Stereoselective 1-arylation of isoquinolines via chiral N-acylisoquinolinium salts

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Dedicated to Prof. Dr. Henk van der Plas on the occasion of his 80th birthday

Abstract
Reaction of isoquinolines with *(R)*-menthyl chlorocarbonate or (*S*)-α-Cbz-aminoacyl fluorides and arenes or heteroarenes gave access to 2-acyl-1-aryl-1,2-dihydroisoquinolines in a Mannich-type reaction via intermediate N-acylisoquinolinium salts. As an alternative, aryl metal compounds could be used. Modest stereoselectivities were achieved. Further reduction and hydrolysis of the products gave access to 1-aryl-1,2,3,4-tetrahydroisoquinolines.

Keywords: Isoquinolines, arylation, stereoselective synthesis, reduction, amino acid derivatives

Introduction

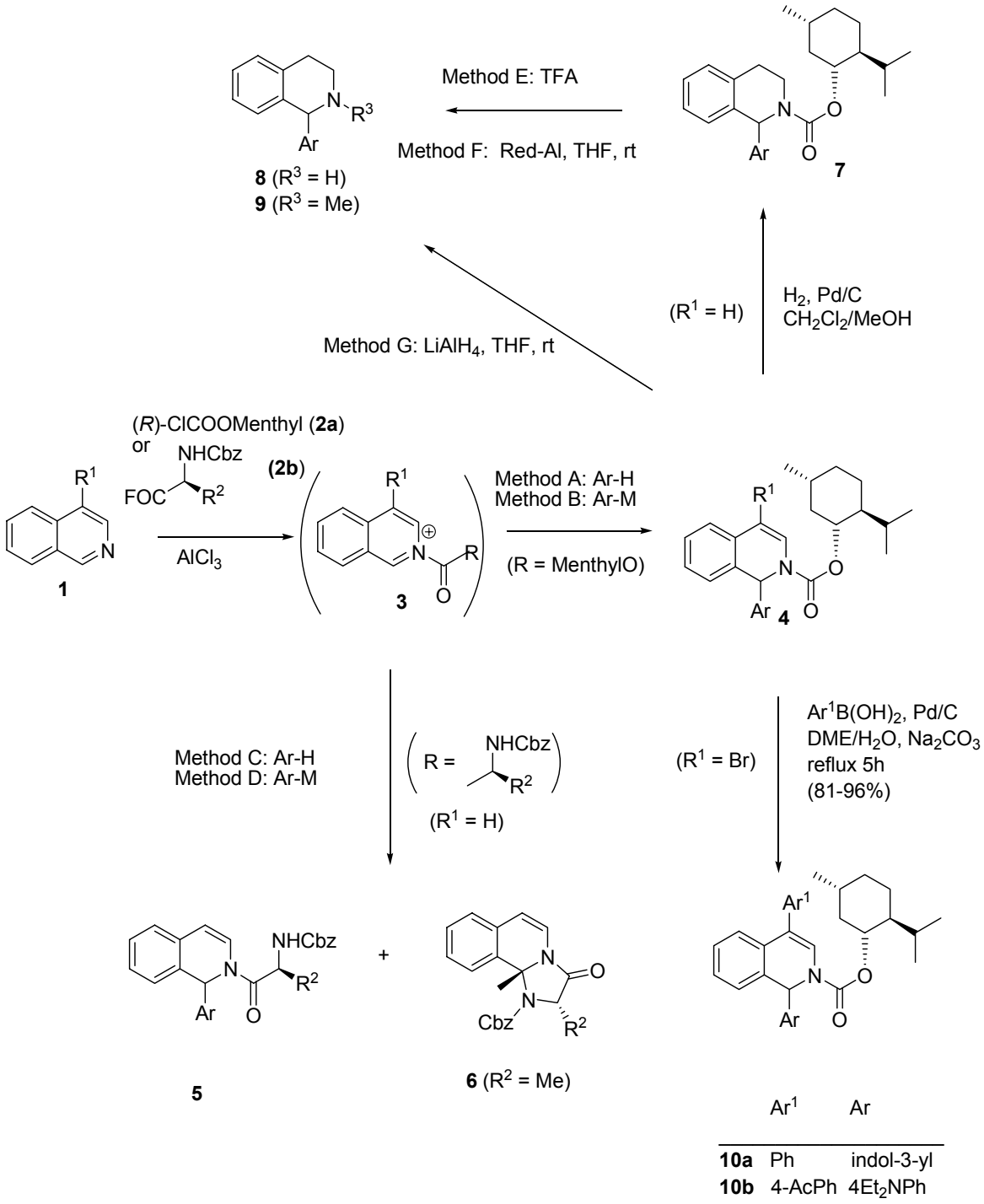
The 1-substituted isoquinoline scaffold has been found in a large group of alkaloids. The 1-aryl-substituted tetrahydroisoquinolines represent potent ligands for the channel binding site of the NMDA-receptor complex.[1] 2-Acyl-1-arylisoquinolines were used as precursors for such ligands.[2,3] 1-Aryldihydroisoquinolines were used as precursors in the synthesis of fused isoquinolines.[4] Certain 2-acyl-1-aryl-1,2,3,4-tetrahydroisoquinolines are potent AMPA receptor antagonists.[5] There are several possible pathways to introduce aryl substituents at position 1 of isoquinolines. A particular useful way consists of a two-step methodology by first activation with carboxylic acid derivatives, chloroformates or carbamoylchlorides giving highly electrophilic N-acyl, N-alkoxycarbonyl or N-aminocarbonylisoquinolinium salts, respectively, followed by the introduction of the aryl group either directly in a Mannich type reaction or by an aryl Grignard reagent. The N-acyl or N-alkoxycarbonyl group can easily be removed from the resulting 1-aryl-1,2-dihydroisoquinolines later on by hydrolysis providing an unsubstituted 2-N-atom which can be further functionalized. A series of such acyl arylations were reported by the group of Sheinkman [6-11] and later on also by others.[12,13] In this way, a variety of electron rich aryl and

