*)-6-phenylhex-3-ene-1-thiol (**6**) in the presence of 10 mol % Sc(OTf)$_3$ in dichloromethane. Interestingly, thia-Prins cyclization proceeded smoothly at room temperature to afford the respective trans-fused hexahydro-1*H*-benzo[*f*]isothiochromene **7a** as a sole product in 86% yield (Table 4, entry **a**). The structure and stereochemistry of (4*S**,4a*S**,10b*R**)-4-(2-fluorophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene **7a** was characterized by NOE experiments. The proton 4-H shows a large coupling of 10.6 Hz with 4a-H, indicating axial orientation of 4-H. Also, 4a-H shows a large coupling (J = 10.6 Hz) with 10b-H, which further shows a large coupling with one of the 1-H protons, indicating that 4a-H and 10b-H are in axial positions. It is further confirmed by the presence of NOE cross-peaks between 4-H, 10b-H, and 2-H as well as cross-peaks between 4a-H and 1-H. From the above observations, it is confirmed that the fusion between the two rings is trans as shown in Figure 4. The thiapyran ring in the molecule adopts the chair form, which is in agreement with the observed couplings and NOE cross-peaks. The double-edged arrows show characteristic NOE correlations. Furthermore, the structure of **7a** was confirmed by X-ray crystallography.[39]

dx.doi.org/10.1021/jo201027u |*J. Org. Chem.* 2011, 76, 7677–7690

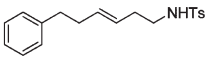
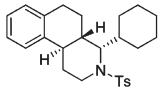
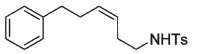
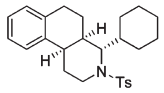
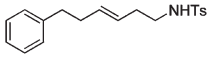
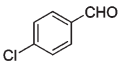
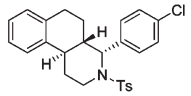
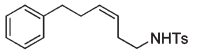
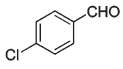
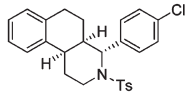
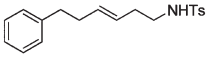
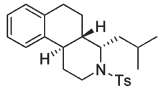
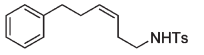
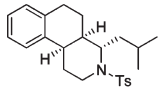
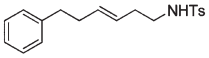
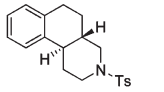
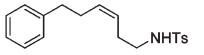
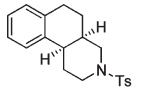
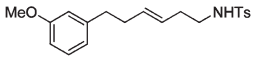
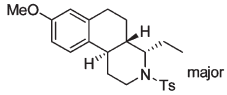
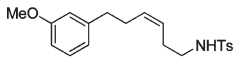
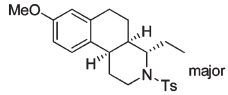
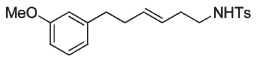
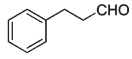
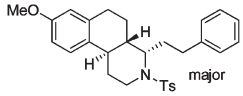
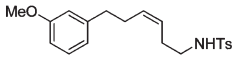
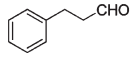
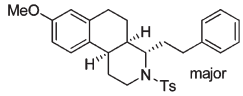
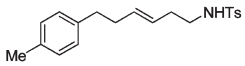
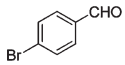
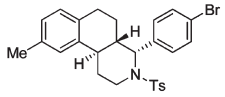
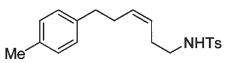
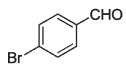
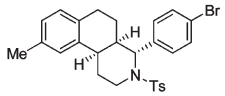
Table 2. Synthesis of Hexahydro-1*H*-benzo[*f*]isochromene Scaffolds via Intramolecular Prins/Friedel–Crafts Cyclizations[a]

Entry	Homoallylic alcohol (**1**)	Aldehyde (**2**)	Product (**3**)[b]	Time (h)	Yield (%)[c]
a			 major	7	92 *trans*:*cis* ratio = 9:1
b				7	88
c				5	86
d				5	84
e				6	86
f				6	80
g			 major	5	60[d]
h			 major	5	58[d]
i			 major	10	56[d]
j			 major	10	56[d]
k				7	90
l				7	85
m				6	84
n				6	86

[a] Reaction was performed with 0.5 mmol of olefin, 0.6 mmol of aldehyde, and 10 mol % $Sc(OTf)_3$ + 30 mol % TsOH in dichloromethane at room temperature. [b] All products were characterized by ^1H and ^{13}C NMR, IR, and mass spectroscopy. [c] Yield refers to pure product after column chromatography. [d] Yield of major regioisomer (regioisomeric ratio = 3:1).

dx.doi.org/10.1021/jo201027u |*J. Org. Chem.* 2011, 76, 7677–7690

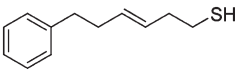
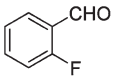
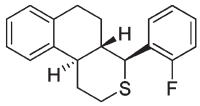
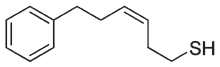
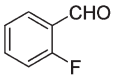
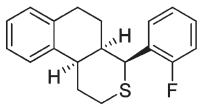
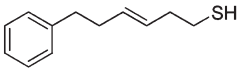
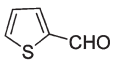
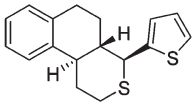
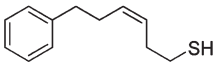
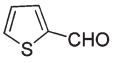
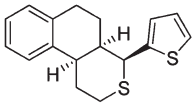
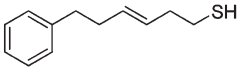
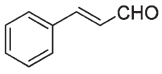
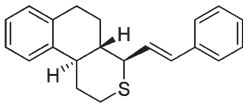
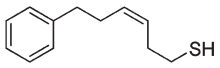
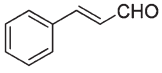
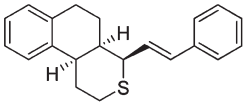
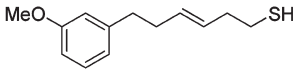
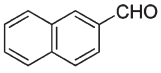
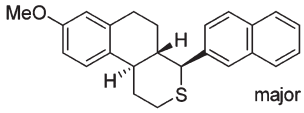
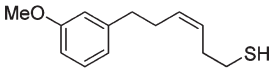
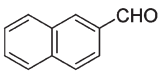
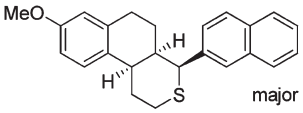
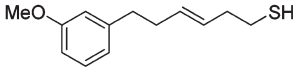
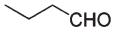
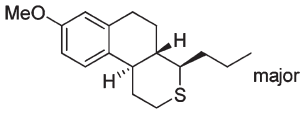
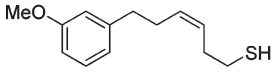
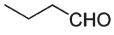
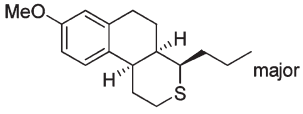
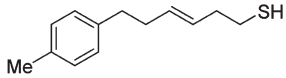
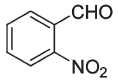
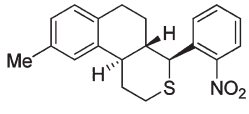
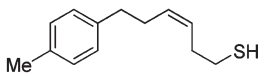
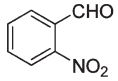
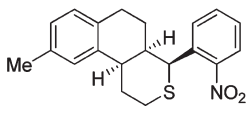
Table 3. $Sc(OTf)_3$-Catalyzed Synthesis of *N*-Tosyl-octahydrobenzo[*f*]isoquinolines[a]

Entry	Homoallylic amine (**4**)	Aldehyde (**2**)	Product (**5**)[b]	Time (h)	Yield (%)[c]
a				7	76
b				7	74
c				14	65
d				14	68
e				7	78
f				7	80
g		$(CH_2O)_n$		4	82
h		$(CH_2O)_n$		4	80
i				6	50[d]
j				6	48[d]
k				7	54[d]
l				7	52[d]
m				14	65
n				14	66
o				8	74
p				8	75

[a] Reaction was performed with 0.5 mmol of olefin, 0.6 mmol of aldehyde, and 10 mol % Sc(OTf)3 in 1,2-dichloroethane at 80 °C. [b,c,d] Same as in Table 2.

dx.doi.org/10.1021/jo201027u |*J. Org. Chem.* 2011, 76, 7677–7690

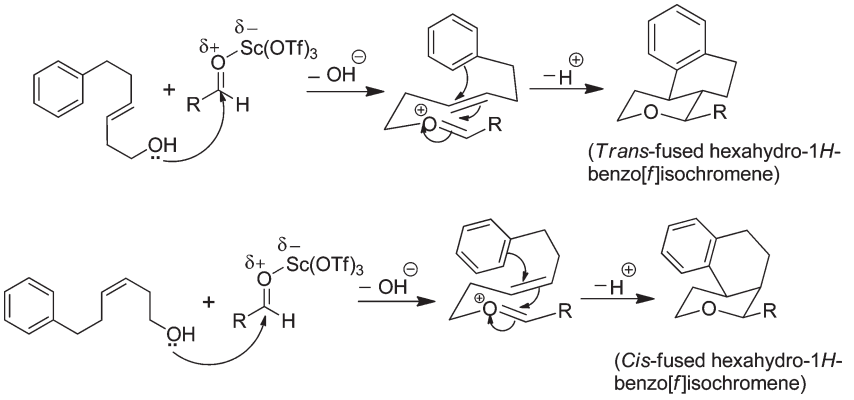
Table 4. Synthesis of Hexahydro-1*H*-benzo[*f*]isothiochromene Scaffolds via Intramolecular Thia-Prins/Friedel−Crafts Cyclization[a]

Entry	Homoallylic thiol (**6**)	Aldehyde (**2**)	Product (**7**)[b]	Time (h)	Yield (%)[c]
a				6	86
b				6	84
c				5	80
d				5	82
e				6	88
f				6	85
g			 major	6	59[d]
h			 major	6	60[d]
i			 major	8	59[d]
j			 major	8	58[d]
k				5	92
l				5	90

