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A simple efficient sequential one-pot intermolecular aza-Michael addition and intramolecular Buchwald–Hartwig α-arylation of amines: synthesis of functionalized tetrahydroisoquinolines

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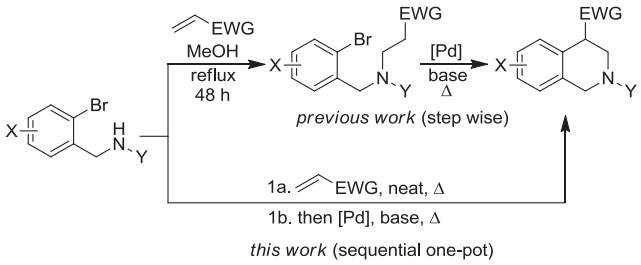
ABSTRACT

An efficient one-pot sequential intermolecular aza-Michael addition and Pd-catalyzed intramolecular Buchwald–Hartwig α-arylation of secondary amines have been investigated, for the synthesis of tetrahydroisoquinolines. This method is simple and furnished products in very good yield and also successfully applied for the synthesis of novel aza-spirotricylcic ethers.

1. Introduction

One-pot synthetic processes are considered as convenient methods to synthesize organic molecules with high degree of complexity, without isolating intermediates.[1] Such one-pot processes could be made possible using one metal complex to catalyze multiple reaction sequence,[2] or various metal catalysts could be added in a sequential manner to achieve multiple reaction sequence.[3] These types of reactions have been called as multi catalytic cascades, pseudo domino strategies, and tandem catalysis. These processes proved to have several advantages over step-wise operations, as it avoids the isolation of intermediate species, thereby considerably reducing the waste generation, increasing efficiency, minimizing the use of solvents, reagents, time, and energy.[4] Moreover, it was also found that in most cases the overall yields in one-pot processes are usually higher than those obtained from the corresponding step-wise operations. Those one-pot process that form multiple C–C bonds and cyclic structures are of great interest, as complex cyclic structures are part of the core structure in many biologically active natural products.

Recently, transition metal catalyzed one-pot processes are gaining much importance due to several procedural advantages.[5,6] Since, most Pd-catalyzed transformations are promoted by base, one-pot processes involving both base promoted and Pd-catalyzed transformations would also be an ideal choice. In continuation of our interest in the development of palladium-catalysis,[7] we recently reported an efficient step-wise strategy for the synthesis of tetrahydroisoquinolines using Pd-catalyzed intramolecular Buchwald–Hartwig α-arylation.[7a] As an extension of our step-wise method, herein we report an efficient one-pot sequential strategy for the synthesis of tetrahydroisoquinolines. Unlike our previous report, the present work is based on an efficient one-pot sequential intermolecular aza-Michael addition–Pd-catalyzed intramolecular α-arylation starting from secondary amines. Moreover, the present strategy has been extensively studied on various secondary amines bearing simple to electron rich aromatic rings and also on different Michael acceptors (Scheme 1).



Scheme 1. Comparison of present one-pot versus previous step-wise processes of our access to tetrahydroisoquinolines.

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1,2,3,4-Tetrahydroisoquinoline moiety is a ubiquitous structural core present in a number of isoquinoline alkaloid natural products,[8] which exhibit very good biological activities, such as antitumor,[9] anti-microbial,[9,10] anti-inflamatory,[11] anti-HIV,[12] and anti-analgesic[13] activities. Representative examples of such structures are cherylline, latifine,[14,15] nor-armepavine, nor-roefractine,[16,17] 6,6a-dihydrodemethoxygaudiscine,[18] dinapsoline,[19] and canadine,[20] (Fig. 1).

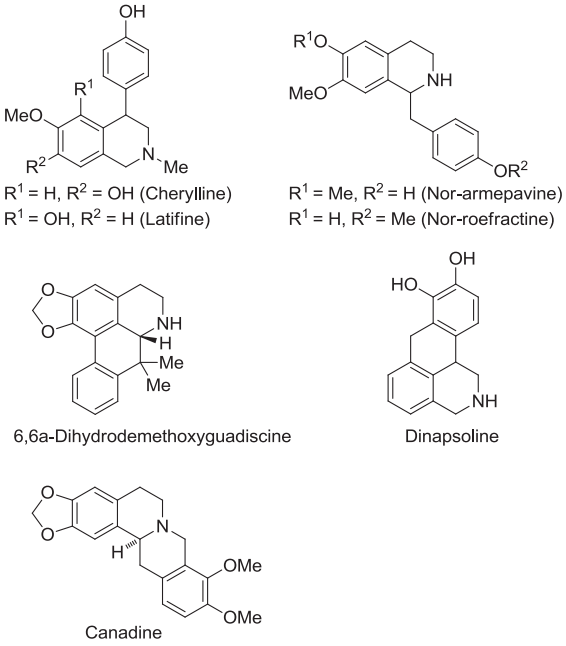


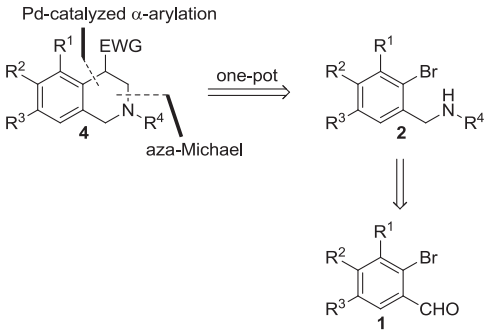
Fig. 1. Representative examples of naturally occurring tetrahydroisoquinoline alkaloid natural products.

Highlighting the importance of transition metal catalysis, as an alternative to Pictet–Spengler reaction for the synthesis of tetrahydroisoquinoline,[21] Hartwig et al., reported the synthesis of a δ-lactam using Pd-mediated intramolecular α-arylation, albeit in poor yield.[22a] Later the research group of Honda improved the strategy, by incorporating an α-aryl group to the amide, thereby increasing the acidity of α-hydrogen atom.[22b] Buchwald and Gaertzen, disclosed Pd-catalyzed α-arylation on esters, wherein ester functionality resides on α-carbon to the nitrogen atom.[22c] Very recently, Daniel Solé et al., reported amino-tethered 2- and 3-iodoindoles.[22d] Our approach was based on one-pot sequential intermolecular aza-Michael addition and intramolecular Buchwald–Hartwig α-arylation of (*N*-2-bromobenzyl)-β-amino-esters, in which the ester functionality is connected to a β-carbon to the nitrogen atom.

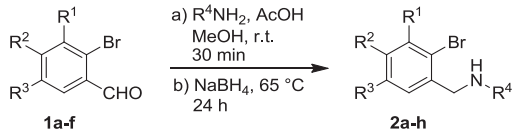
2. Results and discussion

Our approach for the synthesis of substituted 1,2,3,4-tetrahydroisoquinolines **4** is based on a key one-pot aza-Michael–Pd-mediated α-arylation of secondary amine **2**. The required precursors **2** could be obtained from the readily available *ortho*-bromobenzaldehydes **1** by a reductive amination (Scheme 2).

Accordingly, treatment of 2-bromobenzaldehydes **1a**–**f**[23] with benzylamine in refluxing methanol in the presence of a catalytic amount of acetic acid followed by addition of sodium borohydride, led to the secondary amines **2a**–**h** in very good (74–94%) yields (Scheme 3, Table 1).[7a]



Scheme 2. Retrosynthetic analysis for 1,2,3,4-tetrahydroisoquinolines.



