Synthesis N. R. Devi et al. Paper

Synthesis of 4-Vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-Tethered Benzyl-Alkenol Catalyzed by Indium(III) Chloride: Formal Synthesis of (±)-Isocyclocelabenzine

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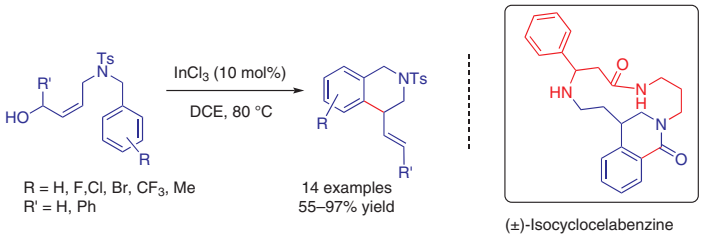


Received: 20.12.2019
Accepted after revision: 20.01.2020
Published online: 12.02.2020
DOI: 10.1055/s-0037-1610750; Art ID: ss-2019-n0438-op

Abstract An intramolecular Friedel–Crafts cyclization reaction catalyzed by indium(III) chloride for the formation of 4-vinyl-1,2,3,4-tetrahydroisoquinoline from *N*-tethered benzyl-alkenol in good yields has been described. The reaction is highly regioselective and generates an exocyclic vinyl functionality in the piperidine ring. The reaction is compatible with a wide range of functional groups. The strategy is demonstrated for the formal synthesis of (±)-isocyclocelabenzine alkaloid.

Key words tetrahydroisoquinoline, (±)-isocyclocelabenzine, indium(III) chloride, regioselectivity, *N*-tethered benzyl-alkenol, Friedel–Crafts

Many *N*-containing heterocycles especially isoquinolines are found to be a major part in naturally occurring alkaloids. Tetrahydroisoquinoline (THIQ) is a substructure found in a number of plant alkaloids as well as in various synthetic compounds. They show an array of medicinal and pharmacological properties such as antihyperglycemic activity,[1] analgesic and anticonvulsant effects,[2] effective against heart disease and liver damages,[3] as calcium channel blocker,[4] treatments against Parkinson's disease,[5] etc. These biological properties of THIQs are attributed to the substitution pattern on the isoquinoline scaffold. For example, nomifensine (**1**), a C4-aryl-substituted THIQ derivative, is used as an antidepressant drug (Figure 1).[6] Another THIQ alkaloid homolaudanosine (**2**), isolated from the plant *Dysoxylum lenticellare* shows cardioactive properties on rat cardiac tissues (Figure 1).[7] In addition to their biological properties, THIQs also act as key intermediates in many reactions for the synthesis of several important substances.[8]

The most common approaches for the synthesis of THIQ derivatives are Pictet–Spengler,[9] Friedel–Crafts,[10] rhodium complex catalyzed [3+2] cycloaddition,[11] Lewis acid catalyzed [3+3] cycloadditions,[12] alkylation of anodically prepared α-amino nitriles,[13] intramolecular oxetane ring opening,[14] and others.[15] Tietze and co-workers have developed a methodology for the synthesis of THIQ by intramolecular Heck reaction (Scheme 1a).[16] Nevertheless, the reaction affords a mixture of olefin isomers from either an unselective β-hydride elimination or olefin isomerization. Wu and You group used palladium catalyst for cyclization of *N*-tethered allylic alkylation of phenols (Scheme 1b).[17] Notably, Bandini and co-workers have recently reported the iron(III) chloride catalyzed cyclization of challenging electron-deficient *N*-tethered benzyl-alkenols to prepare tetrahydroisoquinolines (Scheme 1c).[10] Recently, we have developed a few methodologies for the synthesis of nitrogen heterocyclic compounds via intramolecular C–C/C–O bond formation reactions from *N*-tethered alkanols/alkenols.[18] Very recently, we have synthesized 4-vinylpyrrolidine from *N*-tethered alkyne-alkenols mediated by $InCl_3$.[19] The advantages of indium(III) chloride as Lewis acid over other Lewis acids is due to the fact that they have unique π-acidity, alkynophilicity, relatively low toxicity, air, moisture compatibility, and recyclability. Therefore, $InCl_3$ has long been used for various transformations in organic synthesis including construction of heterocycles.[20] We now report a new strategy in which vinyl-substituted tetrahydroisoquinoline deriva-

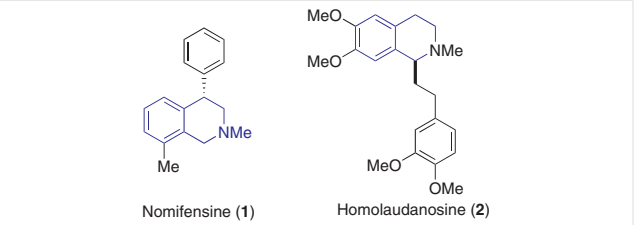
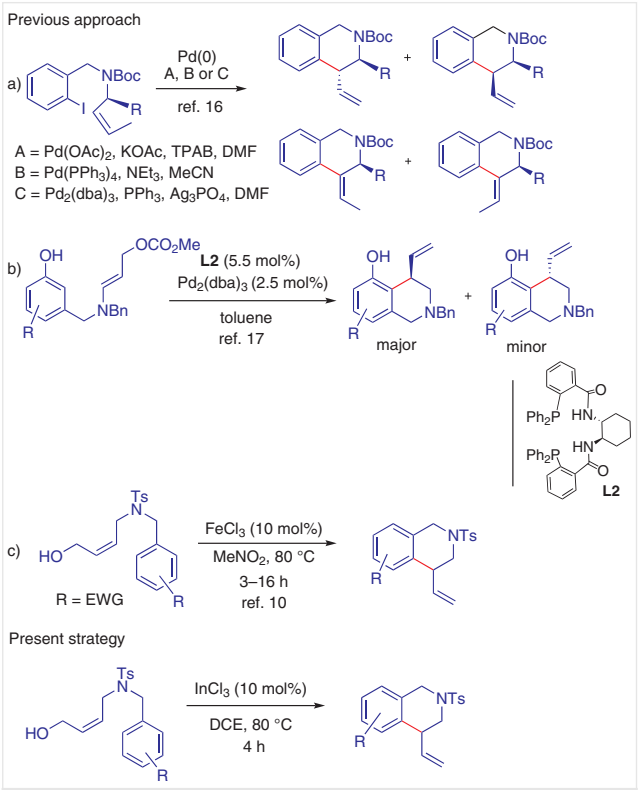


Figure 1 Structures containing isoquinoline alkaloids

tives can be prepared using intramolecular C–C bond formation reaction from *N*-tethered benzyl-alkenols catalyzed by $InCl_3$ in high yields with good regioselectivity.