[a] Reaction was performed with 0.5 mmol of olefin, 0.6 mmol of aldehyde, and 10 mol % $Sc(OTf)_3$ in dichloromethane at room temperature. [b] All products were characterized by ^1H and ^{13}C NMR, IR, and mass spectroscopy. [c] Yield refers to pure product after column chromatography. [d] Yield of major regioisomer (regioisomeric ratio = 3:1).

dx.doi.org/10.1021/jo201027u |*J. Org. Chem.* 2011, 76, 7677–7690

Scheme 2. Plausible Reaction Pathway for Prins/Friedel−Crafts Cyclization



As expected, coupling of (*Z*)-6-phenylhex-3-ene-1-thiol with 2-fluorobenzaldehyde under similar conditions afforded the corresponding cis-fused hexahydro-1*H*-benzo[*f*]isothiochromene **7b** exclusively in 84% yield (Table 4, entry **b**). The scope of the reaction with other aldehydes like thiophene-2-carbaldehyde and cinnamaldehyde is illustrated in Table 4 (entries **c**−**f**). Similarly, other aryl-tethered homoallylic mercaptans such as (*E*)- and (*Z*)-6-(3-methoxyphenyl)hex-3-ene-1-thiol and (*E*)- and (*Z*)-6-*p*-tolylhex-3-ene-1-thiol also underwent smooth intramolecular thia-Prins/Friedel−Crafts cyclization with different aldehydes such as naphthalene-2-carbaldehyde, *n*-butyraldehyde, and 2-nitrobenzaldehyde to afford the respective trans/cis-fused hexahydro-1*H*-benzo[*f*]isothiochromenes **7** (entries **g**−**l**, Table 4). In the case of 6-(3-methoxyphenyl)hex-3-ene-1-thiol, the product was obtained as a 3:1 mixture (determined by ^{1}H NMR spectra of the crude product) of para/ortho-substituted products (entries **g**−**j**, Table 4). These two regioisomers could easily be separated by silica gel column chromatography.

Besides aldehydes, we found that epoxides are also equally effective in Prins- and aza-Prins/Friedel−Crafts cyclizations in the presence of an acid catalyst. It is well known that epoxides undergo a facile rearrangement to aldehydes or ketones in the presence of an acid catalyst.[23,41] In the present study, styrene oxide underwent smooth rearrangement when exposed to 10 mol % $Sc(OTf)_3$ to give the phenylacetaldehyde, which subsequently reacted with (*Z*)-4-methyl-*N*-(6-phenylhex-3-enyl)benzenesulfonamide (**4**) at ambient temperature to furnish the cis-fused *N*-tosyloctahydrobenzo[*f*]isoquinoline **8d** as a sole product in 70% yield (entry g, Table 5). However, the product **8d** was obtained in 78% yield when the reaction was performed with phenylacetaldehyde directly at 80 °C (entry h, Table 5). The above experiments proved that phenylacetaldehyde is a superior substrate to styrene oxide. Other homoallylic substrates such as (*E*)-4-methyl-*N*-(6-*p*-tolylhex-3-enyl)benzenesulfonamide, (*Z*)-6-phenylhex-3-en-1-ol, and (*E*)-6-(3-methoxyphenyl)hex-3-en-1-ol were treated with both styrene oxide and phenylacetaldehyde, and the results are summarized in Table 5.

Other Brønsted acids such as trifluoromethanesulfonic acid (TfOH) and camphorsulfonic acid (CSA) as well as Lewis acids such as $In(OTf)_3$, $La(OTf)_3$, and $InBr_3$ were screened for this conversion. Of these, the combination of $Sc(OTf)_3$ and TsOH (1:3) was found to give the best results in Prins/Friedel−Crafts cyclization (Table 1), whereas $Sc(OTf)_3$ gave excellent results in aza-Prins and thia-Prins/Friedel−Crafts cyclizations (Table 6). Next, we examined the effect of various solvents such as dichloromethane, 1,2-dichloroethane, toluene, and tetrahydrofuran. Among them, dichloromethane and 1,2-dichloroethane gave the best results.

Mechanistically, the reaction is expected to proceed via formation of oxocarbenium ion from hemiacetal which is formed in situ from an aldehyde and a homoallylic alcohol, likely after activation through Sc(III). This is followed by attack of an internal olefin, resulting in formation of carbocation, which is simultaneously trapped by an aryl group, leading to formation of hexahydro-1*H*-benzo[*f*]isochromene as depicted in Scheme 2.

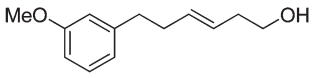
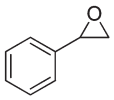
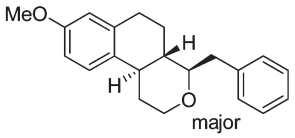
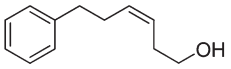
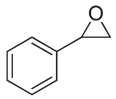
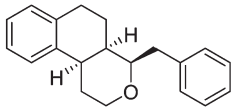
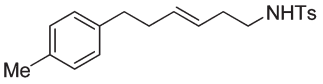
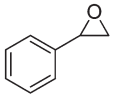
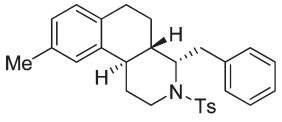
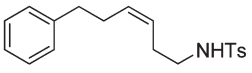
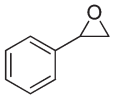
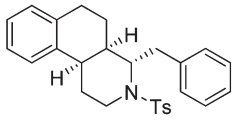
CONCLUSION

In summary, we demonstrated a versatile approach for stereoselective synthesis of a novel class of heterotricycles in a single-step operation. This is the first report on intramolecular aza- and thia-Prins/Friedel−Crafts cyclizations. Our approach is highly stereoselective to provide cis- and trans-fused tricyclic systems. This method provides direct access to the synthesis of biologically active octahydrobenzo[*f*]isoquinolines which are reported as potent σ receptors with regard to psychotomimetic effects. These new products are under biological screening, in particular for CNS activity. We found that the combination of $Sc(OTf)_3$ and TsOH (cocatalysis) works more effectively than either $Sc(OTf)_3$ or TsOH alone in terms of reaction time and yields.

EXPERIMENTAL SECTION

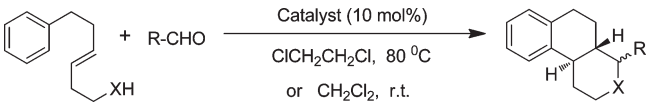
General. All solvents were dried according to standard literature procedures. Reactions were performed in oven-dried round-bottom flask, the flasks were fitted with rubber septa, and reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvent. Crude products were purified by column chromatography on silica gel of 60−120 or 100−200 mesh. Thin layer chromatography plates were visualized by exposure to ultraviolet light, exposure to iodine vapors, and/or exposure to methanolic acidic solution of *p*-anisaldehyde (anis) 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 FT-IR spectrometer. ^{1}H and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in Hertz (Hz). Mass spectra were recorded on a mass spectrometer by the electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Table 5. Comparative Study of Prins- and Aza-Prins/Friedel−Crafts Cyclizations with Phenyl Acetaldehyde and Styrene Oxide[a]

Entry	Substrate	Epoxide / aldehyde	Product (**8**)	Time (h)	Yield (%)[b]
a				24	37[c]
b	,,	$PhCH_2CHO$	,, **8a** (major)	11	60[c]
c				24	45
d	,,	$PhCH_2CHO$	,, **8b**	12	84
e				10	68
f	,,	$PhCH_2CHO$	,, **8c**	6[d]	80
g				10	70
h	,,	$PhCH_2CHO$	,, **8d**	6[d]	78

[a] Reaction was performed with 0.5 mmol of olefin, 0.75 mmol of styrene oxide, or 0.6 mmol of phenylacetaldehyde and 10 mol % Sc(OTf)3 at room temperature. [b] Isolated yield after column chromatography. [c] Reaction afforded a 3:1 ratio of para/ortho-substituted products; yield of major isomer. [d] Reaction was performed at 80 °C.

Table 6. Catalyst Screening for Intramolecular Aza-Prins- and Thia-Prins/Friedel−Crafts Cyclizations[a]



entry	X	R	catalyst	product	time (h)	yield (%)[b]
a	NTs	cyclohexyl	$Sc(OTf)_3$	**5a**	7	76
b			$In(OTf)_3$		7	70
c			$La(OTf)_3$		12	50
d			TsOH		12	55
e	S	*o*-F-phenyl	$InBr_3$	**7a**	12	58
f			$In(OTf)_3$		6	80
g			$Sc(OTf)_3$		6	86
h			$La(OTf)_3$		6	75

[a] Reaction was performed with 0.5 mmol of olefin, 0.6 mmol of aldehyde, and 10 mol % catalyst. [b] Yield refers to pure product after column chromatography.

Typical Procedure for Intramolecular Prins/Friedel−Crafts Cyclization. To a stirred solution of 6-arylhex-3-en-1-ol (**1**; 0.50 mmol) and aldehyde (0.60 mmol) in anhydrous dichloromethane (5 mL) was added $Sc(OTf)_3$ (10 mol %) and *p*-TsOH (30 mol %), and this was stirred at room temperature under a 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 (0.5 mL) and extracted with dichloromethane (2 × 5 mL). The organic phases were combined, washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using ethyl acetate/hexane gradients to afford pure product **3** (Table 2).

(4*S,4a*S**,10b*R**)-4-(4-Bromophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3a; Table 2; Entry a).** The reaction afforded a 90:10 mixture of trans:cis-fused products. The two isomers could be easily separated by silica gel column chromatography. Crystals for XRD were obtained by dissolving the compound in 3 mL of ethanol, followed by slow evaporation of solvent over 4 days. Yield, 158 mg, 92%; white solid, mp 98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47, 7.44 (AA′, 2H), 7.21, 7.18 (BB′, 2H), 7.20−7.16 (m, 1H), 7.15−7.03 (m, 2H), 7.02−6.96 (m, 1H), 4.28 (ddd, J = 11.3, 4.5, and 1.5 Hz, 1H), 4.02 (d, J = 9.8 Hz, 1H), 3.77 (dt, J = 12.1 and 2.3 Hz, 1H), 2.83−2.61 (m, 3H), 2.41−2.30 (m, 1H), 1.85−1.68 (m, 1H), 1.64−1.50 (m, 1H), 1.49−1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.7, 136.3, 131.4, 129.1, 128.9, 126.0, 125.8, 124.7, 121.6, 84.8, 68.5,

dx.doi.org/10.1021/jo201027u |*J. Org. Chem.* 2011, 76, 7677–7690

44.7, 41.4, 30.7, 28.6, 24.5; IR (KBr) ν_{max} 2925, 2846, 1485, 1069, 820, 746 cm^{-1}; ESI-MS m/z 343 $(M + H)^+$; HRMS (ESI) calcd for $C_{19}H_{20}BrO$, 343.0692 $(M + H)^+$; found, 343.0706.