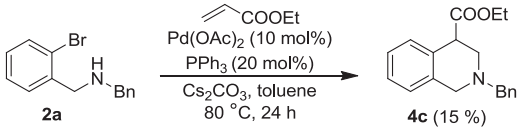
Scheme 3. Synthesis of secondary amines **2a**–**h** using bromobenzaldehydes **1a**–**f**.

Table 1
Synthesis of secondary amine **2a**–**h**[a]

Aldehyde **1**	R^1	R^2	R^3	R^4	Yield of **2**[b] (%)
1a	H	H	H	Bn	**2a** 94
1b	H	OMe	OMe	Bn	**2b** 91
1c	OMe	OMe	OMe	Bn	**2c** 91
1d	H	H	OMe	Bn	**2d** 93
1e	H	OCH_2–	OCH_2–	Bn	**2e** 93
1f	H	H	OBn	Bn	**2f** 74
1a	H	H	H	Me	**2g** 83
1e	H	OCH_2–	OCH_2–	Me	**2h** 74

[a] In case of methylamine, reaction was performed at ice to room temperature and without acetic acid.
[b] Isolated yields of chromatographically pure products.

With the secondary amines **2a**–**h** in hand, initially the key one-pot aza-Michael–Pd-mediated α-arylation of secondary amine **2a** was performed by concomitant addition of both reagent Michael acceptor ethyl acrylate and the palladium catalyst, using similar conditions to that used for Pd-mediated Buchwald–Hartwig α-arylation reaction reported in our previous report. To our disappointment, the outcome was not satisfactory and produced the product **4c**, in very poor yield 15% (Scheme 4). Inferior yield of product may be attributed to a competitive palladium insertion to C–Br bond of the aryl halide prior to aza-Michael addition.



Scheme 4. Attempted one-pot aza-Michael–Pd-mediated α-arylation of secondary amine **2a** by concomitant addition of Michael acceptor ethyl acrylate and Pd-catalyst.

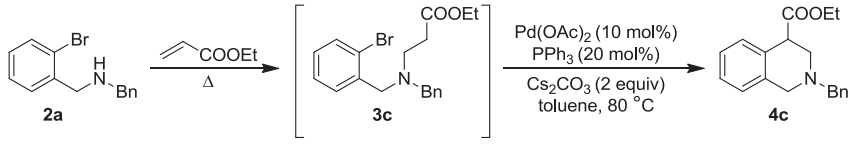
Since one-pot aza-Michael–Pd-mediated α-arylation was found to be inferior by concomitant addition of both reagent Michael acceptor ethyl acrylate and the palladium catalyst, we thought that it may be better, in the first stage to optimize aza-Michael addition reaction and then in situ treatment of the ester intermediate **3c** for subsequent Pd-catalyzed α-arylation. At this stage, it is important to identify suitable conditions for aza-Michael that should also be amenable to subsequent Pd-catalyzed C–H activation, preferably using established conditions for subsequent Pd-catalyzed C–H activation (toluene and Cs_2CO_3 as solvent and base, respectively).[7a]

Thus, aza-Michael addition was explored with Cs_2CO_3 as the base and toluene as aprotic, nonpolar solvent under varying temperature (50–100 °C) conditions. Discouragingly, all these trials furnished the product **3c**, in poor to moderate yields (10–45%) (entries 1–4, Table 2). A similar outcome was observed by omitting base and just heating the reaction mixture at 100 °C in toluene (entries 5 and 6, Table 2). Interestingly, an increment in yield was observed by replacing the solvent toluene with xylene at high temperature 130 °C (entry 7, Table 2). On the other hand, treatment of neat compound under microwave irradiation was also found to be inferior (entry 9, Table 2). Heating the secondary amine **2a** with Michael acceptor (1.5 equiv) without the solvent as well as the base, furnished the product in poor yield (entry 8, Table 2). Low conversion to intermediate **3c** may be attributed to lower boiling point of Michael acceptor ethyl acrylate (100 °C). Therefore, we thought that excess amount of ethyl acrylate might help us to improve yield of **3c**. To our delight, reaction with 5 equiv of ethyl acrylate at 110 °C for 48 h, showed 100% conversion to the addition product **3c**, which on in situ Pd-catalyzed α-arylation, gave us the final cyclized product **4c**, albeit in moderate yield 43% (entry 10, Table 2). Moderate yield of the product **4c**, may be justified due to the intermolecular interference of excess ethyl acrylate with the intermediate aryl-Pd-species. Therefore, in order to minimize the intermolecular interaction with the excess ethyl acrylate, we thought that increasing dilution might help us to improve the yield of product **4c**. Thus the reaction with high dilution slightly improved the yield (entry 11, Table 2), but still the presence of interference due to excess ethyl acrylate remained. Finally, we decided to remove excess ethyl acrylate in order to avoid its interference with aryl-Pd-species. Gratifyingly, simple removal of excess ethyl acrylate under vacuum (10^{-2} mbar) and then subjecting reaction mixture to subsequent Pd-catalyzed α-arylation, furnished the product **4c** in very good yield 77%. It is noteworthy to mention that when aza-Michael reaction was conducted on amine **2a**, reaction time reduced from 48 to 24 h, with 5 equiv of ethyl acrylate (entry 12, Table 2). Though, in the present one-pot process, the yield (77%) of **4c** appears less than that obtained from the stepwise Pd-catalyzed α-arylation of previous report (88% and 82% for reductive amination and Pd-catalyzed α-arylation, respectively, overall yield 72%),[7a] still proved to be better with regards to its overall yield.

After optimizing the reaction conditions, the generality of the reaction was established by a one-pot sequential aza-Michael–Pd-catalyzed α-arylation on various secondary amines **2** using different alkyl acrylates to give the tetrahydroisoquinolines **4**. In general, these results were fairly comparable to that obtained for the secondary amine **2a**, and furnished the tetrahydroisoquinolines **4** possessing simple as well as electron rich aromatic functionality on aromatic rings, in very good yields (Table 3). It was observed that aza-Michael reaction was completed in 24 h in case of ethyl and methyl acrylates, whereas *tert*-butyl acrylate took up to 48 h and subsequent Pd-catalyzed α-arylation was completed in 24–48 h.

Finally, to check the scope and applicability of the method for further extensions, we explored the synthesis of novel 2-benzyl-2,3,4′,7′-tetrahydro-1*H*-spiro[isoquinoline-4,3′-oxepine] system. Spiro-cyclic systems are recognized as useful fragments for drug discovery and exhibit good biological properties. Moreover, spiro-cyclic systems are described as privileged scaffolds because they have been successfully employed as ligands for a variety of targets.[24] We envisioned that target spiro-system can be achieved via C-alkylation of the cyclic ester **4c**, reduction of the ester moiety, O-allylation, and finally ring closing metathesis protocol. Thus, allylation of the ester enolate prepared by lithium diisopropyl amide (LDA), gave the alkylated product **5**, in very good yield. Reduction of the ester with lithium aluminum hydride ($LiAlH_4$), furnished the primary alcohol **6** in excellent yield. Base induced O-allylation transformed the hydroxyl group to the corresponding allyl ether **7**. Finally, ring closing metathesis reaction of the diene **7** with 5 mol % of Grubb's first generation catalyst in methylene chloride at room temperature, smoothly furnished the target spiro-tricyclic system **8**, in very good yield (Scheme 5).