Scheme 1 Synthesis of tetrahydroisoquinolines

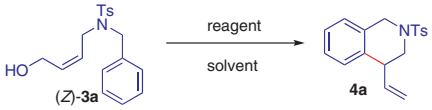
To start with *N*-tethered benzyl-alkenol (*Z*)-**3a** was treated with 0.1 equivalent of indium(III) chloride at 0 °C to room temperature in dichloromethane (DCM) for 12 hours, but the starting material was recovered in 86% yield (Table 1, entry 1). When the reaction was performed at 40 °C, tetrahydroisoquinoline **4a** was formed in 10% yield (entry 2). In order to check the role of solvents, the same reaction was conducted in dichloroethane (DCE) at 40 °C but resulted in 8% yield (entry 3). Having obtained the desired product in both DCM and DCE, the reaction was then performed in dichloroethane at 60 °C and only 7% increment in yield was observed (entry 4). When the reaction was performed at 80 °C, to our delight THIQ **4a** was obtained in 97% yield (entry 5). On careful examination, the same reaction completed in 4 hours in 97% yield (entry 6). On the other hand, indium(III) triflate [$In(OTf)_3$] in DCM at 0 °C to room temperature failed to give the product but starting material was recovered in 82% yield (entry 7), whereas in DCE at 80 °C it gave only 60% yield (entry 8). Other Lewis and Brønsted acids such as bismuth(III) triflate [$Bi(OTf)_3$], *p*-toluenesulfonic acid (*p*-TSA), and triflic acid (TfOH) (entries 9–15) were found to be inappropriate reagents for this reaction.

We examined the substrate scope of the reaction as shown in Table 2. Aromatic rings having both electron-donating and electron-withdrawing groups gave the desired tetrahydroisoquinoline products in high yields. However, with the variation of electronic effect in the aromatic rings, the yields of the reaction also varied. Electron-donating Me group in the aromatic ring of *N*-tethered aryl-alkenol gave 62% yield (Table 2, entry 13). Whereas highly electron-withdrawing NO_2 and electron-donating OMe groups in the aromatic ring gave decomposed products instead of desired products (entries 5 and 14). This may be due to the interaction of the Lewis acid with the oxygen of the NO_2 and OMe groups, respectively.[21] Moreover the methoxy group is electron-withdrawing in this case since the cyclization has to occur at the *meta*-position and the nitro group is *meta*-directing. On the other hand, substrate having highly electron-withdrawing CF_3 group in the benzene ring gave 82% yield (entry 6).

Variation in the *ortho*- and *para*-substituents in the aromatic ring system also gave the tetrahydroisoquinoline products in desirable yields (Table 2, entries 3, 4 and 7, 9, 12). Substrate **3h** with *meta*-substituent in the aromatic ring resulted in two isomeric products **4h** and **4h′** because of the availability of two sites for C-alkylation (entry 8). Disubstituted aromatic rings on *N*-tethered benzyl-alkenol also gave the desired products (entries 10, 11). The reaction with *trans*-allylic alcohol (*E*)-**3a** also works well and gave the desired product in 55% yield (entry 15). After considering *cis*- and *trans*-primary allylic alcohols, the reaction was shifted to secondary allylic alcohol **3o** and gave **4o** in 78% yield (entry 16). The side chain olefin configuration is found to be *E*-configured from the coupling constants of ^1H NMR spectrum. The reaction is highly regioselective, as determined by proton NMR analysis of crude products. Further, the structure of the product is confirmed by X-ray crystallographic analysis of compound **4b** (see the Supporting Information).[22]

Although the aforementioned cyclization can proceed by either a stepwise or concerted process, we favor the former process as outlined in Scheme 2. The reaction is presumably initiated with the coordination of the Lewis acid to the allylic alcohol to generate **A**, which can ionize to generate the allylic carbocation **B**. Intramolecular Friedel–Crafts type addition of the aryl group will generate carbocation **C**, which will undergo rapid rearomatization to afford **4**. The alternative process involving a concerted process is unlikely given the process does not appear to be stereospecific. For example, the cyclization of **3o** to **4o** affords the *E*- rather than *Z*-geometrical isomer.

Table 1 Optimization of the Reaction[a]

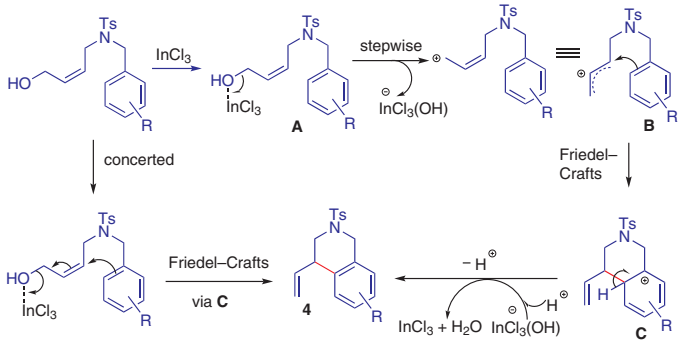


Entry	Reagent (equiv)	Solvent	Temp (°C)	Time (h)	Recovered SM (*Z*)-**3a** (%)[b]	Yield (%)[c] of **4a**
1	$InCl_3$ (0.1)	DCM	0 to rt	12	86	0
2	$InCl_3$ (0.1)	DCM	40	12	78	10
3	$InCl_3$ (0.1)	DCE	40	12	80	8
4	$InCl_3$ (0.1)	DCE	60	12	57	15
5	$InCl_3$ (0.1)	DCE	80	12	0	97
6	$InCl_3$ (0.1)	DCE	80	4	0	97
7	$In(OTf)_3$ (0.1)	DCM	0 to rt	12	82	0
8	$In(OTf)_3$ (0.1)	DCE	80	12	0	60
9	$Bi(OTf)_3$ (0.1)	DCM	0 to rt	12	80	0
10	$Bi(OTf)_3$ (0.1)	DCE	80	12	83	0
11	$BF_3{\cdot}OEt_2$ (1.2)	DCM	0 to rt	12	85	0
12	TfOH (1.2)	DCM	0 to rt	12	0	30[d]
13	*p*-TSA (1.2)	DCM	0 to rt	12	80	0
14	*p*-TSA (1.2)	DCM	40	12	78	15
15	*p*-TSA (1.2)	DCE	80	12	0	66

[a] Reaction conditions: (*Z*)-**3a** (1.0 equiv), solvent (4 mL).
[b] Starting material (SM) recovered up to 86%.
[c] Isolated yield.
[d] Along with decomposed product.

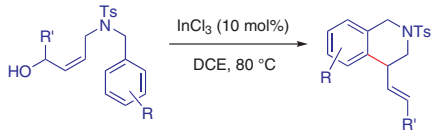
To check the further applicability of the methodology, a formal synthesis of (±)-isocyclocelabenzine was undertaken (Scheme 3).[23] Isocyclocelabenzine is a type of spermidine alkaloid, first isolated from *Maytenus mossmbicensis* by Wagner and co-workers.[24] The alkaloid has a 13-membered lactam ring linked to the benzoyl residue of spermidine unit. We started with compound **4a**, whereby its vinylic functionality was oxidized by using hydroboration and oxidation strategy[25] to give the primary alcohol **5** in 75% yield. The alcohol **5** was detosylated using Mg/MeOH[26] to provide the precursor **6** of (±)-isocyclocelabenzine in 67% yield.