(4*S,4a*R**,10b*R**)-4-(4-Bromophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3b; Table 2; Entry b).** Yield, 151 mg, 88%; white solid, mp 117−119 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45, 7.43 (AA′, 2H), 7.17, 7.15 (BB′, 2H), 7.10−6.95 (m, 4H), 4.62 (broad s, 1H), 4.22−4.15 (m, 1H), 3.76−3.67 (m, 1H), 3.10 (td, J = 11.7, 4.9 Hz, 1H), 2.81−2.71 (m, 1H), 2.66−2.55 (m, 1H), 2.11−2.01 (m, 1H), 1.95−1.83 (m, 1H), 1.82−1.72 (m, 1H), 1.71−1.64 (m, 1H), 1.31−1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 140.4, 135.9, 131.1, 129.0, 128.6, 127.3, 126.0, 125.7, 120.4, 81.0, 68.8, 39.5, 39.4, 31.3, 29.1, 16.6; IR (KBr) ν_{max} 2942, 2843, 1487, 1093, 744 cm^{-1}; ESI-MS m/z 343 $(M + H)^+$; HRMS (ESI) calcd for $C_{19}H_{20}BrO$, 343.0692 $(M + H)^+$; found, 343.0685.

(4*R,4a*S**,10b*R**)-4-Cyclohexyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3c; Table 2; Entry c).** Yield, 116 mg, 86%; white solid, mp 88−90 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−6.96 (m, 4H), 4.15 (ddd, J = 11.3, 4.5, and 1.5 Hz, 1H), 3.55 (dt, J = 12.1 and 2.3 Hz, 1H), 3.01−2.93 (m, 1H), 2.90−2.76 (m, 2H), 2.57−2.44 (m, 1H), 2.27−2.16 (m, 1H), 1.96−1.40 (m, 10H), 1.39−1.07 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 136.3, 128.7, 125.9, 125.7, 124.7, 85.9, 68.3, 41.4, 39.9, 38.7, 31.0, 30.8, 28.9, 27.1, 26.8, 26.7, 25.1, 24.0; IR (KBr) ν_{max} 2925, 2848, 1453, 1089, 741 cm^{-1}; ESI-MS m/z 271 $(M + H)^+$; HRMS (ESI) calcd for $C_{19}H_{27}O$, 271.2056 $(M + H)^+$; found, 271.2060.

(4*R,4a*R**,10b*R**)-4-Cyclohexyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3d; Table 2; Entry d).** Yield, 114 mg, 84%; white solid, mp 98−100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08−6.94 (m, 4H), 4.06−3.97 (m, 1H), 3.56−3.42 (m, 1H), 3.08−2.99 (m, 1H), 2.95−2.69 (m, 3H), 2.21−2.08 (m, 1H), 1.99−1.44 (m, 10H), 1.36−1.07 (m, 3H), 0.98−0.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 136.1, 129.0, 128.6, 125.8, 125.6, 84.7, 68.8, 39.6, 38.8, 34.6, 32.0, 30.7, 29.3, 27.9, 26.6, 26.0, 25.8, 16.8; IR (KBr) ν_{max} 2925, 2840, 1443, 1093, 745 cm^{-1}; ESI-MS m/z 271 $(M + H)^+$; HRMS (ESI) calcd for $C_{19}H_{27}O$, 271.2056 $(M + H)^+$; found, 271.2046.

(4*S,4a*S**,10b*R**)-4-(Thiophen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3e; Table 2; Entry e).** Yield, 116 mg, 86%; solid, mp 64−66 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.20 (m, 2H), 7.19−6.93 (m, 5H), 4.42 (d, J = 9.8 Hz, 1H), 4.36−4.26 (m, 1H), 3.82 (dt, J = 12.1 and 2.3 Hz, 1H), 2.86−2.65 (m, 3H), 2.40−2.30 (m, 1H), 1.90−1.56 (m, 3H), 1.49−1.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 138.7, 136.5, 128.9, 126.2, 126.0, 125.8, 125.6, 125.1, 124.7, 80.5, 68.6, 45.8, 41.5, 30.5, 28.7, 24.8; IR (KBr) ν_{max} 2919, 2844, 1091, 743, 702 cm^{-1}; MS (*APCI*) m/z 271 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{17}H_{19}OS$, 271.1157 $(M + H)^+$; found, 271.1150.

(4*S,4a*R**,10b*R**)-4-(Thiophen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3f; Table 2; Entry f).** Yield, 108 mg, 80%; semisolid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21−7.15 (m, 1H), 7.11−6.93 (m, 5H), 6.87−6.81 (m, 1H), 4.91 (broad s, 1H), 4.23−4.13 (m, 1H), 3.82−3.69 (m, 1H), 3.13−3.01 (m, 1H), 2.89−2.62 (m, 2H), 2.22−2.11 (m, 1H), 2.04−1.76 (m, 2H), 1.73−1.62 (m, 1H), 1.61−1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 140.6, 136.1, 129.1, 128.6, 126.6, 126.1, 125.7, 123.5, 122.0, 79.3, 69.1, 40.3, 39.1, 31.3, 29.2, 17.0; IR (neat) ν_{max} 2925, 2852, 1091, 702 cm^{-1}; MS (*APCI*) m/z 271 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{17}H_{19}OS$, 271.1157 $(M + H)^+$; found, 271.1164.

(4*R,4a*S**,10b*R**)-4-Isobutyl-8-methoxy-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3g; Table 2; Entry g).** The reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 82 mg, 60%; white solid, mp 60−62 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.5 Hz, 1H), 6.63 (dd, J = 8.5 and 2.6 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 4.12 (ddd, J = 11.3, 4.5, and 1.5 Hz, 1H), 3.74 (s, 3H), 3.55 (dt, J = 12.3 and 2.3 Hz, 1H), 3.18−3.07 (m, 1H), 2.91−2.72 (m, 2H), 2.51−2.38 (m, 1H), 2.25−2.13 (m, 1H), 1.98−1.80 (m, 2H), 1.65−1.48 (m, 1H), 1.47−1.12 (m, 4H), 0.98−0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 137.7, 131.9, 125.6, 113.6, 111.5, 79.6, 67.8, 55.2, 44.2, 42.3, 40.7, 30.9, 29.2, 24.6, 24.2, 24.0, 21.5; IR (KBr) ν_{max} 2950, 2834, 1609, 1502, 1462, 1238, 1094, 1037, 819 cm^{-1}; MS (*APCI*) m/z 275 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{18}H_{27}O_2$, 275.2006 $(M + H)^+$; found, 275.2005.

(4*R,4a*R**,10b*R**)-4-Isobutyl-8-methoxy-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3h; Table 2; Entry h).** The reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 79 mg, 58%; viscous liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 8.3 Hz, 1H), 6.61 (dd, J = 8.3 and 2.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 4.01−3.90 (m, 1H), 3.75 (s, 3H), 3.57−3.41 (m, 2H), 2.91−2.64 (m, 3H), 1.91−1.46 (m, 6H), 1.35−1.09 (m, 2H), 0.99−0.81 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 137.3, 133.5, 129.5, 113.2, 112.2, 78.2, 68.6, 55.2, 42.0, 38.8, 37.9, 31.9, 29.7, 24.7, 23.2, 22.6, 16.8; IR (KBr) ν_{max} 2949, 2865, 1610, 1500, 1461, 1266, 1090, 1040, 820 cm^{-1}; MS (*APCI*) m/z 275 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{18}H_{27}O_2$, 275.2006 $(M + H)^+$; found, 275.2011.

Compound 3i (Table 2; Entry i). Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 81 mg, 56%; solid, mp 118−120 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.6 Hz, 1H), 6.63 (dd, J = 8.6 and 2.6 Hz, 1H), 6.52 (d, J = 2.6 Hz, 1H), 3.87−3.63 (m, 5H), 2.92−2.65 (m, 3H), 2.25−2.07 (m, 2H), 1.94−1.61 (m, 4H), 1.60−1.30 (m, 8H), 1.20−1.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 137.7, 132.2, 126.6, 113.5, 111.8, 74.8, 60.2, 55.2, 48.6, 36.6, 34.9, 31.9, 30.6, 26.3, 24.7, 24.3, 21.3, 20.5; IR (KBr) ν_{max} 2933, 2853, 1502, 1234, 1092, 1035, 843 cm^{-1}; MS (*APCI*) m/z 287 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{19}H_{27}O_2$, 287.2006 $(M + H)^+$; found, 287.1996.

Compound 3j (Table 2; Entry j). Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 80 mg, 56%; semisolid; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 8.3 Hz, 1H), 6.61 (dd, J = 8.3 and 2.4 Hz, 1H), 6.52 (broad s, 1H), 3.82−3.59 (m, 5H), 3.17−3.04 (m, 1H), 2.91−2.63 (m, 2H), 2.39−2.20 (m, 1H), 1.95−1.18 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 137.1, 133.6, 129.7, 113.0, 112.2, 73.5, 60.2, 55.1, 39.6, 35.8, 33.3, 31.6, 31.0, 29.8, 26.1, 21.7, 21.6, 17.1; IR (KBr) ν_{max} 2929, 2854, 1501, 1267, 1086, 1042, 819 cm^{-1}; MS (*APCI*) m/z 287 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{19}H_{27}O_2$, 287.2006 $(M + H)^+$; found, 287.2015.