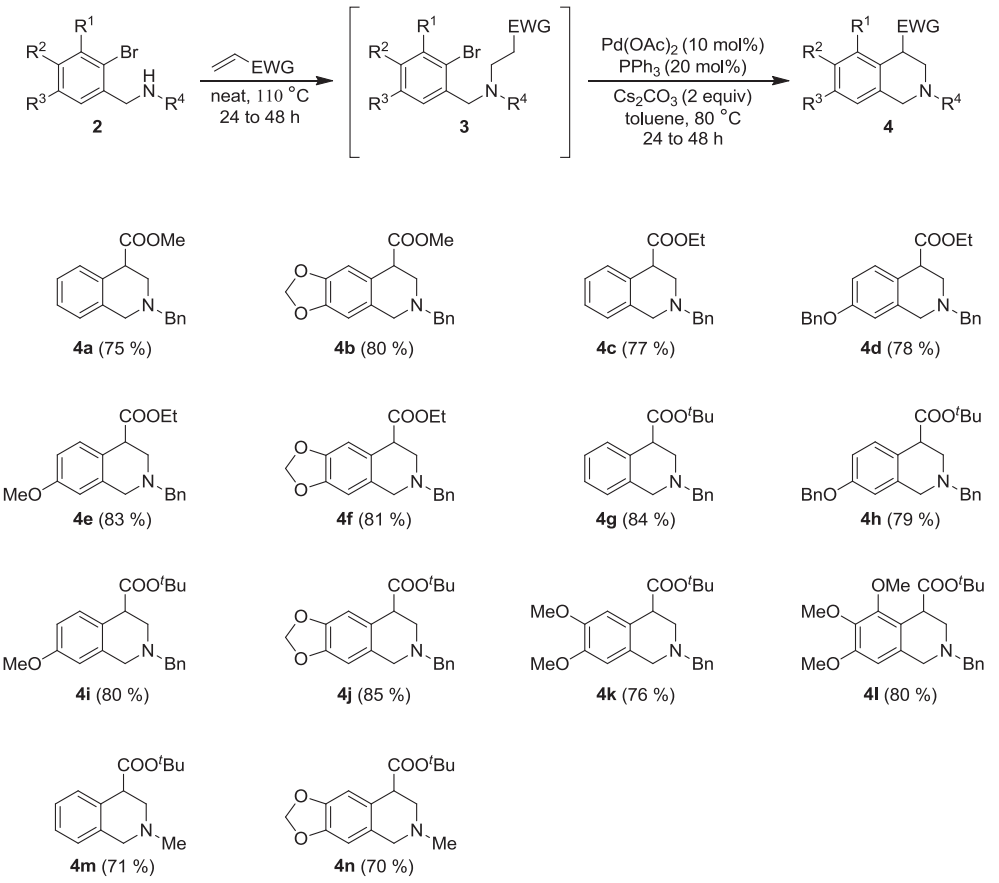
Table 2
Attempted optimization one-pot reaction conditions for the synthesis of 1,2,3,4-tetrahydroisoquinolines



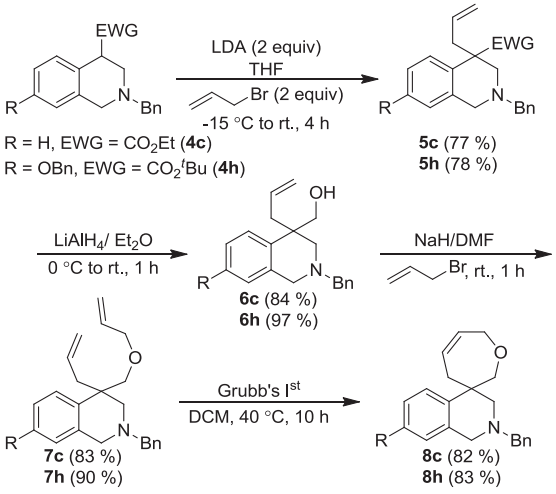
Entry	Reaction conditions for aza-Michael addition						Reaction conditions for Pd-catalyzed α-arylation		
	Ethyl acrylate (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield of **3** (%)	Toluene (mL)	Time (h)	Yield of **4**[h] (%)
1[a]	1.5	Cs_2CO_3	Toluene	80	48	10	—	—	—
2[a]	5	Cs_2CO_3	Toluene	50	24	18	—	—	—
3[a]	5	Cs_2CO_3	Toluene	50	48	30	—	—	—
4[a]	5	Cs_2CO_3	Toluene	100	48	45	—	—	—
5[a]	1.5	—[c]	Toluene	100	48	10	—	—	—
6[a]	5	—[c]	Toluene	100	48	40	—	—	—
7[a]	5	—[c]	Xylene	130	48	60	—	—	—
8[a]	1.5	—[d]	—	110	48	30	—	—	—
9[a]	5	—[d]	—	80 (μw)	1	25	—	—	—
10[b]	5	—[d]	—	110	48	100[e]	4	24	43
11[b]	5	—[d]	—	110	48	100[e]	8	48	48
12[b]	5	—[d]	—	110	24	100[fg]	3	24	77

[a] Isolated yields of chromatographically pure product **3c** and not subjected to the subsequent Pd-catalyzed α-arylation.
[b] The product **3c** was not isolated and the complete conversion of secondary amine **2a** to product **3c** was confirmed by TLC.
[c] Base omitted in these attempts.
[d] Both base and solvent omitted in these entries, only neat reaction conditions were employed.
[e] Reaction was performed on 100 mg scale of secondary amine **2a**.
[f] Reaction performed on 1 mmol scale of secondary amine **2a**.
[g] Excess ethyl acrylate was removed under vacuum (0.02 mbar) just before the addition of Pd-catalyst, base and solvent, for subsequent Pd-catalyzed α-arylation.
[h] Isolated yields of chromatographically pure product **4c**.

Table 3
One-pot sequential aza-Michael–Pd-catalyzed α-arylation for the synthesis of 1,2,3,4-tetrahydroisoquinolines **4** starting from amines **2**[a,b]



[a] For details see Supplementary data.
[b] Isolated yields of chromatographically pure products.



Scheme 5. Synthesis of spiro-tricyclic system **8** from **4**.

3. Conclusion

In summary, we have developed an efficient route to the synthesis of functionalized 1,2,3,4-tetrahydroisoquinolines based on one-pot sequential intermolecular aza-Michael addition and Pd-catalyzed intramolecular Buchwald–Hartwig α-arylation of secondary amines. An optimized method was developed for an intermolecular aza-Michael addition to generate β-aminoesters, which were not isolated and subjected to subsequent Pd-catalyzed intramolecular α-arylation. The strategy is very efficient and amenable for the synthesis of a number of analogues, a structural core present in many tetrahydroisoquinoline based alkaloid natural products, which exhibit very good biological activities. Moreover, the present method has been successfully applied for the synthesis of novel 2-benzyl-2,3,4′,7′-tetrahydro-1*H*-spiro[isoquinoline-4,3′-oxepine] system.