In conclusion, we have developed a mild and efficient method for the synthesis of vinyl-substituted tetrahydroisoquinoloine derivatives via intramolecular cyclization of *N*-tethered benzyl-alkenol in high yields. The methodology is compatible with a wide range of functional groups and catalytic in nature. The advantage of the reaction is the generation of exocyclic vinyl functionality regioselectively at such a position, which can be used for the formal synthesis of (±)-isocyclocelabenzine alkaloid.



Scheme 2 Plausible mechanism of the reaction

Table 2 Synthesis of Tetrahydroisoquinolines[a]



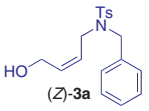
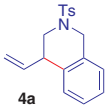
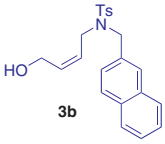
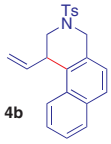
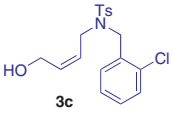
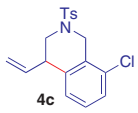
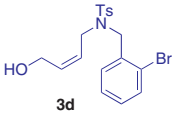
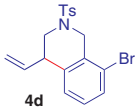
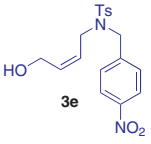
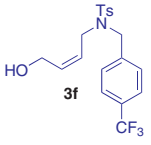
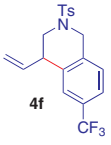
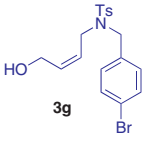
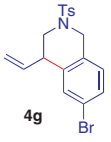
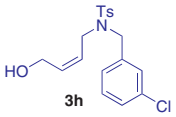
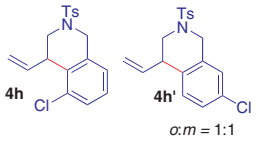
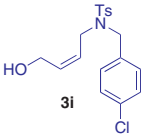
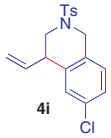
Entry	Substrate **3**	Product **4**	Yield (%)[b]
1	 (*Z*)-**3a**	 **4a**	97
2	 **3b**	 **4b**	70
3	 **3c**	 **4c**	87
4	 **3d**	 **4d**	76
5	 **3e**	 **4e**	0
6	 **3f**	 **4f**	80
7	 **3g**	 **4g**	87
8	 **3h**	 **4h** + **4h'** *o*:*m* = 1:1	77[c]
9	 **3i**	 **4i**	92

Table 2 (continued)

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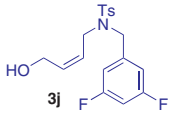
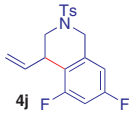
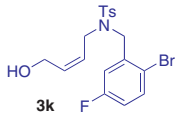
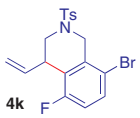
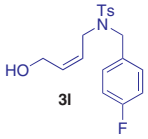
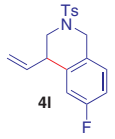
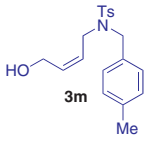
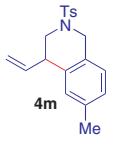
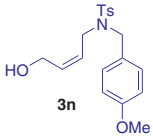
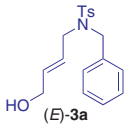
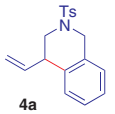
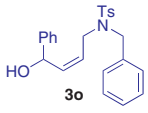
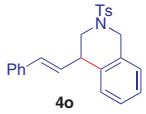
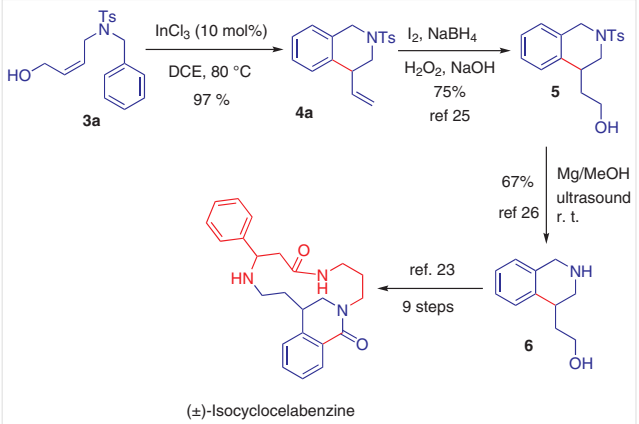
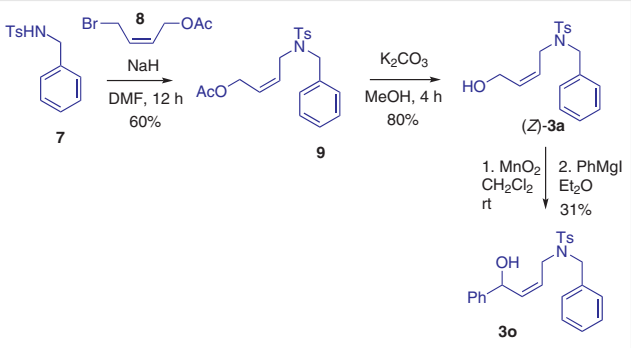
10	 **3j**	 **4j**	73
11	 **3k**	 **4k**	77
12	 **3l**	 **4l**	81
13	 **3m**	 **4m**	62
14	 **3n**	 **4n**	0
15	 (*E*)-**3a**	 **4a**	55
16	 **3o**	 **4o**	78

[a] Reaction conditions: **3** (1.0 equiv), $InCl_3$ (10 mol%), DCE (4.0 mL), 80 °C.
[b] Isolated yield.
[c] Ratio determined by ^1H NMR spectroscopy.



Scheme 3 Formal synthesis of (±)-isocyclocelabenzine



Scheme 4

All the reagents were of reagent grade (AR grade) and used as purchased without further purification. Silica gel (60–120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. FT-IR spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard for ^1H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in hertz (Hz). HRMS spectra were recorded using Q-TOF mass spectrometer.

Starting Materials (*Z*)-*N*-Benzyl-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide [(*Z*)-3a][27a] and (*Z*)-*N*-Benzyl-*N*-(4-hydroxy-4-phenylbut-2-en-1-yl)-4-methylbenzenesulfonamide (3o) (Scheme 4); Typical Procedure

In a round-bottomed flask, NaH (50 mg, 2.10 mmol, 1.1 equiv) was taken under N_2 atmosphere at 0 °C. To the NaH was added a solution of compound **7** (500 mg, 1.91 mmol, 1 equiv) in DMF (15 mL) dropwise. The reaction mixture was stirred for 15 min and then a solution of 4-bromobut-2-en-1-yl acetate (**8**; 405 mg, 2.10 mmol, 1.1 equiv) in DMF (2 mL) was slowly added. The mixture was stirred for 6 h. After the completion of the reaction (checked by TLC), the mixture was quenched by sat. aq NH_4Cl and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography to give (*Z*)-4-(*N*-benzyl-4-methylphenylsulfonamido)but-2-en-1-yl acetate (**9**; 420 mg, 60%). Compound **9** was then treated with K_2CO_3/MeOH at rt for 4 h. After completion of the reaction, MeOH was evaporated and the compound was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried (anhyd Na_2SO_4), and evaporated. The residue was purified by column chromatography to give (*Z*)-**3a**; yield: 300 mg, 0.90 mmol (80%). Compound (*Z*)-**3a** (200 mg, 0.60 mmol, 1 equiv) was then oxidized with MnO_2 (1.5 g, 30 equiv) in DCM at rt under N_2 atmosphere for 12 h. The mixture was filtered and evaporated, purification through column chromatography gave the required aldehyde. The aldehyde was then reacted with PhMgI (prepared in situ) in Et_2O at 0 °C for 30 min. After completion of the reaction as determined by TLC, the mixture was quenched with sat. aq NH_4Cl, and extracted with Et_2O. The combined Et_2O layers were washed with brine, dried (anhyd Na_2SO_4), and evaporated. The residue was purified by column chromatography to give the final compound (*Z*)-**3o**; yield: 46 mg (31% over two steps); colorless oil; R_f = 0.60 (hexane/EtOAc 4:1) (see below for spectral data).