heteroaryl groups could be introduced into position 1 using acyl chlorides, chlorocarbamates or ethyl chloroformate as activating reagents and the aromatic reactant. Acetic anhydride was also useful in such transformations.[14] *Wanner et al*. succeeded in the stereoselective introduction of aryl and heteroaryl groups into position 1 of isoquinoline using a chiral acyl chloride and aryl Grignard reagents in acyl arylation reactions.[2,15] *Comins et al.* could introduce a methyl group by reaction of isoquinoline with (-)-8-phenylmenthyl chlorocarbonate and methyl Grignard reagents in diastereomeric ratios up to 86:14.[19] We used commercial *(R)*-menthyl chlorocarbonate as auxiliary in the Reissert reaction (addition of cyanide to position 1) with isoquinolines but in contrast to first assumptions,[16] the reaction was not stereoselective but gave 1:1 mixtures of epimers.[18,20]

As an extension of our interest in the application of *(R)*- menthyl chlorocarbonate and α-amino acid fluorides as auxiliaries in stereoselective 1,2-additions to isoquinolines[16-18] we sought their application in the stereoselective introduction of aryl groups into position 1.

Results and Discussion

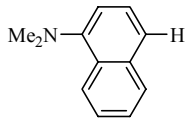
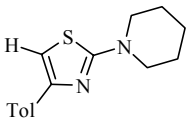
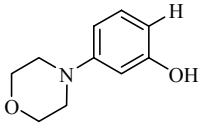
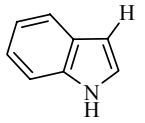
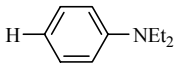
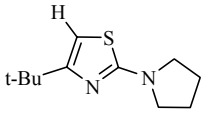
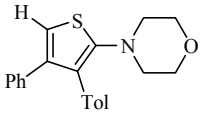
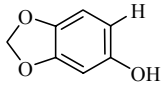
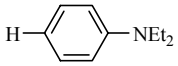
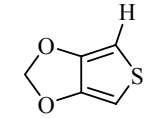
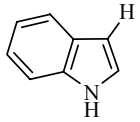
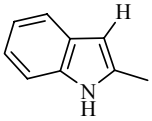
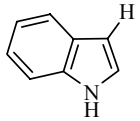
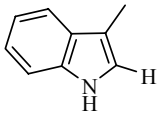
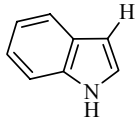
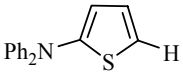
Isoquinolines **1** were treated with *(R)*-menthyl chlorocarbonate **2a** or (S)-α-Cbz-aminoacyl fluorides **2b** in dichloromethane at low temperatures. In order to assist the formation of intermediate N-acyliminium salts **3** $AlCl_3$ was added. Subsequent addition of electron rich arenes or heteroarenes ArH gave the corresponding 2-acyl-1-aryl-1,2-dihydroisoquinolines **4** (Table 1) and **5** (Table 3) in moderate to good yields in a Mannich-type reaction. While modest to high (dr = 6:1) diastereomeric ratios could be achieved with α-Cbz-aminoacid fluorides **2b** (Table 3) the menthyl chlorocarbonate **2a** failed to exert any stereoselectivity. In the latter case NMR and normal HPLC do not reveal indications of the formation of diastereomers, but careful investigation by HPLC at chiral phase clearly showed the appearance of two epimers in equal quantities. Thus the same situation is found as before in the Reissert-reaction of isoquinolines, when menthyl chloroformate was used together with trimethylsilyl cyanide.[18]



Interestingly, we sometimes observed an alternative reaction of isoquinoline and α-Cbz-amino acyl fluorides **2b** in the presence of arenes and hetarenes leading to tricyclic imidazo-isoquinolines **6** without the incorporation of the aromatic reagent. So far, such cyclizations were only observed when strongly electron withdrawing protective groups, such as tosyl were attached to the amino group of the α-aminoacid fluorides, enabling NH-deprotonation and intramolecular

attack of the N-atom at the iminium-C atom of the intermediate iminium salt **3** (R = CH(R^2)NHPG).[17,21]

Table 1. 1-Aryl-1,2-dihydroisoquinolines **4** by Mannich-type reaction (Method A)

4	R^1	Ar-H	Yield (%)	**4**	R^1	Ar-H	Yield (%)
a	H		57	**j**	H		66
b	H		70	**k**	H		83
c	H		42	**l**	H		77
d	H		62	**m**	H		51
e	H		33	**n**	Br		70
f	H		39	**o**	Br		93
g	H		75	**p**	Ph		82
h	H		77	**q**	4-Cl-Ph		97
i	H		83				