4. Experimental section

4.1. General

IR spectra were recorded on Bruker Tensor 37 (FTIR) and BrukerALPHA (FTIR) spectrophotometers. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H=0.00 ppm) or $CHCl_3$ (δ_H=7.25 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at room temperature in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CDCl_3$ [δ_C=77.00 ppm (central line of triplet)]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s=singlet (for C), d=doublet (for CH), t=triplet (for CH_2), and

q=quartet (for CH_3). In the ^1H NMR, the following abbreviations were used throughout: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, m=multiplet, and br s=broad singlet. The assignment of signals was confirmed by ^1H, ^{13}C CPD, and DEPT spectra. High-resolution mass spectra (HRMS) were recorded using Agilent 6538 UHD Q-TOF using multimode [electron spray ionization (ESI^+) and atmospheric pressure chemical ionization ($APCI^+$)] source. All small scale dry reactions were carried out using Schlenk tube and standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under inert (argon or a nitrogen) atmosphere. Solvents: toluene, tetrahydrofuran (THF), and diethyl ether were dried over sodium metal wire, whereas dimethylformamide (DMF) and dichloromethane (DCM) were dried over calcium hydride prior to use. Solvents: petroleum ether, ethyl acetate, dichloromethane, methanol were distilled prior to use; petroleum ether with a boiling range of 60–80 °C was used. Methylamine was used as 25% CH_3NH_2 in methanol. Ethyl acrylate (with purity 99.5%) was purchased from Sigma–Aldrich, whereas methyl acrylate (with purity 99%) and *tert*-butyl acrylate (with purity 98%) were purchased from other commercial sources and used as received. All benzaldehydes (with purity 98%) in order to make corresponding 2-bromobenzaldehydes [except 2-bromobenzaldehyde, which was commercially available (with purity 98%)] were purchased from commercial sources and used as received. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per 1 g of crude material).

4.2. General procedure-1 [for sequential one-pot reaction, for the synthesis of tetrahydroisoquinoline (4)]

To an oven dried Schlenk tube, were added amine **2** (1 mmol) and alkyl (ethyl or methyl or *tert*-butyl) acrylate (5 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 110 °C in an oil bath, for 24 h (in case of methyl as well as ethyl acrylates) and for 48 h (in case of *tert*-butyl acrylate). Progress of the Michael addition was monitored by TLC. The reaction mixture was allowed to attain room temperature, and excess of alkyl acrylate was removed under vacuum (10^{-2} mbar). To the resultant reaction intermediate (i.e., Michael addition product **3**) at room temperature, were added $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and Cs_2CO_3 (2 mmol) followed by toluene (3 mL) under nitrogen atmosphere. The reaction mixture was then allowed to stir at 80 °C for 24 h (in case of **4a**–**c** and **4f**), 36 h (in case of **4d**, **4e**, **4g**, **4i**, **4j** and **4l**–**n**), and 48 h (in case of **4h** and **4k**) in an oil bath and the progress was monitored by TLC. The mixture was cooled to room temperature, treated with aqueous NH_4Cl solution and then extracted with ethyl acetate (3×15 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the tetrahydroisoquinoline **4** (70–85%).

Secondary amines **2a**–**f**,[7a] **2g**,[25] and tetrahydroisoquinolines **4c**–**f**[7a] were already known in the literature.

4.3. *N*-[(6-Bromo-1,3-benzodioxol-5-yl)methyl]-*N*-methylamine (2h)

To an ice cold round bottomed flask containing 2-bromo piperanal **1e** (1.5 g, 6.55 mmol), were added methanol (25 mL) followed by methylamine (609 mg, 19.65 mmol). The reaction mixture was allowed to stir at the same temperature for 1 h. To this ice cold reaction mixture, was added sodium borohydride (374 mg, 9.82 mmol), slowly allowed to attain room temperature, and stirred for an additional 3 h. Solvent was removed under reduced pressure, treated with aqueous NH_4Cl solution, and extracted with ethyl acetate (3×20 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 10:90 to 90:10) furnished the amine **2h** (1.18 g, 74%) as viscous liquid [TLC control (ethyl acetate/methanol 90:10), R_f (**1e**)=0.90, R_f (**2h**)=0.35, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3291, 2893, 1501, 1473, 1408, 1389, 1369, 1230, 1114, 1033, 929, 859, 830, 786, 719, 673, 650 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=6.96 (s, 1H, Ar–H), 6.86 (s, 1H, Ar–H), 5.93 (s, 2H, OCH_2O), 3.71 [s, 2H, Ar–CH_2N(H)Me], 2.50 (br s, 1H, NH), 2.40 (s, 3H, NCH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=147.3 (s, Ar–C), 147.3 (s, Ar–C), 131.7 (s, Ar–C), 114.2 (s, Ar–C), 112.6 (d, Ar–CH), 110.1 (d, Ar–CH), 101.6 (t, OCH_2O), 55.2 [t, $ArCH_2N(H)Me$], 35.4 (q, NCH_3) ppm. HRMS ($APCI^+$) *m*/*z* calculated for $[C_9H_9BrNO_2]^+$=$[M-H]^+$: 241.9811; found 241.9802.

4.4. *tert*-Butyl 2-methyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4m)

GP-1 was followed for the amine **2a** (200 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 36 h. Then treated with $Pd(OAc)_2$ (22.4 mg, 10 mol %), PPh_3 (52.4 mg, 20 mol %), and Cs_2CO_3 (651.6 mg, 2 mmol) in toluene (3 mL) at 80 °C, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20 to 60:40) furnished the tetrahydroisoquinoline **4m** (175 mg, 71%) as colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 20:80), R_f (**2g**)=0.15, R_f (**4m**)=0.45, iodine chamber detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2934, 2773, 1724, 1453, 1367, 1274, 1246, 1138, 1101, 1033, 969, 850, 745 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.19 (dd, 1H, *J*=4.9 and 3.4 Hz, Ar–H), 7.10 (d, 1H, *J*=3.4 Hz, Ar–H), 7.08 (d, 1H, *J*=3.4 Hz, Ar–H), 6.96 (dd, 1H, *J*=4.9 and 3.4 Hz, Ar–H), 3.74 (dd, 1H, *J*=6.5 and 5.9 Hz, $CHCOO^tBu$), 3.58 [d, 1H, *J*=14.9 Hz, N–CH_2(a,b)], 3.44 [d, 1H, *J*=14.9 Hz, N–CH_2(a,b)], 2.91 (dd, 1H, *J*=11.5 and 6.5 Hz, N–$CH_{2a}CHCOO^tBu$), 2.76 (dd, 1H, *J*=11.5 and 5.3 Hz, N–$CH_{2b}CHCOO^tBu$), 2.37 (s, 3H, NCH_3), 1.40 [s, 9H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.3 (s, O=C–O), 134.9 (s, Ar–C), 131.3 (s, Ar–C), 128.9 (d, Ar–CH), 126.6 (d, Ar–CH), 126.5 (d, Ar–CH), 126.2 (d, Ar–CH), 80.9 [s, $COOC(CH_3)_3$], 57.9 (t, N–CH_2), 55.4 (t, N–CH_2), 45.9 (q, NCH_3), 45.8 (d, $CHCOO^tBu$), 28.0 [q, 3C, $C(CH_3)_3$] ppm. HRMS ($APCI^+$) *m*/*z* calculated for $[C_{15}H_{22}NO_2]^+$=$[M+H]^+$: 248.1645; found 248.1646.