(4*S,4a*S**,10b*R**)-9-Methyl-4-(4-nitrophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3k; Table 2; Entry k).** Yield, 145 mg, 90%; white solid, mp 109−111 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21, 8.18 (AA′, 2H), 7.50, 7.47 (BB′, 2H), 7.01 (m, 1H), 6.98−6.84 (m, 2H), 4.43−4.26 (m, 1H), 4.17 (d, J = 9.8 Hz, 1H), 3.88−3.72 (m, 1H), 2.85−2.53 (m, 3H), 2.50−2.25 (m, 4H), 1.90−1.69 (m, 1H), 1.66−1.22 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 147.5, 138.1, 135.3, 132.9, 128.9, 128.3, 126.9, 125.4, 123.5, 84.4, 68.6, 45.1, 41.3, 30.6, 28.2, 24.5, 21.2; IR (KBr) ν_{max} 2919, 2842, 1518, 1346, 1083, 847 cm^{-1}; ESI-MS m/z 324 $(M + H)^+$; HRMS (ESI) calcd for $C_{20}H_{22}NO_3$, 324.1594 $(M + H)^+$; found, 324.1602.

(4*S,4a*R**,10b*R**)-9-Methyl-4-(4-nitrophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3l; Table 2; Entry l).** Yield, 137 mg, 85%; white solid, mp 156−158 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22, 8.19 (AA′, 2H), 7.48, 7.45 (BB′, 2H), 6.94−6.82 (m, 3H), 4.75 (d, J = 1.9 Hz, 1H), 4.28−4.18 (m, 1H), 3.80−3.67 (m, 1H), 3.14−3.00 (m, 1H), 2.80−2.65 (m, 1H), 2.63−2.45 (m, 1H), 2.30 (s, 3H), 2.19−2.06 (m, 1H), 1.99−1.64 (m, 3H), 1.17−1.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 146.9, 140.1, 135.3, 132.5, 129.1, 128.9,

127.1, 126.3, 123.3, 80.9, 68.8, 39.6, 39.4, 31.2, 28.6, 20.9, 16.9; IR (KBr) ν_{max} 2926, 2850, 1516, 1343, 1090, 710 cm^{-1}; ESI-MS m/z 324 $(M + H)^+$; HRMS (ESI) calcd for $C_{20}H_{22}NO_3$, 324.1594 $(M + H)^+$; found, 324.1588.

(4*R,4a*S**,10b*R*,**E*)-9-Methyl-4-styryl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3m; Table 2; Entry m).** Yield, 128 mg, 84%; solid, mp 100−102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.33 (m, 2H), 7.32−7.15 (m, 3H), 6.99 (s, 1H), 6.96−6.85 (m, 2H), 6.61 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 15.9 and 7.6 Hz, 1H), 4.28−4.18 (m, 1H), 3.79−3.64 (m, 2H), 2.85−2.73 (m, 2H), 2.65−2.51 (m, 1H), 2.35−2.23 (m, 4H), 1.98−1.86 (m, 1H), 1.76−1.58 (m, 1H), 1.52−1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 136.7, 135.1, 133.3, 133.1, 128.9, 128.6, 128.5, 127.7, 126.8, 126.5, 125.4, 83.4, 68.0, 43.7, 41.1, 30.6, 28.4, 24.9, 21.2; IR (KBr) ν_{max} 2921, 2838, 1494, 1442, 1088, 967, 750, 693 cm^{-1}; MS (*APCI*) m/z 305 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{22}H_{25}O$, 305.1900 $(M + H)^+$; found, 305.1905.

(4*R,4a*R**,10b*R*,**E*)-9-Methyl-4-styryl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (3n; Table 2; Entry n).** Yield, 131 mg, 86%; white solid, mp 112−114 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 2H), 7.31−7.23 (m, 2H), 7.21−7.14 (m, 1H), 6.95−6.80 (m, 3H), 6.60 (dd, J = 15.9 and 1.5 Hz, 1H), 6.19 (dd, J = 15.9 and 5.2 Hz, 1H), 4.28−4.22 (m, 1H), 4.16−4.07 (m, 1H), 3.71−3.59 (m, 1H), 2.98−2.61 (m, 3H), 2.29 (s, 3H), 2.00−1.73 (m, 4H), 1.69−1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 137.0, 135.1, 132.9, 129.7, 129.2, 129.1, 128.9, 128.5, 127.3, 126.9, 126.3, 80.2, 68.5, 39.1, 38.9, 31.5, 28.9, 21.0, 17.5; IR (KBr) ν_{max} 2925, 2848, 1493, 1441, 1142, 1089, 974, 813, 751, 694 cm^{-1}; MS (*APCI*) m/z 305 $(M + H)^+$; HRMS (*APCI*) calcd for $C_{22}H_{25}O$, 305.1900 $(M + H)^+$; found, 305.1917.

Typical Procedure for Intramolecular Aza-Prins/Friedel−Crafts Cyclization. To a stirred solution of 4-methyl-*N*-(6-arylhex-3-enyl)benzenesulfonamide (**4**; 0.50 mmol) and aldehyde (0.60 mmol) in anhydrous 1,2-dichloroethane (4 mL) was added $Sc(OTf)_3$ (10 mol %), and this 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 over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (60−120 mesh) using ethyl acetate/hexane gradients to afford pure product **5** (Table 3).

(4*S,4a*S**,10b*R**)-4-Cyclohexyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5a; Table 3; Entry a).** Yield, 161 mg, 76%; white solid, mp 124−126 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.73, 7.69 (AA′, 2H), 7.23, 7.19 (BB′, 2H), 7.18−6.95 (m, 4H), 4.06−3.84 (m, 2H), 3.30−3.09 (m, 1H), 3.01−2.48 (m, 3H), 2.36 (s, 3H), 2.18−2.02 (m, 1H), 2.01−1.43 (m, 10H), 1.36−0.92 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 139.1, 138.5, 136.4, 129.6, 129.1, 126.6, 126.4, 125.9, 125.8, 62.2, 44.1, 43.0, 36.5, 35.9, 33.4, 31.1, 30.8, 30.2, 27.7, 26.7, 26.5, 26.1, 21.4; IR (KBr) ν_{max} 2925, 2853, 1334, 1157, 752 cm^{-1}; ESI-MS m/z 424 $(M + H)^+$; HRMS (ESI) calcd for $C_{26}H_{34}NO_2S$, 424.2310 $(M + H)^+$; found, 424.2291.

(4*S,4a*R**,10b*R**)-4-Cyclohexyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5b; Table 3; Entry b).** Yield, 157 mg, 74%; white solid, mp 162−164 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70, 7.67 (AA′, 2H), 7.23, 7.20 (BB′, 2H), 7.08−6.89 (m, 4H), 3.73−3.56 (m, 2H), 3.08−2.65 (m, 4H), 2.41 (s, 3H), 2.17−2.04 (m, 1H), 1.92−1.41 (m, 10H), 1.32−0.92 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4, 140.3, 139.0, 135.8, 129.2, 129.0, 128.8, 126.9, 126.0, 125.6, 64.2, 40.9, 36.1, 34.3, 33.4, 31.4, 29.9, 29.6, 29.5, 26.3, 26.2, 24.1, 21.4; IR (KBr) ν_{max} 2928, 2847, 1321, 1151, 1089, 809, 739 cm^{-1}; ESI-MS m/z 424 $(M + H)^+$; HRMS (ESI) calcd for $C_{26}H_{34}NO_2S$, 424.2310 $(M + H)^+$; found, 424.2319.

(4*R,4a*S**,10b*R**)-4-(4-Chlorophenyl)-3-tosyl-1,2,3,4,4a,5,6,-10b-octahydrobenzo[*f*]isoquinoline (5c; Table 3; Entry c).** Yield, 147 mg, 65%; solid, mp 110−112 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−6.92 (m, 12H), 5.17 (d, J = 5.9 Hz, 1H), 4.13−4.06 (m, 1H), 3.41 (dt, J = 12.8 and 3.0 Hz, 1H), 2.96−2.80 (m, 2H), 2.79−2.64 (m, 1H), 2.59−2.51 (m, 1H), 2.35 (s, 3H), 2.13−2.04 (m, 1H), 1.74−1.62 (m, 2H), 1.07−0.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 137.7, 136.6, 136.3, 136.2, 133.4, 130.4, 129.2, 129.0, 128.0, 126.8, 126.1, 125.9, 60.8, 43.1, 42.8, 34.1, 30.9, 29.5, 26.6, 21.3; IR (KBr) ν_{max} 2924, 1337, 1158, 1094 cm^{-1}; ESI-MS m/z 452 $(M + H)^+$; HRMS (ESI) calcd for $C_{26}H_{27}NO_2SCl$, 452.1451 $(M + H)^+$; found, 452.1459.

(4*R,4a*R**,10b*R**)-4-(4-Chlorophenyl)-3-tosyl-1,2,3,4,4a,5,6,-10b-octahydrobenzo[*f*]isoquinoline (5d; Table 3; Entry d).** Yield, 153 mg, 68%; white solid, mp 122−124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71, 7.69 (AA′, 2H), 7.29−7.19 (m, 6H), 7.08−6.96 (m, 3H), 6.89−6.83 (m, 1H), 5.22 (broad s, 1H), 3.84−3.73 (m, 1H), 3.07 (dt, J = 13.6 and 3.0 Hz, 1H), 3.01−2.79 (m, 2H), 2.74 (td, J = 12.1 and 4.5 Hz, 1H), 2.64−2.53 (m, 1H), 2.44 (s, 3H), 1.98−1.58 (m, 3H), 1.57−1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 139.9, 138.4, 137.4, 135.3, 132.8, 129.6, 129.1, 128.8, 128.7, 128.5, 126.9, 126.3, 125.8, 60.7, 41.4, 36.6, 34.1, 30.0, 29.3, 23.7, 21.5; IR (KBr) ν_{max} 2925, 1491, 1342, 1156, 1092, 710 cm^{-1}; ESI-MS m/z 474 $(M+Na)^+$; HRMS (ESI) calcd for $C_{26}H_{27}NO_2SCl$, 452.1451 $(M + H)^+$; found, 452.1433.