(*Z*)-3a

Mp 65–68 °C; R_f = 0.55 (hexane/EtOAc 3:2).

IR (KBr): 3406, 2921, 2864, 1598, 1495, 1340, 1158, 1091, 1028, 932, 816, 766, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (br s, 1 H), 2.41 (s, 3 H), 3.78 (d, *J* = 7.2 Hz, 2 H), 3.88 (d, *J* = 6.8 Hz, 2 H), 4.32 (s, 2 H), 5.21–5.24 (m, 1 H), 5.56–5.61 (m, 1 H), 7.27–7.30 (m, 5 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-4-methyl-*N*-(naphthalen-2-ylmethyl)benzenesulfonamide (3b)[27b]

IR (KBr, neat): 3420, 2922, 2865, 1598, 1439, 1339, 1158, 1090, 1017, 917, 816, 750, 660, 572 cm^{-1}.

White solid; yield: 300 mg (78%); mp 70–73 °C; R_f = 0.50 (hexane/EtOAc 3:2).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.85 (br s, 1 H), 2.43 (s, 3 H), 3.80 (d, *J* = 7.2 Hz, 2 H), 3.83 (d, *J* = 4.8 Hz, 2 H), 4.46 (s, 2 H), 5.19–5.22 (m, 1 H), 5.53–5.60 (m, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.41 (dd, *J* = 1.2, 7.2 Hz, 1 H), 7.45 (dd, *J* = 7.2, 3.2 Hz, 2 H), 7.62 (s, 1 H), 7.72–7.81 (m, 5 H).

(*Z*)-*N*-(2-Chlorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3c)

Yellow gum; yield: 400 mg (89%); R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3441, 2923, 2867, 1638, 1444, 1340, 1158, 1091, 1036, 911, 755, 657, 550 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.87 (br s, 1 H), 2.44 (s, 3 H), 3.85 (d, *J* = 7.2 Hz, 2 H), 3.95 (d, *J* = 6.4 Hz, 2 H), 4.45 (s, 2 H), 5.23–5.28 (m, 1 H), 5.58–5.64 (m, 1 H), 7.27 (m, 5 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 44.8, 48.5, 58.0, 126.0, 127.3, 127.4, 129.1, 129.6, 130.0, 130.2, 132.9, 133.3, 133.9, 136.8, 143.8.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}ClNO_3S$ $(M + H)^+$: 366.0931; found: 366.0937.

(*Z*)-*N*-(2-Bromobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3d)

White gum; yield: 366 mg (81%); R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3409, 2923, 2859,1596, 1441, 1340, 1158, 1092, 1024, 911, 813, 754, 659, 551 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.85 (br s, 1 H), 2.44 (s, 3 H), 3.85 (d, *J* = 7.2 Hz, 2 H), 3.94 (d, *J* = 6.4 Hz, 2 H), 4.43 (s, 2 H), 5.21–5.28 (m, 1 H), 5.59–5.62 (m, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.26–7.34 (m, 3 H), 7.50–7.54 (m, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 44.9, 51.2, 58.1, 123.3, 125.9, 127.4, 127.9, 129.4, 130.1, 130.2, 132.9, 133.0, 135.5, 136.9, 143.9.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}BrNO_3S$ $(M + H)^+$: 410.0426; found: 410.0438.

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-4-methyl-*N*-(4-nitrobenzyl)benzenesulfonamide (3e)

Yellow gum; yield: 311 mg (73%); R_f = 0.40 (hexane/EtOAc 3:2).

IR (KBr, neat): 3405, 2925, 2862, 1654, 1522, 1346, 1158, 1091, 1017, 914, 771, 658 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.78 (br s, 1 H), 2.46 (s, 3 H), 3.85 (d, *J* = 7.2 Hz, 2 H), 3.97 (d, *J* = 6.4 Hz, 2 H), 4.40 (s, 2 H), 5.19–5.24 (m, 1 H), 5.62–5.68 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 8.17 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 44.8, 50.7, 58.0, 124.0, 125.8, 127.4, 129.1, 130.2, 133.3, 136.7, 144.2, 144.3, 147.8.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}N_2O_5S$ (M + H)$^+$: 377.1171; found: 377.1216.

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-4-methyl-*N*-[4-(trifluoromethyl)benzyl]benzenesulfonamide (3f)

White solid; yield: 350 mg (77%); mp 85–87 °C, R_f = 0.48 (hexane/EtOAc 3:2).

IR (KBr, neat): 3422, 2925, 2865, 1619, 1420, 1326, 1159, 1122, 1066, 1018, 914, 816, 659, 548 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (br s, 1 H), 2.45 (s, 3 H), 3.82 (d, *J* = 7.2 Hz, 2 H), 3.96 (d, *J* = 4.4 Hz, 2 H), 4.37 (s, 2 H), 5.21–5.24 (m, 1 H), 5.61–5.68 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 44.4, 50.9, 58.0, 122.9, 125.7, 125.76, 125.8, 125.84, 126.1, 127.4, 128.7, 130.1, 133.0, 137.0, 140.6, 144.0.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{21}F_3NO_3S$ (M + H)$^+$: 400.1194; found: 400.1213.

(*Z*)-*N*-(4-Bromobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3g)

White solid; yield: 350 mg (78%); mp 80–83 °C; R_f = 0.55 (hexane/EtOAc 3:2).

IR (KBr, neat): 3397, 2922, 2868, 1596, 1488, 1407, 1339, 1158, 1091, 1012, 910, 814, 767, 658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (br s, 1 H), 2.41 (s, 3 H), 3.75 (d, *J* = 6.2 Hz, 2 H), 3.90 (d, *J* = 6.0 Hz, 2 H), 4.22 (s, 2 H), 5.11–5.16 (m, 1 H), 5.56–5.60 (m, 1 H), 7.13 (d *J* = 6.0 Hz, 2 H), 7.30 (d, *J* = 6.0 Hz, 2 H), 7.39 (d, *J* = 6.0 Hz, 2 H), 7.69 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 44.1, 50.7, 58.0, 122.1, 126.2, 127.4, 130.1, 130.2, 131.9, 132.8, 135.4, 137.1, 143.9.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}BrNO_3S$ (M + H)$^+$: 410.0426; found: 410.0433.