4.5. *tert*-Butyl 6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline-8-carboxylate (4n)

GP-1 was followed for the amine **2h** (244 mg, 1 mmol) with *tert*-butyl acrylate (640 mg, 5 mmol) at 110 °C for 48 h. Then treated with $Pd(OAc)_2$ (22.4 mg, 10 mol %), PPh_3 (52.4 mg, 20 mol %), and Cs_2CO_3 (651.6 mg, 2 mmol) in toluene (3 mL) at 80 °C, for 36 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20 to 55:45) furnished the tetrahydroisoquinoline **4n** (204 mg, 70%) as pale yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 20:80), R_f (**2h**)=0.12, R_f (**4n**)=0.43, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2974, 2935, 2789, 1725, 1504, 1483, 1390, 1367, 1250, 1238, 1145, 1125, 1035, 938, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=6.71 (s, 1H, Ar–H), 6.48 (s, 1H, Ar–H), 5.89 (d, 1H, *J*=1.4 Hz, $OCH_{2a}O$), 5.87 (d, 1H, *J*=1.4 Hz, $OCH_{2b}O$), 3.68 (dd, 1H, *J*=6.4 and 5.0 Hz, $CHCOO^tBu$), 3.55 [d, 1H, *J*=14.7 Hz, N–CH_2(a,b)], 3.38 [d, 1H, *J*=14.7 Hz, N–CH_2(a,b)], 2.91 (dd, 1H, *J*=11.4 and 6.4 Hz, N–$CH_{2a}CHCOO^tBu$), 2.76 (dd, 1H, *J*=11.4 and 5.0 Hz, N–$CH_{2b}CHCOO^tBu$), 2.41 (s, 3H, NCH_3), 1.46 [s, 9H, $C(CH_3)_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=172.4 (s, O=C–O), 146.4 (s, Ar–C), 146.1 (s, Ar–C), 128.4 (s, Ar–C), 124.2 (s, Ar–C), 108.7 (d, Ar–CH), 106.2 (d, Ar–CH), 100.8 (t, OCH_2O), 81.0 [s, $COOC(CH_3)_3$], 57.9 (t,

N–CH_2), 55.4 (t, N–CH_2), 45.8 (q, NCH_3), 45.7 (d, *C*HCOO^{t}Bu), 28.1 [q, 3C, C(*C*H_3)$_3$] ppm. HRMS (APCI$^+$) *m*/*z* calculated for $[C_{16}H_{22}NO_4]^+$=$[M+H]^+$: 292.1543; found 292.1538.

4.6. Ethyl 4-allyl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5c)

To a cold (−15 °C), magnetically stirred solution of diisopropylamine (0.10 mL, 1.35 mmol) in dry THF (1 mL) was slowly added a solution of ^{n}BuLi (2.5 M in hexane, 0.43 mL, 1.08 mmol) and the reaction mixture was stirred for 5 min, at the same temperature. To the LDA thus formed, was added drop-wise, a solution of ester **4c** (160 mg, 0.54 mmol) in dry THF (2 mL), and the reaction mixture was stirred for 30 min, at the same temperature. The enolate was treated with allyl bromide (0.09 mL, 1.08 mmol), and stirred at room temperature for 4 h. The progress was monitored by TLC. The reaction mixture was treated with aqueous NH_4Cl solution, and extracted with ethyl acetate (3×15 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the allylated ester **5c** (140.3 mg, 77%) as a pale yellow viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f (**4c**)=0.50, R_f (**5c**)=0.60, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3027, 2978, 2805, 1722, 1638, 1493, 1452, 1367, 1205, 1145, 1093, 1027, 918, 736, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.35 (d, 1H, *J*=7.3 Hz, Ar–H), 7.29 (d, 2H, *J*=7.0 Hz, Ar–H), 7.24 (dd, 2H, *J*=7.0 and 7.0 Hz, Ar–H), 7.18 (dd, 1H, *J*=7.3 and 7.3 Hz, Ar–H), 7.15–7.01 (m, 2H, Ar–H), 6.91 (d, 1H, *J*=7.0 Hz, Ar–H), 5.70–5.31 (m, 1H, CH_2CH=CH_2), 4.99–4.85 (m, 2H, CH_2CH=CH_2), 4.18–3.95 (m, 2H, OCH_2CH_3), 3.58 (s, 2H, NCH_2), 3.54 (s, 2H, NCH_2), 3.06 (d, 1H, *J*=11.5 Hz, N–CH_{2a}CHCOOEt), 2.75–2.60 (m, 3H, CH_2CH=CH_2 and N–CH_{2b}CHCOOEt), 1.12 (t, 3H, *J*=7.1 Hz, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=174.3 (s, O=C–O), 138.3 (s, Ar–C), 135.9 (s, Ar–C), 135.1 (s, Ar–C), 134.2 (d, CH_2CH=CH_2), 129.1 (d, Ar–CH), 128.2 (d, 2C, Ar–CH), 127.9 (d, 2C, Ar–CH), 127.1 (d, Ar–CH), 126.6 (d, Ar–CH), 126.5 (d, Ar–CH), 126.2 (d, Ar–CH), 118.3 (t, CH_2CH=CH_2), 62.8 (t, N–CH_2), 60.9 (t, OCH_2CH_3), 57.0 (t, N–CH_2), 56.7 (t, N–CH_2), 51.0 [s, *C*(COOEt)CH_2CH=CH_2], 42.7 (t, CH_2CH=CH_2), 14.1 (q, OCH_2CH_3) ppm. HRMS (APCI$^+$) *m*/*z* calculated for $[C_{22}H_{26}NO_2]^+$=$[M+H]^+$: 336.1958; found 336.1942.

4.7. *tert*-Butyl 4-allyl-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5h)

The reaction is performed with the ester **4h** (260 mg, 0.61 mmol), diisopropylamine (0.16 mL, 1.51 mmol), ^{n}BuLi (2.5 M in hexane, 0.50 mL, 1.21 mmol), allyl bromide (0.10 mL, 1.21 mmol), and dry THF (3 mL) as described above (cf. **5c**). Purification of the residue by silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 90:10) furnished the allylated ester **5h** (221.6 mg, 78%) as a colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f (**4h**)=0.45, R_f (**5h**)=0.55, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3064, 2976, 1718, 1638, 1609, 1499, 1454, 1366, 1240, 1161, 1135, 1094, 1027, 915, 847, 734, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 11H, Ar–H), 6.82 (dd, 1H, *J*=8.8 and 2.9 Hz, Ar–H), 6.57 (d, 1H, *J*=2.9 Hz, Ar–H), 5.75–5.55 (m, 1H, CH_2CH=CH_2), 5.10–4.90 (m, 4H, CH_2CH=CH_2 and OCH_2Ph), 3.70–3.55 (m, 2H, NCH_2), 3.53 (s, 2H, NCH_2), 3.09 (d, 1H, *J*=11.2 Hz, N–CH_{2a}CHCOO^{t}Bu), 2.77–2.66 (m, 3H, CH_2CH=CH_2 and N–CH_{2b}CHCOO^{t}Bu), 1.41 [s, 9H, OC(CH_3)$_3$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=173.5 (s, O=C–O), 157.2 (s, Ar–C), 138.4 (s, Ar–C), 137.1 (s, Ar–C), 136.4 (s, Ar–C), 134.5 (d, CH_2CH=CH_2), 129.2 (d, Ar–CH), 129.1 (d, 2C, Ar–CH), 128.8 (s, Ar–C), 128.5 (d, 2C, Ar–CH), 128.2 (d, 2C, Ar–CH), 127.9 (d, Ar–CH), 127.4 (d, 2C, Ar–CH), 127.1 (d, Ar–CH), 118.0 (t, CH_2CH=CH_2), 113.3 (d, Ar–CH), 111.9 (d, Ar–CH), 80.8 [s, *C*(CH_3)$_3$], 69.9 (t, OCH_2Ph), 62.9 (t, N–CH_2), 57.5 (t, N–CH_2), 56.8 (t, N–CH_2), 50.8 [s, *C*(COO^{t}Bu) CH_2CH=CH_2], 42.8 (t, CH_2CH=CH_2), 28.0 [q, 3C, *C*(CH_3)$_3$] ppm. HRMS (APCI$^+$) *m*/*z* calculated for $[C_{31}H_{36}NO_3]^+$=$[M+H]^+$: 470.2690; found 470.2698.