(4*S,4a*S**,10b*R**)-4-Isobutyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5e; Table 3; Entry e).** Yield, 155 mg, 78%; solid, mp 125−127 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72, 7.70 (AA′, 2H), 7.23, 7.21 (BB′, 2H), 7.13−6.97 (m, 4H), 4.22−4.15 (m, 1H), 3.92−3.84 (m, 1H), 3.27−3.17 (m, 1H), 2.84−2.69 (m, 3H), 2.38 (s, 3H), 2.17−2.08 (m, 1H), 1.80−1.40 (m, 5H), 1.25−1.04 (m, 2H), 1.02−0.82 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 138.8, 138.7, 136.5, 129.6, 129.1, 126.9, 125.8, 55.8, 42.0, 40.8, 35.4, 34.2, 30.1, 24.2, 24.1, 21.5, 21.4; IR (KBr) ν_{max} 2925, 2864, 1336, 1156, 1092, 744 cm^{-1}; ESI-MS m/z 398 $(M + H)^+$; HRMS (ESI) calcd for $C_{24}H_{32}NO_2S$, 398.2153 $(M + H)^+$; found, 398.2145.

(4*S,4a*R**,10b*R**)-4-Isobutyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5f; Table 3; Entry f).** Crystals for XRD were obtained by dissolving compound in 4 mL of ethanol, followed by slow evaporation of solvent over 4 days. Yield, 159 mg, 80%; white solid, mp 116−118 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70, 7.68 (AA′, 2H), 7.25, 7.23 (BB′, 2H), 7.09−6.96 (m, 4H), 4.03 (dt, J = 6.8 and 1.0 Hz, 1H), 3.72−3.64 (m, 1H), 3.06 (dt, J = 12.7 and 3.0 Hz, 1H), 2.95 (td, J = 11.7 and 4.9 Hz, 1H), 2.88−2.75 (m, 2H), 2.41 (s, 3H), 1.98−1.81 (m, 2H), 1.71−1.48 (m, 5H), 1.44−1.33 (m, 1H), 0.96−0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 140.2, 138.6, 135.8, 129.4, 129.1, 128.9, 127.0, 126.1, 125.6, 56.8, 40.4, 39.0, 36.3, 33.9, 30.4, 29.3, 25.2, 23.7, 23.0, 22.3, 21.4; IR (KBr) ν_{max} 2927, 2869, 1329, 1156, 1093, 744 cm^{-1}; ESI-MS m/z 420 $(M+Na)^+$; HRMS (ESI) calcd for $C_{24}H_{32}NO_2S$, 398.2153 $(M + H)^+$; found, 398.2140.

(4a*S,10b*R**)-3-Tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]isoquinoline (5g; Table 3, Entry g).** Yield, 140 mg, 82%; solid, mp 142−144 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66, 7.64 (AA′, 2H), 7.32, 7.30 (BB′, 2H), 7.14−6.99 (m, 4H), 4.03−3.96 (m, 1H), 3.86−3.80 (m, 1H), 2.97−2.78 (m, 2H), 2.45 (s, 3H), 2.42−2.30 (m, 2H), 2.20−2.12 (m, 1H), 2.02 (t, J = 11.0 Hz, 1H), 1.87−1.56 (m, 3H), 1.45−1.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.8, 136.3, 133.2, 129.6, 129.1, 127.6, 126.1, 125.8, 124.9, 52.0, 46.8, 41.5, 38.4, 29.4, 28.9, 26.7, 21.5; IR (KBr) ν_{max} 2921, 2836, 1339, 1164, 1092, 925, 812, 754, 733, 656 cm^{-1}; ESI-MS m/z 342 $(M + H)^+$; HRMS (ESI) calcd for $C_{20}H_{24}NO_2S$, 342.1528 $(M + H)^+$; found, 342.1519.

(4a*R,10b*R**)-3-Tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]isoquinoline (5h; Table 3, Entry h).** Yield, 136 mg, 80%; solid, mp 167−169 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63, 7.61 (AA′, 2H), 7.31, 7.29 (BB′, 2H), 7.08−6.99 (m, 3H), 6.94−6.90 (m, 1H),

3.75−3.70 (m, 1H), 3.69−3.64 (m, 1H), 2.94−2.79 (m, 2H), 2.63−2.52 (m, 2H), 2.45 (s, 3H), 2.35 (dt, J = 12.0 and 3.0 Hz, 1H), 2.25−2.14 (m, 1H), 2.07−1.99 (m, 1H), 1.97−1.87 (m, 1H), 1.81−1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 139.7, 135.8, 133.1, 129.5, 129.2, 128.5, 127.7, 126.1, 125.7, 51.4, 46.6, 37.8, 33.5, 30.7, 29.1, 22.4, 21.5; IR (KBr) ν_{max} 2926, 2856, 1336, 1159, 1093, 954, 719, 668 cm^{-1}; ESI-MS m/z 342 (M + H)$^+$; HRMS (ESI) calcd for $C_{20}H_{24}NO_2S$, 342.1528 (M + H)$^+$; found, 342.1540.

(4*S,4a*S**,10b*R**)-4-Ethyl-8-methoxy-3-tosyl-1,2,3,4,4a,5,6,-10b-octahydrobenzo[*f*]isoquinoline (5i; Table 3; Entry i).** Reaction afforded a 2:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 100 mg, 50%; solid, mp 119−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74, 7.71 (AA′, 2H), 7.24, 7.21 (BB′, 2H), 7.06 (d, J = 8.7 Hz, 1H), 6.68 (dd, J = 8.7 and 2.6 Hz, 1H) 6.57 (d, J = 2.6 Hz, 1H), 4.08−3.98 (m, 1H), 3.97−3.85 (m, 1H), 3.75 (s, 3H), 3.23−3.09 (m, 1H), 2.81−2.58 (m, 3H), 2.38 (s, 3H), 2.17−2.05 (m, 1H), 1.74−1.38 (m, 5H), 1.19−1.02 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 142.8, 138.9, 137.7, 130.8, 129.6, 126.8, 113.6, 111.9, 59.3, 55.1, 42.3, 40.6, 34.8, 30.3, 26.6, 21.5, 17.9, 11.1; IR (KBr) ν_{max} 2922, 2853, 1490, 1230, 752 cm^{-1}; ESI-MS m/z 400 (M + H)$^+$; HRMS (ESI) calcd for $C_{23}H_{30}NO_3S$, 400.1946 (M + H)$^+$; found, 400.1953.

(4*S,4a*R**,10b*R**)-4-Ethyl-8-methoxy-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5j; Table 3; Entry j).** Reaction afforded a 2:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 96 mg, 48%; white solid, mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69, 7.66 (AA′, 2H), 7.25, 7.22 (BB′, 2H), 6.87 (d, J = 8.3 Hz, 1H), 6.59 (dd, J = 8.3 and 2.3 Hz, 1H) 6.50 (d, J = 2.3 Hz, 1H), 3.86 (dt, J = 7.6 and 1.0 Hz, 1H), 3.72 (s, 3H), 3.70−3.59 (m, 1H), 3.09−2.94 (m, 1H), 2.92−2.66 (m, 3H), 2.41 (s, 3H), 1.94−1.76 (m, 2H), 1.75−1.46 (m, 5H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 142.6, 138.7, 137.0, 132.5, 129.7, 129.4, 126.9, 113.3, 112.2, 60.4, 55.1, 40.3, 35.9, 33.2, 30.5, 29.7, 23.7, 23.0, 21.4, 11.4; IR (KBr) ν_{max} 2929, 2873, 1608, 1499, 1328, 1156, 1090, 755, 666 cm^{-1}; ESI-MS m/z 400 (M + H)$^+$; HRMS (ESI) calcd for $C_{23}H_{30}NO_3S$, 400.1946 (M + H)$^+$; found, 400.1950.

(4*S,4a*S**,10b*R**)-8-Methoxy-4-phenethyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5k; Table 3; Entry k).** Reaction afforded a 2:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 128 mg, 54%; solid, mp 112−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72, 7.70 (AA′, 2H), 7.26−7.18 (m, 4H), 7.17−7.08 (m, 3H), 6.95 (d, J = 8.9 Hz, 1H), 6.58 (dd, J = 8.9 and 3.0 Hz, 1H), 6.46 (d, J = 3.0 Hz, 1H), 4.17−4.09 (m, 1H), 3.99−3.91 (m, 1H), 3.70 (s, 3H), 3.26−3.16 (m, 1H), 2.76−2.52 (m, 5H), 2.38 (s, 3H), 2.13−2.04 (m, 1H), 1.93−1.81 (m, 1H), 1.74−1.58 (m, 2H), 1.54−1.39 (m, 2H), 1.16−1.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 142.9, 142.1, 138.8, 137.6, 130.6, 129.7, 128.3, 126.8, 125.8, 113.6, 111.9, 57.7, 55.1, 42.1, 40.9, 34.8, 32.9, 30.3, 30.2, 27.5, 26.5, 21.4; IR (KBr) ν_{max} 2925, 2861, 1499, 1332, 1155, 754, 707 cm^{-1}; ESI-MS m/z 476 (M + H)$^+$; HRMS (ESI) calcd for $C_{29}H_{34}NO_3S$, 476.2259 (M + H)$^+$; found, 476.2269.

(4*S,4a*R**,10b*R**)-8-Methoxy-4-phenethyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5l; Table 3; Entry l).** Reaction afforded a 2:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 124 mg, 52%; white solid, mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67, 7.65 (AA′, 2H), 7.28−7.18 (m, 4H), 7.17−7.10 (m, 1H), 7.09−7.03 (m, 2H), 6.86 (d, J = 8.3 Hz, 1H), 6.60 (dd, J = 8.3 and 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 1H), 4.00 (dt, J = 7.6 and 0.9 Hz, 1H), 3.79−3.65 (m, 4H), 3.13−2.97 (m, 1H), 2.96−2.84 (m, 1H), 2.83−2.69 (m, 2H), 2.68−2.48 (m, 2H), 2.42 (s, 3H), 1.96−1.74 (m, 4H), 1.68−1.46 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 142.8, 141.5, 138.6, 137.0, 132.4, 129.8, 129.5, 128.4, 128.3, 126.9, 125.9, 113.3, 112.3, 58.6, 55.2, 40.4, 36.5, 33.4, 33.3, 32.3, 30.6, 29.7, 23.6, 21.5; IR (KBr) ν_{max} 2940, 1607, 1501, 1320, 1152, 1098, 963, 921, 711, 670 cm^{-1}; ESI-MS m/z 476 (M + H)$^+$; HRMS (ESI) calcd for $C_{29}H_{34}NO_3S$, 476.2259 (M + H)$^+$; found, 476.2236.