(*Z*)-*N*-(3-Chlorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3h)

Yellow oil; yield: 356 mg (77%); R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3450, 2924, 2825, 1597, 1577, 1437, 1340, 1204, 1157, 1017, 921, 860, 814, 681, 657, 550 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (br, 1 H), 2.44 (s, 3 H), 3.80 (d, *J* = 7.2 Hz, 2 H), 3.93 (d, *J* = 6.4 Hz, 2 H), 4.27 (s, 2 H), 5.16–5.22 (m, 1 H), 5.59–5.65 (m, 1 H), 7.15–7.17 (m, 1 H), 7.22 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 44.1, 51.0, 57.9, 125.8, 126.6, 127.3, 128.2, 128.4, 130.0, 133.0, 134.6, 136.9, 138.3, 143.9.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}ClNO_3S$ (M + H)$^+$: 366.0931; found: 366.0916.

(*Z*)-*N*-(4-Chlorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3i)

Colorless oil; yield: 320 mg (85%); mp 80–82 °C; R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3417, 2923, 2867, 1597, 1492, 1445, 1336, 1158, 1090, 1015, 911, 814, 657, 566 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (br s, 1 H), 2.44 (s, 3 H), 3.78 (d, *J* = 7.0 Hz, 2 H), 3.93 (d, *J* = 6.8 Hz, 2 H), 4.27 (s, 2 H), 5.11–5.18 (m, 1 H), 5.70–5.88 (m, 1 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 44.0, 50.6, 57.9, 126.0, 127.3, 127.33, 128.8, 128.9, 129.8, 130.0, 132.9, 133.8, 134.8, 137.0, 143.8.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}ClNO_2S$ (M + H)$^+$: 366.0926; found: 366.0928.

(*Z*)-*N*-(3,5-Difluorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3j)

Colorless oil; yield: 327 mg (72%); R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3426, 2924, 2853, 1625, 1597, 1460, 1341, 1159, 1118, 992, 813, 660 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (br s, 1 H), 2.36 (s, 3 H), 3.75 (d, *J* = 7.2 Hz, 2 H), 3.89 (d, *J* = 6.4 Hz, 2 H), 4.19 (s, 2 H), 5.11–5.14 (m, 1 H), 5.53–5.58 (m, 1 H), 6.59–6.64 (m, 1 H), 6.74 (d, *J* = 6.0 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 44.5, 50.5, 57.9, 103.4 (t, *J* = 25.0 Hz), 110.1 (d, *J* = 26 Hz) , 125.7, 127.3, 130.1, 133.2, 136.8, 140.8, 144.1, 163.2 (d, *J* = 248 Hz), 163.3 (d, *J* = 247 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}F_2NO_3S$ (M + H)$^+$: 368.1132; found: 368.1134.

(*Z*)-*N*-(2-Bromo-5-fluorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3k)

Colorless gum; yield: 300 mg (66%); R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3357, 2923, 2849, 1598, 1578, 1466, 1341, 1158, 1090, 1028, 813, 658, 556 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (br s, 1 H), 2.45 (s, 3 H), 3.89 (d, *J* = 7.2 Hz, 2 H), 4.00 (d, *J* = 6.6 Hz, 2 H), 4.38 (s, 2 H), 5.25–5.30 (m, 1 H), 5.62–5.67 (m, 1 H), 6.88 (dt, *J* = 3.04, 5.24 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.43–7.47 (m, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 45.3, 51.1, 58.1, 116.6 (d, *J* = 22 Hz), 116.9, 117.1, 125.8, 127.4, 130.2, 133.4, 134.1, 134.2, 136.7, 138.2, 138.3, 144.1, 161.5 (d, *J* = 246.0 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}BrFNO_3S$ (M + H)$^+$: 428.0331; found: 428.0339.

(*Z*)-*N*-(4-Fluorobenzyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (3l)

Colorless oil; yield: 331 mg (72%); R_f = 0.50 (hexane/EtOAc 3:2).

IR (KBr, neat): 3423,2924, 2855, 1603, 1509, 1339, 1226, 1158, 1091, 909, 816, 658, 548 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (br s, 1 H), 2.44 (s, 3 H), 3.78 (d, *J* = 6.8 Hz, 2 H), 3.93 (d, *J* = 6.8 Hz, 2 H), 4.27 (s, 2 H), 5.16–5.22 (m, 2 H), 5.58–5.63 (m, 2 H), 6.96–7.01 (m, 2 H), 7.23–7.26 (m, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 43.9, 50.6, 57.9, 115.6 (d, J = 21.0 Hz) 126.0, 127.3, 130.0, 130.1, 130.2, 131.8, 131.9, 132.7, 137.0, 143.8, 162.5 (d, *J* = 244.9 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}FNO_3S$ (M + H)$^+$: 350.1226; found: 350.1215.

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-4-methyl-*N*-(4-methylbenzyl)benzenesulfonamide (3m)

Colorless oil; yield: 372 mg (81%); R_f = 0.45 (hexane/EtOAc 3:2).

IR (KBr, neat): 3444, 2923, 2864, 1597, 1513, 1438, 1340, 1157, 1090, 1019, 909, 814, 657, 577 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.09 (br s, 1 H), 2.31 (s, 3 H), 2.42 (s, 3 H), 3.76 (d, *J* = 7.2 Hz, 2 H), 3.89 (d, *J* = 6.8 Hz, 2 H), 4.26 (s, 2 H), 5.16–5.23 (m, 1 H), 5.22–5.61 (m, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.13(d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.6, 43.6, 50.9, 57.9, 126.2, 127.3, 128.5, 129.4, 129.9, 132.5, 132.9, 137.2, 137.8, 143.6.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{24}NO_3S$ (M + H)$^+$: 346.1477; found: 346.1470.

(*Z*)-*N*-(4-Hydroxybut-2-en-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide (3n)

Colorless oil; yield: 320 mg (71%); R_f = 0.40 (hexane/EtOAc 3:2).

IR (KBr, neat): 3451, 2924, 2855, 1612, 1511, 1458, 1336, 1249, 1156, 1093, 1031, 906, 814, 658, 548 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.74 (br s, 1 H), 2.45 (s, 3 H), 3.77 (d, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 3.93 (d, *J* = 6.4 Hz, 2 H), 4.32 (s, 2 H), 5.33–5.38 (m, 1 H), 5.52–5.56 (m, 1 H), 7.2–7.33 (m, 7 H), 7.73 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 43.6, 50.8, 55.5, 58.0, 114.2, 126.6, 127.4, 127.9, 129.9, 130.0, 132.4, 137.3, 143.7, 159.6.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{23}NO_4S$ (M + H)$^+$: 362.1421; found: 362.1427.

(*E*)-*N*-(4-Hydroxybut-2-en-1-yl)-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonamide [(*E*)-3a][28]

Colorless oil; yield: 332 mg (70%); R_f = 0.40 (hexane/EtOAc 3:2).