4.8. (4-Allyl-2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl) methanol (6c)

To a cold (0 °C), magnetically stirred solution of an ester **5c** (100 mg, 0.30 mmol) in dry ether (10 mL), was added $LiAlH_4$ (34 mg, 0.89 mmol). Then the reaction mixture stirred for 1 h. The reaction mixture was quenched with drop wise addition of ethyl acetate, treated with aqueous NH_4Cl solution, and extracted with ethyl acetate (3×15 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure, and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 80:20 to 70:30) furnished the alcohol **6c** (73.3 mg, 84%) as colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f (**5c**)=0.60, R_f (**6c**)=0.30, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3396, 3065, 3028, 2915, 2813, 1638, 1493, 1451, 1368, 1094, 1072, 1034, 916, 755, 734, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.30–7.10 (m, 7H, Ar–H), 7.05 (dd, 1H, *J*=7.5 and 7.5 Hz, Ar–H), 6.89 (d, 1H, *J*=7.5 Hz, Ar–H), 5.50–5.35 (m, 1H, CH_2CH=CH_2), 5.33 (br s, 1H, OH), 4.92 (d, 1H, *J*=17.1 Hz, CH_2CH=CH_{2trans}), 4.88 (d, 1H, *J*=10.2 Hz, CH_2CH=CH_{2cis}), 3.78–3.65 (m, 2H, CH_2OH), 3.66–3.55 (m, 2H, NCH_2Ar), 3.51 (d, 1H, *J*=12.8 Hz, NCH_{2a}Ph), 3.23 (d, 1H, *J*=12.8 Hz, NCH_{2b}Ph), 2.87 [dd, 1H, *J*=11.5 and 1.6 Hz, NCH_{2a}C(CH_2OH)CH_2CH=CH_2], 2.53 [dd, 1H, *J*=11.5 and 2.5 Hz, N–CH_{2b}C(CH_2OH)CH_2CH=CH_2], 2.42 (dd, 1H, *J*=14.4 and 6.0 Hz, CH_{2a}CH=CH_2), 2.11 (dd, 1H, *J*=14.4 and 8.4 Hz, CH_{2b}CH=CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=137.6 (s, Ar–C), 136.9 (s, Ar–C), 135.6 (s, Ar–C), 133.7 (d, CH_2CH=CH_2), 129.1 (d, 2C, Ar–CH), 128.6 (d, 2C, Ar–CH), 127.6 (d, Ar–CH), 127.0 (d, Ar–CH), 126.3 (d, Ar–CH), 126.2 (d, Ar–CH), 125.8 (d, Ar–CH), 118.0 (t, CH_2CH=CH_2), 75.3 (t, CH_2OH), 63.0 (t, N–CH_2), 60.7 (t, N–CH_2), 56.6 (t, N–CH_2), 41.7 [s, *C*(CH_2OH)CH_2CH=CH_2], 40.0 (t, CH_2CH=CH_2) ppm. HRMS (APCI$^+$) *m*/*z* calculated for $[C_{20}H_{24}NO]^+$=$[M+H]^+$: 294.1852; found 294.1845.

4.9. [4-Allyl-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinolin-4-yl]methanol (6h)

The reaction is performed with the ester **5h** (191 mg, 0.41 mmol), ether (10 mL), and $LiAlH_4$ (46.4 mg, 1.22 mmol) as described above (cf. **6c**). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 80:20 to 60:40) furnished the alcohol **6h** (158.5 mg, 97%) as colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 75:25), R_f(**5h**)=0.65, R_f(**6h**)=0.30, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3295, 3029, 2912, 2824, 1637, 1609, 1500, 1453, 1382, 1319, 1278, 1241, 1091, 1073, 1026, 909, 731, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 11H, Ar–H), 6.88 (dd, 1H, *J*=8.8 and 2.9 Hz, Ar–H), 6.59 (d, 1H, *J*=2.9 Hz, Ar–H), 5.65–5.40 (m, 1H, CH_2CH=CH_2), 5.38 (br s, 1H, OH), 5.10–4.91 (m, 4H, OCH_2Ph and CH_2CH=CH_2), 3.85–3.55 (m, 5H, CH_2OH, NCH_2Ar and NCH_{2a}Ph), 3.29 (d, 1H, *J*=14.7 Hz, NCH_{2b}Ph), 2.94 [dd, 1H, *J*=11.7 and 2.0 Hz, N–CH_{2a}C(CH_2OH)CH_2CH=CH_2], 2.53 [dd, 1H, *J*=11.7 and 2.5 Hz, N–CH_{2b}C(CH_2OH)CH_2CH=CH_2], 2.42 (dd, 1H, *J*=14.7 and 6.3 Hz, CH_{2a}CH=CH_2), 2.11 (dd, 1H, *J*=14.7 and 8.8 Hz, CH_{2b}CH=CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.1 (s, Ar–C), 137.0 (s, Ar–C), 136.9 (s, Ar–C), 136.8 (s, Ar–C), 133.8 (d, CH_2CH=CH_2), 129.9 (s, Ar–C), 129.1 (d, 2C, Ar–CH), 128.6 (d, 2C, Ar–CH), 128.5 (d, 2C, Ar–CH), 127.9 (d, Ar–CH), 127.6 (d, Ar–CH), 127.4 (d, 2C, Ar–CH), 126.9 (d, Ar–CH),

117.9 (t, $CH_2CH{=}CH_2$), 114.3 (d, Ar–CH), 111.7 (d, Ar–CH), 75.2 (t, OCH_2Ph), 69.9 (t, CH_2OH), 63.0 (t, N–CH_2), 60.9 (t, N–CH_2), 56.8 (t, N–CH_2), 41.2 [s, $C(CH_2OH)CH_2CH{=}CH_2$], 40.0 (t, $CH_2CH{=}CH_2$) ppm. HRMS ($APCI^+$) m/z calculated for $[C_{27}H_{28}NO_2]^+=[M-H]^+$: 398.2115; found 398.2104.