(4*R,4a*S**,10b*R**)-4-(4-Bromophenyl)-9-methyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5m; Table 3; Entry m).** Yield, 166 mg, 65%; white solid, mp 190−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.16 (m, 4H), 7.10−6.95 (m, 5H), 6.85 (s, 2H), 5.13 (d, J = 5.7 Hz, 1H), 4.17−4.04 (m, 1H), 3.39 (dt, J = 12.8 and 3.2 Hz, 1H), 2.92−2.72 (m, 2H), 2.71−2.48 (m, 2H), 2.36 (s, 3H), 2.27 (s, 3H), 2.13−1.98 (m, 1H), 1.75−1.56 (m, 2H), 1.06−0.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 137.4, 137.1, 136.3, 135.4, 133.1, 131.0, 130.7, 129.1, 129.0, 127.0, 126.8, 126.6, 121.5, 61.0, 43.2, 42.8, 34.0, 31.0, 29.2, 26.7, 21.4, 21.1; IR (KBr) ν_{max} 2921, 2858, 1334, 1154, 1106, 1001, 809, 583 cm^{-1}; ESI-MS m/z 510 (M + H)$^+$; HRMS (ESI) calcd for $C_{27}H_{29}NO_2SBr$, 510.1102 (M + H)$^+$; found, 510.1084.

(4*R,4a*R**,10b*R**)-4-(4-Bromophenyl)-9-methyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5n; Table 3; Entry n).** Yield, 168 mg, 66%; white solid, mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71, 7.69 (AA′, 2H), 7.41, 7.38 (A_1A_1', 2H), 7.26, 7.24 (BB′, 2H), 7.17, 7.14 (B_1B_1', 2H), 6.95−6.80 (m, 2H), 6.67 (s, 1H), 5.19 (broad s, 1H), 3.86−3.72 (m, 1H), 3.13−2.97 (m, 1H), 2.96−2.62 (m, 3H), 2.61−2.50 (m, 1H), 2.44 (s, 3H), 2.21 (s, 3H), 1.96−1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 139.7, 138.3, 138.0, 135.3, 132.1, 131.7, 129.5, 129.3, 128.9, 128.8, 127.2, 126.9, 120.9, 60.8, 41.5, 36.6, 34.1, 29.9, 28.9, 23.8, 21.5, 20.8; IR (KBr) ν_{max} 2916, 2863, 1334, 1156, 1092, 947, 812, 546 cm^{-1}; ESI-MS m/z 510 (M + H)$^+$; HRMS (ESI) calcd for $C_{27}H_{29}NO_2SBr$, 510.1102 (M + H)$^+$; found, 510.1114.

(4*S,4a*S**,10b*R**,*E*)-9-Methyl-4-styryl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5o; Table 3; Entry o).** Yield, 169 mg, 74%; white solid, mp 190−192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62, 7.60 (AA′, 2H), 7.22, 7.20 (BB′, 2H), 7.19−7.13 (m, 1H), 7.11−7.03 (m, 4H), 6.94 (s, 1H), 6.90−6.83 (m, 2H), 6.46 (d, J = 15.8 Hz, 1H), 5.90 (dd, J = 15.8 and 7.9 Hz, 1H), 4.74−4.69 (m, 1H), 4.02−3.95 (m, 1H), 3.15 (dt, J = 12.8 and 3.0 Hz, 1H), 2.89−2.78 (m, 1H), 2.77−2.69 (m, 1H), 2.66−2.57 (m, 1H), 2.44−2.36 (m, 1H), 2.27 (s, 6H), 1.95−1.86 (m, 1H), 1.79−1.72 (m, 1H), 1.64−1.52 (m, 1H), 1.51−1.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 137.8, 136.9, 136.3, 135.3, 134.8, 133.3, 129.3, 129.1, 128.3, 127.7, 127.5, 126.9, 126.3, 120.8, 60.5, 43.3, 42.1, 36.1, 31.0, 29.2, 26.7, 21.3, 21.1; IR (KBr) ν_{max} 2923, 1337, 1155, 660 cm^{-1}; ESI-MS m/z 458 (M + H)$^+$; HRMS (ESI) calcd for $C_{29}H_{32}NO_2S$, 458.2153 (M + H)$^+$; found, 458.2144.

(4*S,4a*R**,10b*R**,*E*)-9-Methyl-4-styryl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (5p; Table 3; Entry p).** Yield, 172 mg, 75%; white solid, mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70, 7.68 (AA′, 2H), 7.33−7.16 (m, 5H), 7.11 (m, 2H), 7.04−6.89 (m, 2H), 6.82 (s, 1H), 6.39 (d, J = 15.9 Hz, 1H), 6.04 (dd, J = 15.9 and 6.0 Hz, 1H), 4.72 (dd, J = 6.0 and 1.0 Hz, 1H), 3.89−3.77 (m, 1H), 3.12 (dt, J = 12.8 and 3.0 Hz, 1H), 2.98−2.74 (m, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.19−2.01 (m, 2H), 1.93−1.65 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 139.9, 137.6, 136.5, 135.2, 132.5, 129.4, 129.3, 129.0, 128.4, 127.6, 127.4, 127.2, 126.2, 126.0, 60.4, 41.4, 39.1, 34.4, 30.7, 28.8, 23.3, 21.4, 20.9; IR (KBr) ν_{max} 2929, 2858, 1333, 1154, 1094, 974, 746, 677 cm^{-1}; ESI-MS m/z 458 (M + H)$^+$; HRMS (ESI) calcd for $C_{29}H_{32}NO_2S$, 458.2153 (M + H)$^+$; found, 458.2147.

Typical Procedure for Intramolecular Thia-Prins/Friedel−Crafts Cyclization. To a stirred solution of 6-arylhex-3-ene-1-thiol (**6**; 0.50 mmol) and aldehyde (0.60 mmol) in anhydrous dichloromethane (5 mL) was added $Sc(OTf)_3$ (10 mol %), and this was stirred at room temperature under a nitrogen atmosphere for the specified time

(Table 4). 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 over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using ethyl acetate/hexane gradients to afford pure product 7 (Table 4).

(4*S,4a*S**,10b*R**)-4-(2-Fluorophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7a; Table 4; Entry a).** Crystals for XRD were obtained by dissolving compound in 4 mL of ethanol, followed by slow evaporation of solvent over 4 days. Yield, 128 mg, 86%; solid, mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dt, J = 7.6 and 1.5 Hz, 1H), 7.31−7.16 (m, 2H), 7.15−6.95 (m, 5H), 4.16 (d, J = 10.6 Hz, 1H), 3.20−3.05 (m, 1H), 2.92−2.78 (m, 2H), 2.77−2.56 (m, 3H), 2.10−1.94 (m, 1H), 1.91−1.73 (m, 1H), 1.68−1.55 (m, 1H), 1.42−1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (d, J = 245.9 Hz), 138.9, 137.0, 130.0 (d, J = 26.9 Hz), 129.0, 128.7 (d, J = 8.8 Hz), 125.9, 125.6, 124.6 (d, J = 3.3. Hz), 115.4 (d, J = 23.1 Hz), 46.5, 44.0, 33.1, 30.7, 29.6, 26.6; IR (KBr) ν_{max} 2920, 2852, 1484, 1223, 1087, 751 cm^{-1}; MS (*APCI*) m/z 299 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{19}H_{20}FS$, 299.1270 (M + H)$^+$; found, 299.1275.

(4*S,4a*R**,10b*R**)-4-(2-Fluorophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7b; Table 4; Entry b).** Yield, 125 mg, 84%; solid, mp 94−96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.32 (m, 1H), 7.30−6.99 (m, 7H), 4.72 (d, J = 2.0 Hz, 1H), 3.05 (dt, J = 13.1 and 3.0 Hz, 1H), 2.99−2.92 (m, 1H), 2.89−2.76 (m, 2H), 2.70−2.59 (m, 1H), 2.40−2.31 (m, 1H), 2.31−2.21 (m, 1H), 2.04−1.97 (m, 1H), 1.96−1.85 (m, 1H), 1.48−1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (d, J = 245.9 Hz), 141.4, 135.9, 130.5 (d, J = 18.1 Hz), 129.9 (d, J = 3.8 Hz), 129.0, 128.8, 126.0, 125.6, 123.7 (d, J = 3.3. Hz), 115.3 (d, J = 22.0 Hz), 44.9, 42.5, 38.9, 31.4, 30.5, 29.0,16.9; IR (KBr) ν_{max} 2923, 2855, 1489, 1453, 1228, 759 cm^{-1}; MS (*APCI*) m/z 299 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{19}H_{20}FS$, 299.1270 (M + H)$^+$; found, 299.1259.

(4*S,4a*S**,10b*R**)-4-(Thiophen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7c; Table 4; Entry c).** Yield, 115 mg, 80%; solid, mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.14−7.03 (m, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 3.4 Hz, 1H), 6.93−6.88 (m, 1H), 4.06 (d, J = 10.2 Hz, 1H), 3.12−3.03 (m, 1H), 2.88−2.65 (m, 4H), 2.61−2.52 (m, 1H), 2.00−1.90 (m, 1H), 1.88−1.76 (m, 2H), 1.33−1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 138.7, 137.0, 128.9, 126.4, 125.8, 125.7, 125.6, 124.5, 49.0, 47.3, 44.0, 32.9, 30.8, 29.7, 26.8; IR (KBr) ν_{max} 2905, 2852, 743, 695 cm^{-1}; MS (*APCI*) m/z 287 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{17}H_{19}S_2$, 287.0928 (M + H)$^+$; found, 287.0917.