IR (KBr, neat): 3131, 3013, 2859, 1598, 1401, 1339, 1157, 1092, 1013, 896, 730, 550 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.73 (d, *J* = 6.5 Hz, 2 H), 3.93 (d, *J* = 5.2 Hz, 2 H), 3.93 (d, *J* = 6.4 Hz, 2 H), 4.26 (s, 2 H), 5.17–5.24 (m, 1 H), 5.58–5.64 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

(*Z*)-*N*-Benzyl-*N*-(4-hydroxy-4-phenylbut-2-en-1-yl)-4-methylbenzenesulfonamide (3o)

IR (KBr, neat): 3426, 2843, 1610, 1448, 1323, 1253, 1150, 1045, 1012, 810, 650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.77 (dd, *J* = 6.8, 7.0 Hz, 2 H), 4.23 (d, *J* = 14.8 Hz, 1 H), 4.33 (d, *J* = 14.8 Hz, 1 H), 5.00 (d, *J* = 5.4 Hz, 1 H), 5.39–5.46 (m, 1 H), 5.55 (dd, *J* = 15.4, 6.2 Hz, 1 H), 7.19 (d, *J* = 7.2 Hz, 4 H), 7.25–7.34 (m, 8 H), 7.71 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 49.0, 51.2, 74.4, 125.6, 126.3, 127.5, 128.0, 128.1, 127.6, 128.7, 128.8, 130.0, 136.4, 137.1, 137.4, 142.4, 143.6.

Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.84; H, 6.25; N, 3.48.

2-Tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4a)[27c]; Typical Procedure

To a solution of (*E*)-**3a** (150 mg, 0.45 mmol, 1 equiv) in anhyd 1,2-dichloroethane (4 mL) was added $InCl_3$ (10 mol%, 10 mg) at 80 °C. The reaction mixture was refluxed for 4 h. After the completion of the reaction, as determined by TLC, the mixture was washed with sat. aq $NaHCO_3$ and brine, and extracted with EtOAc (2 × 15 mL). The combined organic extarcts were dried (anhyd Na_2SO_4) and evaporation to give the crude product, which was purified by column chromatography using EtOAc and hexane as eluents (hexane/EtOAc 9:1); yellow solid; yield: 137 mg (97%); mp 80–82 °C; R_f = 0.60 (hexane/EtOAc 9:1).

IR (KBr, neat): 2964, 2922, 2849, 1598, 1493, 1353, 1165, 1091, 956, 813, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.07 (dd, *J* = 4.8, 6.8 Hz, 1 H), 3.36 (dd, *J* = 6.8, 4.8 Hz, 1 H), 3.56 (dt, *J* = 5.6, 7.2 Hz, 1 H), 4.16 (dd, *J* = 14.8, 13.2 Hz, 2 H), 5.11–5.16 (m, 2 H), 5.70–5.77 (m, 1 H), 6.95–6.97 (m, 1 H), 7.08–7.09 (m, 3 H), 7.26(d, *J* = 8.4 Hz, 2 H), 7.65(d, *J* = 8.4 Hz, 2 H).

3-Tosyl-1-vinyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinoline (4b)[27b]

Brown solid; yield: 100 mg (70%); mp 160–162 °C; R_f = 0.50 (hexane/EtOAc 9:1).

IR (KBr, neat): 2921, 2851, 1597, 1458, 1341, 1307, 1163, 1090, 810, 746, 661 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.90 (dd, *J* = 3.5, 7.8 Hz, 1 H), 3.97 (d, *J* = 15.4 Hz, 1 H), 4.06–4.15 (m, 2 H), 4.77 (d, *J* = 15.2 Hz, 1 H), 4.99 (dt, *J* = 1.3, 17.2 Hz, 1 H), 5.19 (dt, *J* = 10.2, 1.2 Hz, 1 H), 6.10–6.17 (m, 1 H), 7.13 (d, *J* = 8.5 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.42–7.52 (m, 2 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.76–7.80 (m, 3 H), 7.93 (d, *J* = 8.4 Hz, 1 H).

8-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4c)

Brown solid; yield: 125 mg (87%); mp 100–102 °C; R_f = 0.45 (hexane/EtOAc 9:1).

IR (KBr, neat): 3070, 2976, 2921, 2849, 1597, 1443, 1352, 1164, 1093, 1058, 950, 814, 779, 662, 549 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.17 (dd, *J* = 6.4, 5.2 Hz, 1 H), 3.38 (dd, *J* = 7.2, 4.4 Hz, 1 H), 3.61–3.64 (m, 1 H), 4.18 (d, *J* = 16.0 Hz, 1 H), 4.24, (d, *J* = 16.0 Hz, 1 H), 5.20 (s, 1 H), 5.19–5.24 (m, 2 H), 7.08 (m, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.19–7.22 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 43.7, 46.4, 48.1, 118.2, 127.6, 127.8, 127.9, 129.7, 130.0, 132.2, 133.1, 137.8, 138.2, 144.1.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}ClNO_2S$ (M + H)$^+$: 348.0820; found: 348.0827.

8-Bromo-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4d)

Brown solid; yield: 109 mg (76%); mp 104–106 °C; R_f = 0.45 (hexane/EtOAc 9:1).

IR (KBr, neat): 3068, 2921, 2853, 1597, 1563, 1438, 1350, 1163, 1091, 958, 813, 661, 550 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.17 (dd, *J* = 6.8, 4.8 Hz, 1 H), 3.37 (dd, *J* = 7.2, 4.4 Hz, 1 H), 3.61–3.64 (m, 1 H), 4.12–4.17 (m, 2 H), 5.22 (d, *J* = 14.0 Hz, 1 H), 5.75–5.83 (m, 1 H), 7.5 (t, *J* = 7.0 Hz, 1 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.75 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 43.9, 48.2, 49.0, 118.2, 122.6, 127.9, 128.3, 128.4, 130.1, 131.0, 131.1, 131.2, 133.1, 138.1, 138.3, 144.2.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}BrNO_2S$ (M + H)$^+$: 392.0320; found: 392.0307.

2-Tosyl-6-(trifluoromethyl)-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4f)

Brown solid; yield: 114 mg (80%); mp 90–92 °C; R_f = 0.45 (hexane/EtOAc 9:1).

IR (KBr, neat): 2927, 2849, 1598, 1458, 1423, 1336, 1166, 1123, 817, 661, 568 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.12 (dd, *J* = 7.0, 4.8 Hz, 1 H), 3.49 (dd, *J* = 4.6, 7.2 Hz, 1 H), 3.68 (dd, *J* = 7.0, 6.6 Hz, 1 H), 4.22 (d, *J* = 15.6 Hz, 1 H), 4.33 (d, *J* = 15.6 Hz, 1 H), 5.24–5.29 (m, 2 H), 5.74–5.84 (m, 1 H), 7.17 (d, *J* = 8.2 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.41–7.43 (m, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 44.4, 50.9, 58.0, 125.8 (q, *J* = 14.6, 15.0 Hz), 126.1, 127.4, 128.7, 130.1, 132.9, 137.0, 140.6, 144.0.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{19}F_3NO_2S$ $(M + H)^+$: 382.1084; found: 382.1106.