4.10. 4-Allyl-4-[(allyloxy)methyl]-2-benzyl-1,2,3,4-tetrahydroisoquinoline (7c)

To an oven dried round bottomed flask, were added alcohol **6c** (47 mg, 0.16 mmol), sodium hydride (19 mg, 0.48 mmol) in dry DMF (3 mL) followed by addition of allyl bromide (58.2 mg, 0.48 mmol) under nitrogen atmosphere at room temperature and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was treated with aqueous NH_4Cl solution, and extracted with ethyl acetate (3×10 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 95:5) furnished the allyl ether **7c** (44.2 mg, 83%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 85:15), R_f (**6c**)=0.35, R_f (**7c**)=0.75, UV detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3064, 3027, 2924, 2853, 1639, 1493, 1452, 1368, 1345, 1145, 1090, 1027, 996, 916, 757, 730, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.45–7.20 (m, 6H, Ar–H), 7.15 (dd, 1H, J=7.2 and 7.2 Hz, Ar–H), 7.10 (dd, 1H, J=7.4 and 7.4 Hz, Ar–H), 6.96 (d, 1H, J=7.4 Hz, Ar–H), 5.95–5.75 (m, 1H, $CH_2CH{=}CH_2$), 5.65–5.50 (m, 1H, $CH_2CH{=}CH_2$), 5.19 (d, 1H, J=17.2 Hz, $CH_2CH{=}CH_{2trans}$), 5.10 (d, 1H, J=10.4 Hz, $CH_2CH{=}CH_{2cis}$), 4.96 (d, 1H, J=17.4 Hz, $CH_2CH{=}CH_{2trans}$), 4.91 (d, 1H, J=10.4 Hz, $CH_2CH{=}CH_{2cis}$), 3.95–3.84 (m, 2H, $CH_2OCH_2CH{=}CH_2$), 3.72–3.56 (m, 4H, $CH_2OCH_2CH{=}CH_2$ and NCH_2Ar), 3.45 (dd, 2H, J=16.6 and 9.4 Hz, NCH_2Ph), 2.82 (d, 1H, J=11.4 Hz, $CH_{2a}CH{=}CH_2$), 2.62 [dd, 1H, J=14.3 and 6.4 Hz, N–$CH_{2a}C(CH_2OCH_2CH{=}CH_2)CH_2CH{=}CH_2$], 2.53 [dd, 1H, J=14.3 and 7.9 Hz, N–$CH_{2a}C(CH_2OCH_2CH{=}CH_2)CH_2CH{=}CH_2$], 2.46 (d, 1H, J=11.5 Hz, $CH_{2b}CH{=}CH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=138.8 (s, Ar–C), 138.5 (s, Ar–C), 135.8 (s, Ar–C), 135.3 (d, $CH_2CH{=}CH_2$), 135.2 (d, $CH_2CH{=}CH_2$), 128.9 (d, 2C, Ar–CH), 128.2 (d, 2C, Ar–CH), 127.2 (d, Ar–CH), 127.0 (d, Ar–CH), 126.5 (d, Ar–CH), 126.0 (d, Ar–CH), 125.9 (d, Ar–CH), 117.1 (t, $CH_2CH{=}CH_2$), 116.3 (t, $CH_2CH{=}CH_2$), 76.6 (t, $OCH_2CH{=}CH_2$), 72.3 (t, $CH_2OCH_2CH{=}CH_2$), 62.9 (t, N–CH_2), 57.2 (t, N–CH_2), 56.7 (t, N–CH_2), 42.9 [s, $C(CH_2OCH_2CH{=}CH_2)CH_2CH{=}CH_2$], 40.8 (t, $CH_2CH{=}CH_2$) ppm. HRMS ($APCI^+$) m/z calculated for $[C_{23}H_{28}NO]^+=[M+H]^+$: 334.2165; found 334.2150.

4.11. 4-Allyl-4-[(allyloxy)methyl]-2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (7h)

The reaction is performed with the alcohol **6h** (132.0 mg, 0.33 mmol), sodium hydride (23.8 mg, 0.99 mmol), dry DMF (3 mL), and allyl bromide (120.1 mg, 0.99 mmol) as described above (cf. **7c**). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 90:10) furnished the allyl ether **7h** (130.8 mg, 90%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 75:25), R_f (**6h**)=0.30, R_f (**7h**)=0.75, iodine chamber detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3064, 3029, 2851, 1637, 1609, 1578, 1499, 1453, 1342, 1278, 1240, 1139, 1091, 1019, 915, 843, 735, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.50–7.20 (m, 11H, Ar–H), 6.80 (dd, 1H, J=8.8 and 2.4 Hz, Ar–H), 6.59 (d, 1H, J=2.4 Hz, Ar–H), 5.90–5.75 (m, 1H, $CH_2CH{=}CH_2$), 5.70–5.50 (m, 1H, $CH_2CH{=}CH_2$), 5.20 (d, 1H, J=17.2 Hz, $CH_2CH{=}CH_{2trans}$), 5.11 (d, 1H, J=10.4 Hz, $CH_2CH{=}CH_{2cis}$), 4.98 (s, 2H, OCH_2Ph), 5.00–4.90 (m, 2H, $CH_2CH{=}CH_2$), 3.95–3.84 (m, 2H, $CH_2OCH_2CH{=}CH_2$), 3.70–3.55 (m, 4H, $CH_2OCH_2CH{=}CH_2$ and NCH_2Ar), 3.41 (dd, 2H, J=16.6 and 9.3 Hz, NCH_2Ph), 2.79 (d, 1H, J=11.7 Hz, $CH_{2a}CH{=}CH_2$), 2.59 [dd, 1H, J=14.2 and 6.4 Hz, N–$CH_{2a}C(CH_2OCH_2CH{=}CH_2)CH_2CH{=}CH_2$], 2.50 [dd, 1H, J=14.2 and 7.8 Hz, N–$CH_{2a}C(CH_2OCH_2CH{=}CH_2)CH_2CH{=}CH_2$], 2.46 (d, 1H, J=11.2 Hz, $CH_{2b}CH{=}CH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=156.9 (s, Ar–C), 138.8 (s, Ar–C), 137.2 (s, Ar–C), 137.1 (s, Ar–C), 135.4 (d, $CH_2CH{=}CH_2$), 135.2 (d, $CH_2CH{=}CH_2$), 130.9 (s, Ar–C), 128.9 (d, 2C, Ar–CH), 128.5 (d, 2C, Ar–CH), 128.3 (d, Ar–CH), 128.2 (d, 2C, Ar–CH), 127.9 (d, Ar–CH), 127.4 (d, 2C, Ar–CH), 127.0 (d, Ar–CH), 117.1 (t, $CH_2CH{=}CH_2$), 116.3 (t, $CH_2CH{=}CH_2$), 113.2 (d, Ar–CH), 111.9 (d, Ar–CH), 76.6 (t, $OCH_2CH{=}CH_2$), 72.2 (t, $CH_2OCH_2CH{=}CH_2$), 69.9 (t, OCH_2Ph), 62.8 (t, N–CH_2), 57.4 (t, N–CH_2), 56.8 (t, N–CH_2), 42.3 [s, $C(CH_2OCH_2CH{=}CH_2)CH_2CH{=}CH_2$], 40.8 (t, $CH_2CH{=}CH_2$) ppm. HRMS ($APCI^+$) m/z calculated for $[C_{30}H_{34}NO_2]^+=[M+H]^+$: 440.2584; found 440.2581.