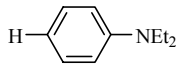
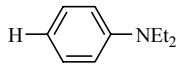
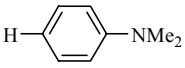
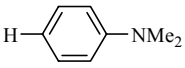
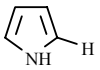
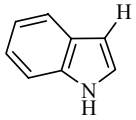
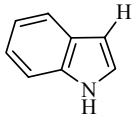
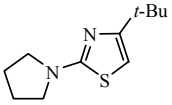
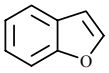
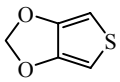
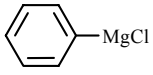
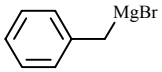
Arenes and heteroarenes lacking π-electron excess are not suitable for the Mannich-type reaction. For such cases we chose an alternative methodology applying arenes as organometallics, i.e. Grignard reagents or diorgano zinc compounds (Method B and D, see Tables 2 and 3, respectively). Unlike in the Mannich-type reaction, the *(R)*-menthyl chlorocarbonate **2a** gave asymmetric induction in the reactions with organometallics to some extent. Diastereomeric ratios up to 70:30 could be achieved. Again the epimers of **4** behaved very similar and separation by simple column chromatography was not possible. NMR spectra of the mixtures of these isomers showed only one set of signals and thus looked identical regardless of the diastereomeric ratios (see first three entries in Table 2). Finally the diastereomeric ratio could be determined by HPLC.

Table 2. 1-Aryl-1,2-dihydroisoquinolines **4** (R^1 = H) by reactions with organometallics (Method B)

4	Aryl-M	Solvent	Yield (%)	dr[a]
r	Ph-Mg-Br	THF	82	55:45
r	Ph_2Zn	THF	76	64:36
r	Ph_2Zn	Ph-CH_3	78	70:30
s	4-Br-C_6H_4-Mg-Br	THF	62	1:1
t	Bn-Mg-Br	THF	55	60:40
t	Bn_2Zn	THF	87	60:40

[a] Determined by HPLC.

Table 3. 2-(α-Cbz-aminoacyl)-1-aryl-1,2-dihydroisoquinolines **5** and Imidazoisoquinolines **6**

R^2	Nu	Product (Method/yield)	dr
Me		**5a** (C/21%)	6:1
Bn		**5b** (C/48%)	3:1
Bn		**5c** (C/44%)	3.55:1
Me		**5d** / **6** C)[a]	[a]
Me		**5e** (C/47%)	5:1
Bn		**5f** (C/63%)	2:1
Me		**5g** (C/56%)	2:1
Me		**6** (C/55%)	1:1
Me		**6** (C/35%)	2.6:1
Me		**6** (C/35%)	3.5:1
Me		**5h** (D/50%)	2.7:1
Me		**5i** (D/69%)	2:1

[a] 1:1.6 mixture of **5d** and **6**. Yield and dr were not determined.

Most probably, an interaction of the metal atom of the organometallic reagent ArM with the carbonyl O-atom of the intermediate N-acyliminium salt **3** gives rise to a more rigid transition state where unwanted formation of rotamers along the N-CO bond can not occur (Fig. 1) und thus better face selectivity is achieved. Unfortunately we were not able to separate the epimers and to assign configurations to the major and minor products. Using this methodology (Method B), benzyl groups which are particularly desirable for alkaloid structures and pharmacologically active compounds[22] can be introduced at position 1 of isoquinoline too (product **4t**).

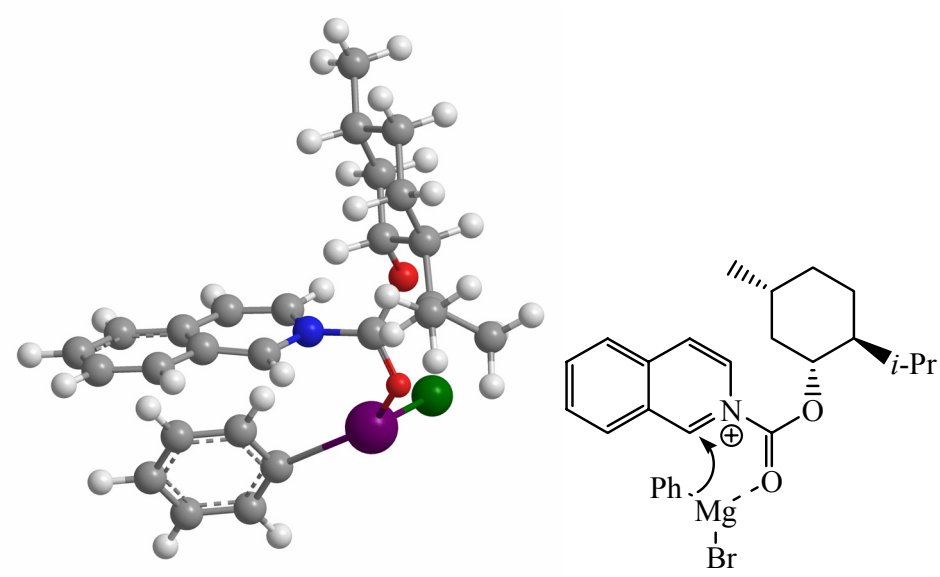


Figure 1. Proposed transition state of reaction of isoquinoline with *(R)*-menthyl chlorocarbonate and PhMgBr (geometry was optimized by MM2 energy minimisation).

Lower yields were obtained when α-Cbz-aminoacid fluorides and Grignard reagents were used (Method D, Table 3) while the stereoselectivity remained in the same range (maximal dr 73:27).