6-Bromo-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4g)

White solid; yield: 135 mg (87%); mp 128–130 °C; R_f = 0.66 (hexane/EtOAc 9:1).

IR (KBr, neat): 2972, 2923, 2847, 1479, 1456, 1343, 1162, 1089, 806, 709, 652 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.06 (dd, *J* = 4.8, 6.8 Hz, 1 H), 3.44 (dd, *J* = 6.8, 5.2 Hz, 1 H), 3.58–3.62 (m, 1 H), 4.09 (d, *J* = 15.2 Hz, 1 H), 4.22 (d, *J* = 15.2 Hz, 1 H), 5.22–5.26 (m, 2 H), 5.71–5.80 (m, 1 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 7.26–7.29 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 43.5, 47.6, 48.4, 77.6, 118.7, 120.8, 127.9, 128.2, 130.0, 130.1, 130.6, 132.0, 133.1, 137.6, 137.8, 144.1.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}BrNO_2S$ $(M + H)^+$: 392.0320; found: 392.0311.

7-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4h)

Brown solid; yield: 50 mg (34%); mp 80–81 °C; R_f = 0.55 (hexane/EtOAc 9:1).

IR (KBr, neat): 2976, 2922, 2856, 1597, 1458, 1352, 1164, 1091, 964, 814, 753, 670, 586 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.11 (dd, *J* = 7.2, 4.8 Hz, 1 H), 3.43 (dd, *J* = 4.8, 7.2 Hz, 1 H), 3.59 (dd, *J* = 6.8, 6.0 Hz, 1 H), 4.13 (d, *J* = 15.2 Hz, 1 H), 4.23 (d, *J* = 15.2 Hz, 1 H) 5.21–5.23 (m, 2 H), 5.72–5.81 (m, 1 H), 7.03 (s, 1 H), 7.06–7.14 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 43.2, 47.7, 48.2, 118.3, 126.4, 127.4, 128.0, 130.0, 130.6, 132.7, 133.3, 133.8, 138.2, 144.2.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$: 348.0820; found: 348.0819.

5-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4h')

Brown solid; yield: 48 mg (33%); mp 108–110 °C; R_f = 0.50 (hexane/EtOAc 9:1).

IR (KBr, neat): 2921, 2850, 1596, 1458, 1444, 1351, 1165, 1091, 956, 816, 777, 657, 549 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.74 (dd, *J* = 3.4, 8.2 Hz, 1 H), 3.76–3.84 (m, 2 H), 3.99 (d, *J* = 11.6 Hz, 1 H), 4.66 (d, *J* = 15.2 Hz, 1 H), 4.99 (d, *J* = 17.2 Hz, 1 H), 5.17 (d, *J* = 10.28 Hz, 1 H), 5.92–6.00 (m, 1 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H) 7.34 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 40.4, 47.4, 48.4, 117.4, 125.3, 127.9, 128.0, 128.1, 128.3, 130.0, 133.2, 133.0, 133.9, 134.9, 137.1, 144.1.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$: 348.0820; found: 348.0829.

6-Chloro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4i)

White solid; yield: 125 mg (92%); mp 133–135 °C; R_f = 0.66 (hexane/EtOAc 9:1).

IR (KBr, neat): 2925, 1843, 1639, 1597, 1486, 1457, 1345, 1162, 1093, 1050, 811, 772, 684, 658, 575 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.99 (dd, *J* = 4.4, 7.2 Hz 1 H), 3.38 (dd, *J* = 6.8, 4.8 Hz 1 H), 3.53 (dt, *J* = 6.0, 7.2 Hz, 1 H), 4.05 (d, *J* = 14.8 Hz, 1 H), 4.17 (d, *J* = 14.8 Hz, 1 H), 5.15–5.19 (m, 2 H), 5.65–5.72 (m, 1 H), 6.9 (d, *J* = 8.8 Hz, 1 H), 7.06–7.08 (m, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 43.6, 47.6, 48.5, 118.7, 127.3, 127.9, 128.0, 129.0, 130.0, 130.1, 133.0, 137.2, 137.8, 144.2.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}ClNO_2S$ $(M + H)^+$: 348.0825; found: 348.0834.

5,7-Difluoro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4j)

Brown solid; yield 105 mg (73%); mp 128–130 °C; R_f = 0.45 (hexane/EtOAc 9:1).

IR (KBr, neat): 3084, 2923, 2853, 1627, 1598, 1489, 1441, 1344, 1161, 1118, 994, 949, 850, 815, 765, 664, 554 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.80 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.68–3.71 (m, 1 H), 3.78 (d, *J* = 15.6 Hz, 1 H), 3.85 (d, *J* = 12.0 Hz, 1 H), 4.59 (d, *J* = 15.6 Hz, 1 H), 5.07 (dd, *J* = 16.4, 1.0 Hz, 1 H), 5.14 (d, *J* = 10.4 Hz, 1 H), 5.93–5.98 (m, 1 H), 6.60–6.68 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 36.7, 47.4, 48.1, 102.6 (t, *J* = 25.0 Hz) , 108.8 (q, *J* = 18.2 Hz), 116.7, 119.2, 119.3, 127.9, 130.0, 133.0, 135.0, 135.1, 137.5, 144.2, 161.2 (dd, *J* = 248.5, 12.2 Hz), 161.7 (dd, *J* = 246.2, 12.8 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}F_2NO_2S$ $(M + H)^+$: 350.1026; found: 350.1037.

8-Bromo-5-fluoro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4k)

Yellow solid; yield: 110 mg (77%); mp 120–123 °C; R_f = 0.50 (hexane/EtOAc 9:1).

IR (KBr, neat): 2923, 2853, 1597, 1456, 1354, 1339, 1254, 1165, 1091, 1028, 955, 814, 773, 658, 549 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.73 (dd, *J* = 11.8, 3.5 Hz, 1 H), 3.62 (d, *J* = 14.8 Hz, 1 H), 3.75–3.78 (m, 1 H), 3.89 (d, *J* = 11.8 Hz, 1 H), 4.64 (d, *J* = 16.2 Hz, 1 H), 5.09 (d, *J* = 17.2 Hz, 1 H), 5.17 (d, *J* = 10.2 Hz, 1 H), 5.97–6.03 (m, 1 H), 6.83 (t, *J* = 8.8 Hz, 1 H), 7.35–7.40 (m, 3 H), 7.75 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.8, 37.4, 47.6, 48.8, 115.4 (d, *J* = 23.0 Hz), 116.6, 116.64, 117.2, 126.0 (d, *J* = 18.5 Hz), 128.0, 130.1, 131.9 (d, *J* = 8.5 Hz), 133.2 (d, *J* = 9.1 Hz), 137.2, 144.2, 160.1 (d, *J* = 246.4 Hz).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}BrFNO_2S$ $(M + H)^+$: 410.0221; found: 410.0241.

6-Fluoro-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4l)

Yellow solid; yield: 125 mg (81%); mp 92–94 °C; R_f = 0.6 (hexane/EtOAc 9:1).