(4*S,4a*R**,10b*R**)-4-(Thiophen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7d; Table 4; Entry d).** Yield, 117 mg, 82%; solid, mp 105−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 4.6 Hz, 1H), 7.09−6.96 (m, 4H), 6.95−6.88 (m, 2H), 4.52 (d, J = 2.7 Hz, 1H), 2.98 (dt, J = 12.8 and 3.6 Hz, 1H), 2.92−2.82 (m, 2H), 2.81−2.68 (m, 2H), 2.45−2.36 (m, 1H), 2.29−2.16 (m, 1H), 2.01−1.85 (m, 2H), 171−1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 141.3, 136.0, 129.0, 128.7, 126.6, 126.1, 125.6, 124.5, 123.8, 47.2, 42.4, 41.3, 31.4, 30.7, 29.0, 17.3; IR (KBr) ν_{max} 2925, 2855, 1224, 1034, 698 cm^{-1}; MS (*APCI*) m/z 287 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{17}H_{19}S_2$, 287.0928 (M + H)$^+$; found, 287.0929.

(4*R,4a*S**,10b*R**,*E*)-4-Styryl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7e; Table 4; Entry e).** Yield, 135 mg, 88%; solid, mp 96−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.02 (m, 9H), 6.62 (d, J = 15.8 Hz, 1H), 6.10 (dd, J = 15.8 and 9.8 Hz, 1H), 3.49 (t, J = 9.8 Hz, 1H), 3.17−3.04 (m, 1H), 2.89−2.62 (m, 3H), 2.59−2.46 (m, 1H), 2.44−2.21 (m, 1H), 2.20−2.07 (m, 1H), 1.85−1.62 (m, 2H), 1.46−1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 137.1, 136.6, 133.1, 129.0, 128.9, 128.5, 127.6, 126.3, 125.8, 50.3, 46.5, 43.2, 33.0, 29.8, 27.5,; IR (KBr) ν_{max} 2922, 2853, 1489, 1445, 966, 740, 693 cm^{-1}; MS (*APCI*) m/z 307 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{21}H_{23}S$, 307.1515 (M + H)$^+$; found, 307.1510.

(4*R,4a*R**,10bR*,*E*)-4-Styryl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7f; Table 4; Entry f).** Yield, 130 mg, 85%; solid, mp 84−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.31 (m, 2H), 7.31−7.09 (m, 4H), 7.08−6.93 (m, 3H), 6.55 (d, J = 15.9 Hz, 1H), 6.22 (dd, J = 15.9 and 6.8 Hz, 1H), 3.89 (d, J = 6.8 Hz, 1H), 2.99−2.56 (m, 5H), 2.42−2.14 (m, 3H), 1.98−1.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 136.8, 136.0, 131.8, 129.0, 128.9, 128.7, 128.5, 127.5, 126.3, 126.0, 125.6, 49.4, 42.2, 39.5, 31.4, 29.9, 29.1, 17.4; IR (neat) ν_{max} 2923, 2853, 1492, 1449, 963, 745, 696 cm^{-1}; MS (*APCI*) m/z 307 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{21}H_{23}S$, 307.1515 (M + H)$^+$; found, 307.1524.

(4*S,4a*S**,10b*R**)-8-Methoxy-4-(naphthalen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7g; Table 4; Entry g).** Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 106 mg, 59%; solid, mp 125−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88−7.76 (m, 4H), 7.55−7.41 (m, 3H), 7.26 (d, J = 8.8 Hz, 1H), 6.75 (dd, J = 8.8 and 2.0 Hz, 1H), 6.58 (d, J = 2 Hz, 1H), 3.92 (d, J = 9.8 Hz, 1H), 3.76 (s, 3H), 3.20−3.11 (m, 1H), 2.90−2.79 (m, 2H), 2.76−2.56 (m, 3H), 2.20−2.09 (m, 1H), 1.91−1.78 (m, 1H), 1.67−1.57 (m, 1H), 1.37−1.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 138.4, 133.4, 132.9, 131.2, 128.4, 127.8, 127.6, 127.3, 126.8, 126.1, 126.0, 125.8, 113.5, 112.0, 55.2, 52.8, 46.9, 43.5, 33.4, 30.8, 30.0, 27.0; IR (KBr) ν_{max} 2924, 2855, 1498, 1240, 1034, 783 cm^{-1}; MS (*APCI*) m/z 361 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{24}H_{25}OS$, 361.1621 (M + H)$^+$; found, 361.1630.

(4*S,4a*R**,10b*R**)-8-Methoxy-4-(naphthalen-2-yl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7h; Table 4; Entry h).** Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 108 mg, 60%; solid, mp 142−144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.73 (m, 3H), 7.69 (s, 1H), 7.47−7.35 (m, 3H), 6.93 (d, J = 7.9 Hz, 1H), 6.63 (dd, J = 7.9 and 2.0 Hz, 1H), 6.49 (d, J = 2 Hz, 1H), 4.45 (d, J = 3.0 Hz, 1H), 3.72 (s, 3H), 2.98 (dt, J = 12.8 and 3.0 Hz, 1H), 2.91−2.84 (m, 1H), 2.83−2.73 (m, 2H), 2.62−2.51 (m, 1H), 2.40−2.33 (m, 1H), 2.28−2.17 (m, 1H), 2.02−1.82 (m, 2H), 1.51−1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 138.7, 137.2, 133.9, 133.2, 132.4, 129.6, 127.9, 127.8, 127.5, 126.5, 126.2, 126.1, 125.7, 113.2, 112.2, 55.2, 52.3, 42.3, 41.3, 31.7, 30.4, 29.4, 16.6; IR (KBr) ν_{max} 2932, 2845, 1497, 1226, 1156, 1034, 818, 755 cm^{-1}; MS (*APCI*) m/z 361 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{24}H_{25}OS$, 361.1621 (M + H)$^+$; found, 361.1612.

(4*R,4a*S**,10b*R**)-8-Methoxy-4-propyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7i; Table 4; Entry i).** Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 81 mg, 59%; viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 9.1 Hz, 1H), 6.72 (dd, J = 9.1 and 3.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 3.83−3.75 (m, 4H), 3.01−2.87 (m, 1H), 2.85−2.65 (m, 4H), 2.47−2.34 (m, 1H), 2.26−2.14 (m, 1H), 1.91−1.76 (m, 1H), 1.72−1.23 (m, 6H) 0.94 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 138.2, 131.7, 126.9, 113.3, 111.8, 55.1, 47.2, 46.7, 43.3, 34.6, 33.6, 30.1, 29.1, 25.9, 19.6, 14.2; IR (neat) ν_{max} 2925, 2865, 1610, 1501, 1459, 1254, 1043, 777 cm^{-1}; MS (*APCI*) m/z 277 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{17}H_{25}OS$, 277.1621 (M + H)$^+$; found, 277.1627.

(4*R,4a*R**,10b*R**)-8-Methoxy-4-propyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7j; Table 4; Entry j).** Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column

chromatography. Yield of major regioisomer, 80 mg, 58%; viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, J = 7.9 Hz, 1H), 6.60 (dd, J = 7.9 and 2.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 3.73 (s, 3H), 3.03−2.95 (m, 1H), 2.93−2.70 (m, 3H), 2.62−2.52 (m, 2H), 2.20−2.07 (m, 1H), 2.06−1.98 (m, 1H), 1.90−1.71 (m, 2H) 1.69−1.61 (m, 1H), 1.60−1.38 (m, 4H), 0.95 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 137.3, 134.3, 129.6, 113.2, 112.0, 55.1, 47.0, 41.9, 38.5, 35.3, 32.2, 29.9, 29.4, 20.4, 16.6, 13.0; IR (neat) ν_{max} 2925, 2860, 1608, 1499, 1460, 1263, 1153, 1043, 776 cm^{-1}; MS (*APCI*) m/z 277 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{17}H_{25}OS$, 277.1621 (M + H)$^+$; found, 277.1618.

(4*S,4a*S**,10b*R**)-9-Methyl-4-(2-nitrophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7k; Table 4; Entry k).** Yield, 156 mg, 92%; solid, mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.62−7.56 (m, 1H), 7.42−7.37 (m, 1H), 7.14 (s, 1H), 6.98−6.92 (m, 2H), 4.43 (d, J = 10.9 Hz, 1H), 3.19−3.09 (m, 1H), 2.93−2.82 (m, 2H), 2.72−2.60 (m, 3H), 2.32 (s, 3H), 2.13−2.02 (m, 1H), 1.88−1.76 (m, 1H), 1.55−1.47 (m, 1H), 1.46−1.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 138.3, 135.3, 133.6, 132.9, 129.5, 128.9, 128.0, 126.8, 126.3, 124.0, 47.4, 45.3, 43.8, 33.2, 30.9, 29.2, 26.8, 21.3; IR (KBr) ν_{max} 2925, 2846, 1532, 1342, 801, 742 cm^{-1}; MS (*APCI*) m/z 340 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{20}H_{22}NO_2S$, 340.1366 (M + H)$^+$; found, 340.1357.

(4*S,4a*R**,10b*R**)-9-Methyl-4-(2-nitrophenyl)-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isothiochromene (7l; Table 4; Entry l).** Yield, 153 mg, 90%; solid, mp 130−132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 1H), 7.60−7.54 (m, 2H), 7.44−7.37 (m, 1H), 6.90−6.81 (m, 3H), 4.89 (d, J = 2.7 Hz, 1H), 3.01 (dt, J = 12.8 and 2.7 Hz, 1H), 2.93−2.86 (m, 1H), 2.85−2.73 (m, 2H), 2.68−2.55 (m, 1H), 2.48−2.39 (m, 1H), 2.36−2.24 (m, 4H), 2.06−1.95 (m, 1H), 1.95−1.83 (m, 1H), 1.51−1.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 138.7, 135.8, 135.2, 133.1, 132.4, 130.8, 130.5, 128.9, 128.3, 127.5, 124.3, 47.0, 42.5, 38.9, 35.3, 32.6, 29.3, 27.1, 21.0; IR (KBr) ν_{max} 2919, 2847, 1523, 1340, 794, 747 cm^{-1}; MS (*APCI*) m/z 340 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{20}H_{22}NO_2S$, 340.1366 (M + H)$^+$; found, 340.1382.

Typical Procedure for Intramolecular Prins- and Aza-Prins/Friedel−Crafts Cyclization with Styrene Oxide. To a stirred solution of homoallylic substrate (0.50 mmol) and styrene oxide (0.75 mmol) in anhydrous dichloroethane (5 mL) was added $Sc(OTf)_3$ (10 mol %) and stirred at room temperature under nitrogen atmosphere for the specified time (Table 5). 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 over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography using ethyl acetate/hexane gradients to afford pure product **8** (Table 5). (Yields are reported with respect to phenyl acetaldehyde since it afforded higher yield than styrene oxide).