4-Bromoisoquinoline was subject of Pd-catalyzed cross coupling reactions.[23] We could make use of the 4-bromo substituted dihydroisoquinolines **4** (R^1 = Br) in order to introduce aryl groups in position 4 by Suzuki-reaction. A convenient procedure was applied using Pd/C as Pd-catalyst.[24] The corresponding 4-aryldihydroisoquinolines **10** were obtained in high yields.

The removal of the menthyloxycarbonyl group from the carbamates **4** turned out to be difficult. A procedure used by *Comins et al.* for cleaving the carbamate in menthyloxycarbonyl-dihydropyridones by reaction with sodium methoxide left the dihydroisoquinolines **4** unchanged. The same occurred under basic hydrolytic conditions or heating with hydrazine in dihydroxyethane. Treatment of **4** with TMS iodide gave complex mixtures. Thus we applied reductive conditions. Catalytic hydrogenation in the presence of Pd/C just hydrogenated the C-C double bond of the acyl enamine unit of **4** leading to tetrahydroisoquinolines **7** (Table 4) while reduction with $LiAlH_4$ (Method G) additionally transformed the menthyloxycarbonyl moiety into

a methyl group thus leading to 2-methyltetrahydroisoquinolines **9** (Table 5, **9b**). This overall transformation of **4** into **9** can also be achieved in a two step mode by first hydrogenating to tetrahydroisoquinolines **7** followed by reduction of the carbamate to the methyl group by Red-Al (Method F, Table 5, **9a**). Product **9b** did not show optical rotation, thus proving that the precursor **4k** was formed as a 1:1 mixture of epimers in the Mannich-type reaction.

Table 4. Tetrahydroisoquinolines **7**

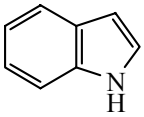
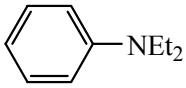
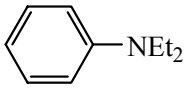
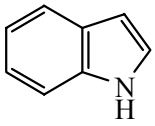
Product	Ar	Yield (%)
7a		84
7b		83
7c	Ph	54
7d	3-$MeOC_6H_4$	98

Table 5. Tetrahydroisoquinolines **8** and **9**

	Ar	Method	R^3	Yield (%)
8a		E	H	69 61[a]
8b	Ph	E	H	90
8c	3-$MeOC_6H_4$	E	H	96
8d	4-$MeOC_6H_4$	E	H	59
9a	3-$MeOC_6H_4$	F	Me	45
9b		G	Me	40

[a] with 6 M HCl.

We revisited the possibility of splitting off the menthyloxycarbonyl group hydrolytically at the stage of tetrahydroisoquinolines **7** and found heating in trifluoroacetic acid (Method E) or 6M hydrochloric acid appropriate to synthesize N-unsubstituted 1-aryl-tetrahydroisoquinolines **8** (Table 5).

In summary, isoquinolines could be transformed into 2-α-aminoacyl- and 2-menthyloxycarbonyl-substituted 1-aryldihydroisoquinolines. The syntheses proceed via intermediate N-acylisoquinolinium salts formed with (*R*)-menthyl chlorocarbonate or 2-α-aminoacid fluorides which react further in a Mannich-type fashion with arenes or heteroarenes or with organometallics. Stereoselectivity was observed in a number of cases. The 1-aryl-2-

menthyloxycarbonyldihydroisoquinolines could be hydrogenated to tetrahydroisoquinolines and the carbamate could be split off or reduced to the methyl group.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75.5 MHz, respectively, on a Bruker AC-300 with TMS as internal standard. ESI-mass spectra were measured with Varian CH-7a MAT (EI 70 eV) LDQ FT Finnigan ESI with MeOH as solvent. Silica gel 60 (0.04-0.063 mm, Merck) was used for preparative column chromatography and a Chiracel-OD-column for chiral HPLC. Unless otherwise mentioned, all chemicals were purchased.

Synthesis of 1-aryl-substituted 1,2-Dihydroisoquinolines 4 by Mannich-type reaction
Method A. General procedure
Anhydrous $AlCl_3$ (20 mol%) was added to a solution of (-)-*(R)*-menthyl chloroformate (2.00 mmol) in dry dichloromethane (50 ml) at -40 °C. After 5 min a solution of the isoquinoline **1** (2.00 mmol) in dry dichloromethane (5 ml) was added slowly under the exclusion of humidity. After the solution had turned yellow (about 45 – 60 min) it was cooled down to -78 °C. A solution of ArH (2.00 mmol) in dichloromethane (20 ml) was added over a period of 45 min. After stirring overnight the mixture was allowed to warm up to rt. The solvent was removed under vacuum and the residue was purified by column chromatography.