IR (KBr, neat): 2972, 2923, 2847, 1479, 1456, 1343, 1162, 1089, 806, 709, 652 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.05 (dd, *J* = 7.2, 4.4 Hz, 1 H), 3.59–3.61 (m, 1 H), 3.61 (dd, *J* = 7.2, 5.6 Hz, 1 H), 4.11 (d, *J* = 14.8 Hz, 1 H), 4.26 (d, *J* = 14.8 Hz, 1 H), 5.22–5.26 (m, 2 H), 5.74–5.79 (m, 1 H), 6.84–6.89 (m, 2 H), 6.99–7.02 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 43.7, 47.6, 48.4, 114.3 (d, *J* = 21.7 Hz), 115.5 (d, *J* = 21.6 Hz), 118.6, 127.1, 127.2, 127.9, 128.0, 128.1, 129.9, 133.2, 137.5, 137.9, 144.1, 161.7 (d, *J* = 243.9 Hz);

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}FNO_2S$ $(M + H)^+$: 332.1121; found: 332.1115.

6-Methyl-2-tosyl-4-vinyl-1,2,3,4-tetrahydroisoquinoline (4m)

White gum; yield: 100 mg (62%); R_f = 0.50 (hexane/EtOAc 9:1).

IR (KBr, neat): 2976, 2922, 2856, 1597, 1458, 1352, 1164, 1091, 964, 814, 753, 670, 586 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 2.41 (s, 3 H), 3.12 (dd, *J* = 7.2, 4.4 Hz, 1 H), 3.41 (dd, *J* = 4.8, 6.8 Hz, 1 H), 3.58 (dd, *J* = 7.2, 5.6 Hz, 1 H), 4.10–4.24 (m, 2 H), 5.17–5.23 (m, 2 H), 5.76–5.86 (m, 1 H), 6.91–6.96 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.7, 43.6, 47.8, 48.8, 117.6, 126.4, 127.8, 127.9, 128.5, 129.5, 129.9, 133.3, 135.1, 136.7, 138.8, 143.9.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{22}NO_2S$ $(M + H)^+$: 328.1371; found: 328.1381.

(*E*)-4-Styryl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (4o)

White gum; yield 35 mg (78%); R_f = 0.55 (hexane/EtOAc 4:1).

IR (KBr, neat): 2925, 2916, 2867, 1357, 1124, 1056, 912, 845, 746, 660 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 3.14 (dd, *J* = 11.8, 7.2 Hz, 1 H), 3.57 (dd, *J* = 11.8, 6.0 Hz, 1 H), 3.82 (dd, *J* = 12.8, 7.2 Hz, 1 H), 4.20 (d, *J* = 15.0 Hz, 1 H), 4.36 (d, *J* = 15.0 Hz, 1 H), 6.15 (dd, *J* = 15.8, 8.7 Hz, 1 H), 6.57 (d, *J* = 15.8 Hz, 1 H), 7.06–7.08 (m, 1 H), 7.16–7.26 (m, 4 H), 7.28–7.36 (m, 6 H), 7.73 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 43.0, 48.0, 49.0, 126.6 (2 C), 127.1, 127.2, 127.8, 128.0, 128.8, 129.3, 130.0, 130.1, 131.6, 132.9, 133.3, 135.6, 137.0, 143.9.

Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60. Found: C, 74.09; H, 5.98; N, 3.53.

2-(2-Tosyl-1,2,3,4-tetrahydroisoquinolin-4-yl)ethanol (5)

To a septum-capped round-bottomed flask charged with anhyd THF (15 mL) was added $NaBH_4$ (185 mg, 4.75 mmol). I_2 (360 mg, 2.85 mmol) in anhyd THF (10 mL) was then added under N_2 atmosphere at 0 °C and the reaction mixture was stirred for 2 h. A THF solution of compound **4a** (600 mg, 1.9 mmol) was added and the mixture was stirred for 12 h at 25 °C. The mixture was quenched with H_2O (2 mL) and THF (10 mL) and oxidized with 30% H_2O_2 [10 mL/aq NaOH (3 N, 10 mL)]. The organic layer was extracted with Et_2O (2 × 30 mL) and the combined organic layers were washed with brine, and dried (anhyd Na_2SO_4). Evaporation of solvent and purification by column chromatography gave the desired compound **5** as a white solid; yield: 470 mg (75%); mp 117–119 °C; R_f = 0.55 (hexane/EtOAc 3:2).

IR (KBr, neat): 3425, 2926, 2857, 1644, 1598, 1455, 1337, 1163, 1090, 1034, 949, 812, 669, 553 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.81 (s, 1 H), 1.87–1.95 (m, 1 H), 2.02–2.10 (m, 1 H), 2.42 (s, 3 H), 2.78 (dd, *J* = 8.4, 3.6 Hz, 1 H), 3.06–3.12 (m, 1 H), 3.76–3.89 (m, 4 H), 4.61 (d, *J* = 14.8 Hz, 1 H), 7.01–7.03 (m, 1 H), 7.12–7.17 (m, 3 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 7.73 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.7, 35.5, 38.1, 47.1, 47.8, 60.6, 126.6, 126.7, 127.0, 127.9, 129.1, 130.0, 131.4, 133.2, 137.7, 144.0.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{22}NO_3S$ $(M + H)^+$: 332.1320; found: 332.1330.

2-(1,2,3,4-Tetrahydroisoquinolin-4-yl)ethanol (6)

To a solution of **5** (180 mg, 0.48 mmol) in anhyd MeOH was added Mg turnings (230 mg, 9.6 mmol) and the reaction mixture was stirred under sonication for 5 h at rr.t. After the completion of the reaction, the mixture was quenched with brine, and extracted with $CHCl_3$. The combined organic layers were dried (anhyd Na_2SO_4) and concentrated in vacuo. The product was purified by column chromatography on silica gel (DCM/MeOH 9:1) to give **6** as a colorless oil; yield: 56 mg (67%); R_f = 0.55 (DCM/MeOH 9:1).

IR (KBr, neat): 3383, 2924, 2854, 1730, 1641, 1462, 1376, 1283, 909, 761, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.02 (m, 1 H), 2.07–2.013 (m, 1 H), 3.26–3.38 (m, 3 H), 3.49 (d, *J* = 11.8 Hz, 1 H), 3.62–3.67 (m, 1 H), 4.19 (d, *J* = 16.0 Hz, 1 H), 4.32 (d, *J* = 16.0 Hz, 1 H), 6.90 (br s, 2 H), 7.04 (d, *J* = 7.4 Hz, 1 H), 7.12–7.21 (m, 3 H)

^{13}C NMR (150 MHz, $CDCl_3$): δ = 35.6, 39.5, 46.8, 47.9, 57.7, 126.7, 126.8, 127.3, 129.1, 133.2, 135.5.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}NO$ $(M + H)^+$: 178.1227; found: 178.1238.

Funding Information

This work was supported by Council of Scientific & Industrial Research (CSIR), New Delhi (grant no. 02(0364)/19/EMR-II).

Acknowledgment

N.R.D. gratefully acknowledges the Indian Institute of Technology Guwahati for her fellowship. The authors are also thankful to the Central Instrument Facility (CIF) of IIT Guwahati for NMR facilities and X-ray crystallography.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610750.

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