4.12. 2-Benzyl-2,3,4′,7′-tetrahydro-1*H*-spiro[isoquinoline-4,3′-oxepine] (8c)

To an oven dried round bottomed flask containing allyl ether **7c** (29 mg, 0.09 mmol) in dry DCM (7 mL) under nitrogen atmosphere at room temperature, was added Grubb's first generation catalyst (3.6 mg, 5 mol %) (Note: usually room temperature is in the range of 35–40 °C in this hot summer, in India), and stirred at the same temperature for 10 h and progress was monitored by TLC. Solvent was removed under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 93:7) furnished the oxepine **8c** (22 mg, 82%) as colorless liquid [TLC control (petroleum ether/ethyl acetate 95:5), R_f (**7c**)=0.50, R_f (**8c**)=0.45, iodine chamber detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3061, 3023, 2926, 2753, 1603, 1492, 1452, 1368, 1264, 1247, 1138, 1099, 1074, 1026, 922, 755, 732, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.47 (dd, 1H, J=7.8 and 1.0 Hz, Ar–H), 7.38 (d, 2H, J=7.3 Hz, Ar–H), 7.31 (dd, 2H, J=7.3 and 7.3 Hz, Ar–H), 7.25 (t, 1H, J=7.3 Hz, Ar–H), 7.18 (dd, 1H, J=7.8 and 7.8 Hz, Ar–H), 7.10 (ddd, 1H, J=7.8, 7.8 and 1.0 Hz, Ar–H), 6.95 (d, 1H, J=7.8 Hz, Ar–H), 5.77–5.64 (m, 1H, $CH_a{=}CH_b$), 5.63–5.50 (m, 1H, $CH_a{=}CH_b$), 4.38–4.20 (m, 2H, $CH_2OCH_2CH{=}CH$), 4.00 (d, 1H, J=12.2 Hz, $CH_{2a}OCH_2CH{=}CH$), 3.77 (d, 1H, J=12.2 Hz, $CH_{2b}OCH_2CH{=}CH$), 3.76 (d, 1H, J=13.2 Hz, $NCH_{2a}Ar$), 3.56 (d, 1H, J=14.7 Hz, $NCH_{2a}Ph$), 3.55 (d, 1H, J=13.2 Hz, $NCH_{2b}Ar$), 3.50 (d, 1H, J=14.7 Hz, $NCH_{2b}Ph$), 2.69 [d, 1H, J=11.7 Hz, N–$CH_{2a}C(CH_2OCH_2)CH_2CH{=}CH$], 2.63–2.44 [m, 3H, N–$CH_{2b}C(CH_2OCH_2)CH_2CH{=}CH$ and $CH_2CH{=}CH$] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=141.4 (s, Ar–C), 138.6 (s, Ar–C), 134.7 (s, Ar–C), 129.4 (d, $CH_a{=}CH_b$), 128.9 (d, 2C, Ar–CH), 128.2 (d, 2C, Ar–CH), 128.0 (d, Ar–CH), 127.0 (d, Ar–CH), 126.7 (d, Ar–CH), 126.6 (d, Ar–CH), 126.3 (d, Ar–CH), 126.0 (d, $CH_a{=}CH_b$), 78.9 (t, $OCH_2CH{=}CH$), 71.7 (t, $CH_2OCH_2CH{=}CH$), 62.8 (t, N–CH_2), 58.7 (t, N–CH_2), 56.7 (t, N–CH_2), 44.9 [s, $C(CH_2OCH_2)CH_2CH{=}CH$], 37.1 (t, $CH_2CH{=}CH$) ppm. HRMS (ESI^+) m/z calculated for $[C_{21}H_{23}NNaO]^+=[M+Na]^+$: 328.1672; found 328.1686.

4.13. 2-Benzyl-7-(benzyloxy)-2,3,4′,7′-tetrahydro-1*H*-spiro[isoquinoline-4,3′-oxepine] (8h)

The reaction is performed with the allyl ether **7h** (37 mg, 0.08 mmol), Grubb's first generation catalyst (3.5 mg, 5 mol %), and dry DCM (6 mL) as described above (cf. **8c**). Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 94:6) furnished the oxepine **8h** (29.0 mg, 83%) as colorless viscous liquid [TLC control (petroleum ether/ethyl acetate 90:10), R_f (**7h**)=0.55, R_f (**8h**)=0.45, iodine chamber detection]. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3062, 3026, 2926, 1609, 1580, 1499, 1454, 1318, 1239, 1134, 1097, 1021, 908, 732, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.40–7.10 (m, 11H, Ar–H), 6.74 (dd, 1H, J=8.8 and 2.9 Hz, Ar–H), 6.49 (d, 1H, J=2.9 Hz, Ar–H), 5.70–5.57 (m, 1H, $CH_a{=}CH_b$), 5.55–5.45 (m, 1H, $CH_a{=}CH_b$), 4.90 (s, 2H, OCH_2Ph), 4.25–4.18 (m, 2H, $CH_2OCH_2CH{=}CH$), 3.93 (d, 1H, J=12.2 Hz, $CH_{2a}OCH_2CH{=}CH$), 3.68 (d, 1H, J=13.2 Hz, $NCH_{2a}Ar$), 3.65 (d, 1H,

J=12.2 Hz, CH_{2b}OCH$_2$CH=CH), 3.47 (d, 1H, J=13.2 Hz, NCH$_{2b}$Ar), 3.42 (d, 1H, J=14.7 Hz, NCH$_{2a}$Ph), 3.38 (d, 1H, J=14.7 Hz, NCH$_{2b}$Ph), 2.62 [d, 1H, J=11.2 Hz, N–CH_{2a}C(CH$_2$OCH$_2$)CH$_2$CH=CH], 2.52–2.35 [m, 3H, N–CH_{2b}C(CH$_2$OCH$_2$)CH$_2$CH=CH and CH_2CH=CH] ppm. ^{13}C NMR (CDCl$_3$, 100 MHz): δ=156.9 (s, Ar–C), 138.6 (s, Ar–C), 137.1 (s, Ar–C), 136.1 (s, Ar–C), 133.8 (s, Ar–C), 129.4 (d, CH_a=CH$_b$), 128.8 (d, 2C, Ar–CH), 128.5 (d, 2C, Ar–CH), 128.2 (d, 2C, Ar–CH), 128.0 (d, Ar–CH), 127.9 (d, Ar–CH), 127.8 (d, CH$_a$=CH_b), 127.4 (d, 2C, Ar–C), 127.0 (d, Ar–CH), 113.8 (d, Ar–CH), 111.6 (d, Ar–CH), 78.9 (t, OCH_2CH=CH), 71.6 (t, CH_2OCH$_2$CH=CH), 69.9 (t, OCH$_2$Ph), 62.8 (t, N–CH$_2$), 58.8 (t, N–CH$_2$), 56.8 (t, N–CH$_2$), 44.2 [s, C(CH$_2$OCH$_2$)CH$_2$CH=CH], 37.2 (t, CH$_2$CH=CH) ppm. HRMS (ESI$^+$) m/z calculated for [C$_{28}$H$_{30}$NO$_2$]$^+$=[M+H]$^+$: 412.2271; found 412.2279.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.06.106.

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