(1*R*)-Menthyl 1-(4-(Dimethylamino)-naphthalen-1-yl)-1,2-dihydroisoquinoline-2 carboxylate (4a). 57% yield of the product was obtained as slightly yellow foam. R_f: 0.63 (DCM). **^{1}H-NMR** ($CDCl_3$): δ =0.4-2.13 (m, 18H, Menthyl), 2.81 (s, 6H, N($C\underline{H}_3$)$_2$), 4.50 (m, 1H, CH-O), 5.88 (d, *J* = 7.55 Hz, 1H, C$\underline{H}$=CH-N), 6.79-7.43 (m, 7H, CH_{ar}), 7.44-7.56 (m, 1H, CH_{ar}), 7.55-7.85 (m, 2H, CH_{ar}), 8.28 (d, *J* = 8.22 Hz, 1H, CH_{ar}), 8.37-8.96 (m, 1H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ =16.4 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.3 (CH_2), 26.4 (CH), 31.4 (CH), 34.1 (CH_2), 41.4 (CH_2), 45.2 (CH), 46.6 , 54.3 (CH), 76.3 (CH), 105.6 ($\underline{C}$H=CH-N), 114.3 (CH_{ar}), 123.5 (CH_{ar}), 124.7 (CH_{ar}), 125.3 (CH_{ar}), 126.0 ($C_{q,ar}$), 126.2 (CH_{ar}), 126.8 (CH_{ar}), 127.4 (CH_{ar}), 127.5 (CH_{ar}), 128.8 ($C_{q,ar}$), 133.8 ($C_{q,ar}$), 137.6 ($C_{q,ar}$), 137.9 ($C_{q,ar}$), 150.5 ($C_{q,ar}$), 153.7(CO).
Elemental analysis: $C_{32}H_{38}N_2O_2$
calcd. C: 79.63 H: 7.94 N: 5.80
found C: 79.50 H: 8.34 N: 5.57
HRMS (EI) *m/z*: $C_{32}H_{38}N_2O_2$: calcd. 482.29333
found 482.29337

(1*R*)-Menthyl 1-(2-hydroxy-4-morpholinophenyl)-1,2-dihydroisoquinoline-2-carboxyl- ate (4b). 70 % yield of **4b** was obtained as colourless foam. R_f: 0.22 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 3.03 (dd, *J* = 5.42, 4.31 Hz, 4H, CH_2-N), 3.68-3.75 (m, 4H, CH_2-O), 4.57-4.80 (m, 1H, CH-O), 5.93 (t, *J* = 7.36, 7.36 Hz, 1H, C<u>H</u>=CH-N), 6.14 (td, *J* = 8.47, 2.77 Hz, 1H, CH_{ar}), 6.29-6.49 (m, 3H, CH_{ar}), 6.58 (dd, *J* = 11.00, 7.92 Hz, 1H, CH_{ar}), 6.93 (d, *J* = 7.44 Hz, 1H, CH=C<u>H</u>-N), 7.04-7.16 (m, 2H, CH_{ar}), 7.15-7.25 (m, 1H, CH_{ar}), 9.26 (s, 1H, OH).
^{13}C-NMR ($CDCl_3$): δ = 16.4 (CH_3), 20.7 (CH_3), 21.9 (CH_3), 23.4 (CH_2), 26.1 (CH), 31.4 (CH), 34.1 (CH_2), 41.1 (CH_2), 47.1 (CH), 48.4 (CH_2-N), 52.2 (CH), 67.0 (CH_2-O), 78.0 (CH-O), 104.1 (CH_{ar}), 107.1 (<u>C</u>H=CH-N), 109.9 (CH_{ar}), 119.1 ($C_{q,ar}$), 123.5 (CH_{ar}), 124.7 (CH_{ar}), 127.4 (CH_{ar}), 127.9 (CH_{ar}), 130.5 ($C_{q,ar}$), 131.3(<u>C</u>H=CH-N), 131.9 ($C_{q,ar}$), 152.1 (CO), 154.8 ($C_{q,ar}$), 155.1 ($C_{q,ar}$).
HRMS (EI) *m/z*: $C_{30}H_{38}N_2O_4$ calcd. 490.28316
found 490.28315

(1*R*)-Menthyl 1-(1-methyl-1*H*-pyrrol-2-yl)-1,2-dihydroisoquinoline-2-carboxylate (4c). 42 % yield of the product was obtained as reddish foam. R_f: 0.48(DCM).
^{1}H-NMR ($CDCl_3$): δ = 3.48 (s, 3H, N-CH_3), 4.70-4.85 (m, 1H, CH-O), 5.83 (dd, *J* = 7.61, 2.21 Hz, 1H, C<u>H</u>=CH-N), 5.88-5.99 (m, 1H, CH_{ar}), 6.00-6.17 (m, 1H, CH_{ar}), 6.18-6.34 (m, 1H, CH_{ar}), 6.37-6.54 (m, 1H), 6.79 (t, *J* = 7.30, 7.30 Hz, 1H, CH_{ar}), 6.97-7.37 (m, 5H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.5 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.4 (CH_2), 26.2 (CH), 31.4 (CH), 34.3 (CH_2), 36.1 (N-CH_3), 41.2 (CH_2), 47.3 (CH), 52.2 (CH), 107.6 (CH_{ar}), 107.9 (<u>C</u>H=CH-N), 108.2 (CH_{ar}), 120.4 (CH_{ar}), 121.6 (CH_{ar}), 124.5 (CH_{ar}), 124.7 (CH_{ar}), 125.4 ($C_{q,ar}$), 125.7 (CH_{ar}), 126.8 (CH_{ar}), 127.4 (CH_{ar}), 130.6 ($C_{q,ar}$), 132.6 ($C_{q,ar}$), 153.1 (CO).
Elemental analysis: $C_{25}H_{32}N_2O_2$
calcd. C: 75.88 H: 8.10 N: 6.81
found C: 76.49 H: 8.22 N: 7.14
HRMS (EI) *m/z*: $C_{25}H_{32}N_2O_2$ calcd. 392.24628
found 392.24632