(4*R,4a*S**,10b*R**)-4-Benzyl-8-methoxy-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (8a; Table 5; Entry a).** Reaction afforded a 3:1 mixture of para/ortho-substituted products. The two regioisomers could be easily separated by silica gel column chromatography. Yield of major regioisomer, 94 mg, 61%; white solid, mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.09 (m, 5H), 7.04 (d, J = 8.5 Hz, 1H), 6.63 (dd, J = 8.5 and 2.5 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 4.16−4.04 (m, 1H), 3.74 (s, 3H), 3.58−3.44 (m, 1H), 3.43−3.31 (m, 1H), 3.06 (dd, J = 14.3 and 2.3 Hz, 1H), 2.89−2.78 (m, 2H), 2.74−2.61 (m, 1H), 2.55−2.40 (m, 1H), 2.24−1.99 (m, 2H), 1.65−1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 139,3, 137.6, 131.7, 129.4, 128.1, 125.9, 125.6, 113.5, 111.5, 82.2, 67.9, 55.2, 43.2, 40.6, 39.3, 30.7, 29.1, 24.9; IR (KBr) ν_{max} 2920, 2834, 1605, 1498, 1453, 1236, 1127, 1095, 1026, 743, 697 cm^{-1}; MS (*APCI*) m/z 309 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{21}H_{25}O_2$, 309.1849 (M + H)$^+$; found, 309.1858.

(4*R,4a*R**,10b*R**)-4-Benzyl-2,4,4a,5,6,10b-hexahydro-1*H*-benzo[*f*]isochromene (8b; Table 5; Entry b).** Yield, 117 mg, 84%; viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.17 (m, 5H), 7.14−7.00 (m, 4H), 4.06−3.99 (m, 1H), 3.79−3.72 (m, 1H), 3.60−3.51 (m, 1H), 3.02−2.89 (m, 2H), 2.88−2.82 (m, 1H), 2.82−2.72 (m, 2H), 2.04−1.92 (m, 2H), 1.91−1.75 (m, 2H), 1.65−1.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 139.2, 136.0, 129.1, 128.9, 128.5, 128.3, 126.1, 125.9, 125.6, 81.3, 68.8, 39.6, 39.2, 36.9, 31.6, 29.1, 16.9; IR (KBr) ν_{max} 2941, 2844, 1088, 749, 700 cm^{-1}; MS (*APCI*) m/z 279 (M + H)$^+$; HRMS (*APCI*) calcd for $C_{20}H_{23}O$, 279.1743 (M + H)$^+$; found, 279.1735.

(4*S,4a*S**,10b*R**)-4-Benzyl-9-methyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (8c; Table 5; Entry c).** Yield, 178 mg, 80%; white solid, mp 182−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.09 (m, 7H), 7.06−6.95 (m, 3H), 6.94−6.83 (m, 2H), 4.61−4.48 (m, 1H), 3.75−3.62 (m, 1H), 3.29−3.13 (m, 1H), 2.97−2.68 (m, 5H), 2.34 (s, 3H), 2.32−2.23 (m, 4H), 2.00−1.86 (m, 1H), 1.85−1.73 (m, 1H), 1.66−1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 138.8, 138.3, 137.7, 135.3, 133.3, 129.3, 129.2, 129.1, 128.4, 127.1, 126.8, 126.5, 126.2, 59.0, 43.1, 40.9, 35.6, 32.0, 30.5, 29.7, 27.1, 21.4, 21.2; IR (KBr) ν_{max} 2928, 2871, 1316, 1151, 1011, 749, 703 cm^{-1}; ESI-MS m/z 446 (M + H)$^+$; HRMS (ESI) calcd for $C_{28}H_{32}NO_2S$, 446.2153 (M + H)$^+$; found, 446.2133.

(4*S,4a*R**,10b*R**)-4-Benzyl-3-tosyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]isoquinoline (8d; Table 5; Entry d).** Yield, 168 mg, 78%; white solid, mp 150−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53, 7.50 (AA′, 2H), 7.29−7.10 (m, 7H), 7.09−6.93 (m, 4H), 4.28−4.18 (m, 1H), 3.73−3.61 (m, 1H), 3.23−2.93 (m, 3H), 2.89−2.63 (m, 3H), 2.40 (s, 3H), 2.10−1.57 (m, 4H), 1.55−1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 140.1, 138.5, 138.2, 135.9, 129.5, 129.2, 129.1, 128.9, 128.6, 127.0, 126.4, 126.2, 125.7, 60.2, 40.6, 36.3, 34.2, 33.9, 30.5, 29.1, 23.5, 21.4; IR (KBr) ν_{max} 2926, 1312, 1150, 1092, 952, 751, 694 cm^{-1}; ESI-MS m/z 449 (M+NH_4)$^+$; HRMS (ESI) calcd for $C_{27}H_{30}NO_2S$, 432.1997 (M + H)$^+$; found, 432.1996.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of products (**3a−n, 5a−p, 7a−l**, and **8a−d**), preparation of starting materials, and X-ray data of compounds (**3a, 5f**, and **7a**) are provided in the CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Fax: 0091-40-27160512. E-mail:basireddy@iict.res.in; yadavpub@iict.res.in.

■ ACKNOWLEDGMENT

This research was performed as part of the Indo-French "Joint Laboratory for Sustainable Chemistry at Interfaces". We thank CSIR and CNRS for support. P.B. thanks CSIR, New Delhi for the award of a fellowship.

■ DEDICATION

Dedicated to Prof. E. J. Corey on the occasion of his 82nd birthday

■ REFERENCES

(1) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1072.
(2) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1510.

(3) Adams, D. R.; Bhatnagar, S. R. *Synthesis* **1977**, 661–672.
(4) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505–555.
(5) Reviews on Prins reactions, see: (a) Olier, C.; Kaafarani, M.; Gastaldi, S. S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445 and references cited therein. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957.
(6) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. L. *Org. Lett.* **2006**, *8*, 3837–3840.
(7) Yadav, J. S.; Reddy, B. V. S.; Chaya, D. N.; Narayan Kumar, G. G. K. S.; Aravind, S.; Kunwar, A. C.; Madavi, C. *Tetrahedron Lett.* **2008**, *49*, 3330–3334.
(8) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064–6071.
(9) Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876–3878.
(10) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739–747.
(11) Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480–16481.
(12) Albizati, K. F.; Perron, F. *J. Org. Chem.* **1987**, *52*, 4128–4130.
(13) Reddy, B. V. S.; Ramesh, K.; Ganesh, A. V.; Kumar, G. G. K. S. N.; Yadav, J. S.; Gree, R. *Tetrahedron Lett.* **2011**, *52*, 495–498.
(14) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, 1912–1916.
(15) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679–8682.
(16) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605–2608.
(17) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, 1625–1630.
(18) Kinoshita, H.; Ingham, J. O.; Ong, W. W.; Beeler, B. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 6412–6418.
(19) Yadav, J. S.; Reddy, B. V. S.; Ganesh, A. V.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2010**, *51*, 2963–2966.
(20) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316–8326.
(21) (a) Elsworth, J. D.; Willis, C. L. *Chem. Commun.* **2008**, 1587–1589. (b) Suginome, M.; Ohmori, Y.; Ito, Y. *Chem. Commun.* **2001**, 1090–1091.
(22) Yadav, J. S.; Chakravarthy, P. P.; Borkar, P.; Reddy, B. V. S.; Sarma, A. V. S. *Tetrahedron Lett.* **2009**, *50*, 5998–6000.
(23) Yadav, J. S.; Borkar, P.; Chakravarthy, P. P.; Reddy, B. V. S.; Sarma, A. V. S.; Sridhar, B.; Grée, R. *J. Org. Chem.* **2010**, *75*, 2081–2084.
(24) Reddy, B. V. S.; Borkar, P.; Chakravarthy, P. P.; Yadav, J. S.; Gree, R. *Tetrahedron Lett.* **2010**, *51*, 3412–3416.
(25) Kuo, Y.-J.; Hsiao, P.-C.; Zhang, L.-J.; Wu, M.-D.; Liang, Y.-H.; Ho, H.-O.; Kuo, Y.-H. *J. Nat. Prod.* **2009**, *72*, 1097–1101.
(26) Abas, F.; Lajis, N. H.; Shaari, K.; Israf, D. A.; Stanslas, J.; Yusuf, U. K.; Raof, S. M. *J. Nat. Prod.* **2005**, *68*, 1090–1093.
(27) Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Nobe, A. J. *J. Med. Chem.* **1992**, *35*, 2025–2033.
(28) Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss; Wong, E. H. F. *J. Med. Chem.* **1992**, *35*, 2033–2039.
(29) Romero, A. G. EP 0309695, 1992.
(30) Hartmen, G. D.; Phillips, B. T. US 4670443, 1987.
(31) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852–853.
(32) Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1397–1404.
(33) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978.
(34) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213.
(35) Yadav, J. S.; Thrimurtulu, N.; Gayathri, K. U.; Reddy, B. V. S.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 6617–6620.
(36) Yadav, J. S.; Lakshmi, K. L.; Reddy, N. M.; Prasad, A. R.; Reddy, B. V. S. *Tetrahedron* **2010**, *44*, 334–338.
(37) Yadav, J. S.; Padmavani, B.; Reddy, B. V. S.; Venugopal, Ch.; Rao, A. B. *Synlett* **2007**, *13*, 2045–2048.
(38) (a) Greeves, N.; Aspinall, H. C.; Bissett, J. S.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 319–321. (b) Greeves, N.; Aspinall, H. C.; Bissett, J. S.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 323–325.
(39) Supplementary crystallographic data (CIF File) and respective ORTEP diagrams (Figures S1−S3) for these compounds have been provided in the Supporting Information. Also, (a) CCDC-806707, (b) CCDC-806708, and (c) CCDC-806709 contain the supplementary crystallographic data for these compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(40) (a) Rodriquez, L.; Lu, N.; Yang, N.-L. *Synlett* **1990**, 227–228. (b) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.
(41) (a)Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Sindona, G.; Tagarelli, A. *Synlett* **2004**, 2633–2635.