(1*R*)-Menthyl 1-(4-*tert*-butyl-2-(pyrrolidin-1-yl)thiazol-5-yl)-1,2-dihydroisoquinoline-2-carboxylate (4d). 62 % yield of the product was obtained as yellow foam. R_f: 0.27(DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.65-2.01 (m, 27H, Menthyl+*t*-Butyl), 3.22 (t, *J* = 6.35 Hz, 4H, 2xCH_2), 3.36 (t, *J* = 6.54 Hz, 4H, 2xCH_2-N), 4.62 (m, 1H, CH-O), 5.83 (d, *J* = 7.80 Hz, 1H, C<u>H</u>=CH-N), 6.83 (s, 1H, CH-N), 7.02-6.95 (m, 1H, CH_{ar}), 7.06 (dt, *J* = 6.41, 1.61 Hz, 2H, CH_{ar}), 7.22-7.10 (m, 2H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.1 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.5 (CH_2), 25.7 (CH_2), 26.3 (CH), 29.7 (CH), 31.3 (CH_3), 34.2 (CH_2), 37.5 (<u>C</u>(CH_3)$_3$), 41.2 (CH_2), 47.2 (CH), 48.9 (CH_2), 51.9 (CH), 76.6 (CH-O), 96.8 (<u>C</u>H=CH-N), 120.6 (CH_{ar}), 125.0 (CH_{ar}), 126.4 (CH_{ar}), 127.0 (CH_{ar}), 127.4 (CH_{ar}), 129.0 ($C_{q,ar}$), 133.9 ($C_{q,ar}$).

HRMS (EI) *m/z*: $C_{31}H_{43}N_3O_2S$ calcd. 521.30760
found 521.30763

(1*R*)-Menthyl 1-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-1,2-dihydroisoquinoline-2-carboxylate (4e). 33 % yield of the product was obtained as colourless foam. R_f: 0.57 (DCM).
^{1}H-NMR ($CDCl_3$): δ =0.62-2.13 (m, 18H, Menthyl), 4.74 (dq, *J* = 10.77, 4.40 Hz, 1H, CH-O), 5.77 (s, 2H, O-CH_2-O), 5.97 (t, *J* = 7.49 Hz, 1H, C<u>H</u>=CH-N), 6.10 (d, *J* = 11.52 Hz, 1H, CH_{ar}), 6.57-6.45 (m, 2H, CH_{ar}), 6.70 (dd, *J* = 11.45, 7.84 Hz, 1H, CH_{ar}), 6.99 (d, *J* = 7.70 Hz, 1H, CH_{ar}), 7.16 (dd, *J* = 11.77, 5.92 Hz, 2H, CH_{ar}), 7.25 (t, *J* = 7.05 Hz, 1H, CH_{ar}), 9.16 (s, 1H, OH).
^{13}C-NMR ($CDCl_3$): δ = 16.4 (CH_3), 20.8 (CH_3), 21.9 (CH_3), 23.5 (CH_2), 26.3 (CH), 31.4 (CH), 34.1 (CH_2), 41.1 (CH_2), 47.2 (CH), 52.6 (CH), 78.1 (CH-O), 100.1 (CH_{ar}), 101.0 (O-CH_2-O), 109.0 (<u>C</u>H=CH-N), 109.6 (CH_{ar}), 120.3 ($C_{q,ar}$-CH), 123.5 (CH_{ar}), 125.0 (CH_{ar}), 127.5 (CH_{ar}), 128.1 (CH_{ar}), 130.2 ($C_{q,ar}$), 132.0 ($C_{q,ar}$), 141.2 ($C_{q,ar}$-O), 148.0 ($C_{q,ar}$-O), 149.0 ($C_{q,ar}$-OH), 155.3 (CO).
Elemental analysis: $C_{27}H_{31}NO_5$
calcd. C: 72.14 H: 6.95 N: 3.12
found C: 72.27 H: 7.29 N: 3.09
HRMS (EI) *m/z*: $C_{27}H_{31}NO_5$ calcd. 449.22022
found 449.22021

(1*R*)-Menthyl 1-(thieno[3,4-d][1,3]dioxol-4-yl)-1,2-dihydroisoquinoline-2-carboxylate (4f). 39 % yield of the product was obtained as colourless foam. R_f: 0.44 (DCM).
^{1}H-NMR ($CDCl_3$): δ =0.51-2.02 (m, 18H, Menthyl), 4.04-4.11 (m, 2H, CH_2-O), 4.14 (d, *J* = 4.21 Hz, 2H, CH_2-O), 4.60 (dt, *J* = 10.82, 3.93 Hz, 1H, CH-O), 5.82 (t, *J* = 7.44 Hz, 1H, C<u>H</u>=CH), 5.89-6.00 (m, 1H, CH_{ar}), 6.49-6.77 (m, 1H, CH_{ar}), 6.80-7.31 (m, 5H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ =16.6 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.5 (CH_2), 26.5 (CH), 31.4 (CH), 34.2 (CH_2), 41.1 (CH_2), 47.3 (CH), 51.3 (CH), 64.5 (O-CH_2-O), 76.6 (CH-O), 96.6 (C<u>H</u>=CH-N), 108.3 (<u>C</u>$_{ar,thiophen}$-CH), 118.9 ($C_{q,ar}$), 124.7 (CH_{ar}), 125.0 (CH_{ar}), 125.7 (CH_{ar}), 126.6 (CH_{ar}), 127.0 (CH_{ar}), 127.1 (CH_{ar}), 127.9 (CH_{ar}), 129.7 ($C_{q,ar}$), 132.2 ($C_{q,ar}$), 141.0 ($C_{q,ar}$-O), 152.4 ($C_{q,ar}$-O), 153.1 (CO).
Elemental analysis: $C_{25}H_{29}NO_4S$
calcd C: 68.85 H: 6.84 N: 3.10 S: 7.07
found C: 68.25 H: 6.86 N: 3.09 S: 6.93

(1*R*)-Menthyl 1-(2-methyl-1*H*-indol-3-yl)-1,2-dihydroisoquinoline-2-carboxylate (4g). 75 % yield of the product was obtained as yellow-orange foam. R_f: 0.42 (DCM).
^{1}H-NMR ($CDCl_3$): δ =0.51-2.12 (m, 18H, Menthyl) 2.47 (s, 3H, $C_{q,ar}$-CH_3), 4.67-4.39 (m, 1H, CH-O), 5.88 (d, *J* = 7.96 Hz, 1H, C<u>H</u>=CH-N), 6.63 (s, 1H, CH-$C_{q,ar}$), 6.93 (m, 7H, CH_{ar}), 7.10 (d, *J* = 8.30 Hz, 1H, N-C<u>H</u>=CH), 7.57 (s, 1H, CH_{ar}), 7.75 (s, 1H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ =12.4 (CH_3), 16.3 (CH_3), 20.7 (CH_3), 21.9 (CH_3), 23.4 (CH_2), 31.4 (CH), 34.2 (CH_2), 41.4 (CH_2), 47.3 (CH), 51.9 (CH), 76.0 (CH-O), 106.5 ($\underline{C}_{ar,Indol}$-CH), 110.0 ($\underline{C}$H=CH-N), 119.4 (CH_{ar}), 120.9 (CH_{ar}), 124.5 (CH_{ar}), 126.6 ($C_{q,ar}$), 126.9 (CH_{ar}), 127.1 (CH_{ar}), 127.2 (CH_{ar}), 132.7 (CH_{ar}), 132.8 ($C_{q,ar}$), 135.0 ($C_{q,ar}$), 151.8 (CO).
Elemental analysis: $C_{29}H_{34}N_2O_2$
calcd. C: 78.70 H: 7.74 N: 6.33
found C: 78.33 H: 7.99 N: 6.27

(1*R*)-Menthyl 1-(3-methyl-1*H*-indol-2-yl)-1,2-dihydroisoquinoline-2-carboxylate (4h). 77 % yield of the product was obtained as brownish solid. R_f: 0.68 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.49-2.18 (m, 18H, Menthyl), 2.23 (s, 3H, $C_{q,ar}$-CH_3), 4.63 (dq, *J* = 10.95, 4.29 Hz, 1H, CH-O), 5.85 (d, *J* = 7.54 Hz, 1H C$\underline{H}$=CH-N), 6.80 (s, 1H, CH-$C_{q,ar}$), 6.90-7.15 (m, 8H, CH_{ar}), 7.20 (d, *J* = 7.76 Hz, 1H, CH_{ar}), 7.40 (dd, *J* = 7.20, 4.25 Hz, 1H, CH_{ar}), 7.48 (d, *J* = 7.58 Hz, 1H, CH=C$\underline{H}$-N), 8.09 (s, 1H, NH).
^{13}C-NMR ($CDCl_3$): δ = 9.7 (CH_3), 16.4 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.5 (CH_2), 26.3 (CH), 31.4 (CH), 34.6 (CH_2), 41.4 (CH_2), 47.4 (CH), 51.4 (CH), 77.3 (CH), 107.6 (CH_{ar}), 110.7 ($\underline{C}$H=CH-N), 111.6 ($C_{q,Indol}$-CH_3), 118.8 (CH_{ar}), 119.1 (CH_{ar}), 121.6(CH_{ar}), 121.9 (CH_{ar}), 122.3(CH_{ar}), 125.0(CH_{ar}), 127.7, 128.2(CH_{ar}), 135.4 ($C_{q,ar}$), 136.3 ($C_{q,ar}$), 153.2 (CO).
HRMS (EI) *m/z*: $C_{29}H_{34}N_2O_2$ calcd. 442.26203
found 442.26205

(1*R*)-Menthyl 1-(5-(diphenylamino)-thien-2-yl)-1,2-dihydroisoquinoline-2-carboxylate (4i). 83 % yield of the product was obtained as yellow-greenish foam. R_f: 0.57 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.56-2.08 (m, 18H, Menthyl), 4.68 (dt, *J* = 10.68, 4.24 Hz, 1H, CH-O), 5.83 (m, 1H, C$\underline{H}$=CH-N), 6.24 (m Hz, 1H, CH_{ar}), 6.33 (d, *J* = 3.66 Hz, 1H, CH_{ar}), 6.55 (s, 1H, CH-$C_{q,Thiophen}$), 6.75 (dd, *J* = 7.11, 5.37 Hz, 1H, CH_{ar}), 6.83-7.07 (m, 8H, CH_{ar}), 7.07-7.26 (m, 7H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.5 (CH_3), 20.7 (CH_3), 22.0 (CH_3), 23.6 (CH_2), 26.6 (CH), 31.4 (CH), 34.2 (CH_2), 41.2 (CH_2), 47.4 (CH), 54.1 (CH), 76.8 (CH-O), 108.4 ($\underline{C}$H=CH-N), 120.2 (CH_{ar}), 122.4 (CH_{ar}), 122.5 (CH_{ar}), 124.2 (CH_{ar}), 124.8 (CH_{ar}), 127.1 (CH_{ar}), 128.2 (CH_{ar}), 129.0 (CH_{ar}), 130.5 ($C_{q,ar}$), 139.4 ($C_{q,ar}$), 147.7 (2x$C_{q,Ph}$-N), 150.9 ($C_{q,ar}$-CH), 152.8.
Elemental analysis: $C_{36}H_{38}N_2O_2S$
calcd. C: 76.83 H: 6.81 N: 4.98 S: 5.70
found C: 76.70 H: 6.84 N: 4.89 S: 5.62

(1*R*)-Menthyl 1-(2-(piperidin-1-yl)-4-(*p*-tolyl)-thiazol-5-yl)-1,2-dihydroisoquinoline-2-carboxylate (4j). 66 % yield of the product was obtained as yellow viscous oil. R_f: 0.38 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.62-2.13 (m, 20H, Menthyl + CH_2), 2.44 (s, 1H, C$\underline{H}_3$-Ph), 3.41 (s, 4H, 2x CH_2), 4.63-4.88 (m, 1H, CH-O), 5.92 (d, *J* = 7.81 Hz, 1H, C$\underline{H}$=CH-N), 6.90 (s, 1H, C$\underline{H}$-

$C_{q,Thiazol}$), 7.02 (dd, *J* = 14.59, 7.08 Hz, 2H, CH_{ar}), 7.16 (dd, *J* = 17.26, 7.28 Hz, 3H, CH_{ar}), 7.26-7.36 (m, 2H, CH_{ar}), 7.64-7.94 (m, 3H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.1 (CH_3), 21.0 (CH_3), 21.9 (CH_3), 22.2 (CH_3), 23.1 (CH_2), 24.1 (CH_2), 25.1 (CH_2), 31.6 (CH), 34.5 (CH_2), 41.2 (CH_2), 49.1 (CH_2), 50.1 (CH), 52.8 (CH), 76.7 (CH), 100.0 (CH=CH-N), 125.9 ($C_{q,ar}$), 126.0 (CH_{ar}), 127.1 (CH_{ar}), 127.6 (CH_{ar}), 128.8 (CH_{ar}), 129.0 (CH_{ar}), 129.2 (CH_{ar}), 130.8 ($C_{q,ar}$), 132.8 ($C_{q,ar}$), 137.3 ($C_{q,ar}$).
HRMS (EI) *m/z*: $C_{35}H_{43}N_3O_2S$ calcd. 569.30760
found 569.30764

(1*R*)-Menthyl 1-(1*H*-indol-3-yl)-dihydroisoquinoline-2-carboxylate (4k). 83 % yield of the product was obtained as red foam. R_f: 0.55 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.65-2.04 (m, 18H, Menthyl), 4.50-4.81 (m, 1H, CH-O), 5.89 (d, *J* = 7.68 Hz, 1H, CH=CH-N), 6.53-6.75 (m, 1H, CH_{ar}), 6.80 (d, *J* = 5.73 Hz, 1H, CH_{ar}), 6.96-7.15 (m, 6H, CH_{ar}), 7.14-7.29 (m, 2H, CH_{ar}), 7.84 (dd, *J* = 15.96, 10.60 Hz, 2H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.2 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.4 (CH_2), 26.1 (CH), 31.4 (CH), 34.2 (CH_2), 41.4 (CH_2), 47.3 (CH), 51.3 (CH), 76.3 (CH-O), 108.7 ($C_{q,Indol}$-CH), 109.4 (CH_{ar}), 110.9 (CH=CH-N), 119.8 (CH_{ar}), 120.4 (CH_{ar}), 122.0 (CH_{ar}), 124.5 (CH_{ar}), 127.0 (CH_{ar}) (CH_{ar}), 127.6 (CH_{ar}), 130.8 ($C_{q,ar}$), 132.2 ($C_{q,ar}$), 136.4 ($C_{q,ar}$), 153.1 (CO).
Elemental analysis: $C_{28}H_{32}N_2O_2$
calcd. C: 78.47 H: 7.53 N: 6.54
found C: 78.43 H: 7.75 N: 6.47

(1*R*)-Menthyl 1-(4-(diethylamino)phenyl)-1,2-dihydroisoquinoline-2-carboxylate (4l).
77 % yield of the product was obtained as yellow viscous oil. R_f: 0.62 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.61-2.10 (m, 24H, Menthyl+ 2xCH_3), 3.18 (q, *J* = 7.01 Hz, 4H, 2x CH_2), 4.64 (dt, *J* = 10.79, 10.75, 4.27 Hz, 1H. CH-O), 5.79 (dd, *J* = 14.50, 7.84 Hz, 1H, CH=CH-N), 6.42 (d, *J* = 8.62 Hz, 2H, CH_{ar}), 6.73 (t, *J* = 7.32, 7.32 Hz, 1H, CH_{ar}), 7.04 (m, 7H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 12.6 (CH_3), 16.4 (CH_3), 20.9 (CH_3), 22.0 (CH_3), 23.5 (CH_2), 26.3 (CH), 31.4 (CH), 34.2 (CH_2), 41.4 (CH_2), 44.2 (CH_2), 47.3 (CH), 57.0 (CH), 108.2 (CH=CH-N), 111.10 (CH_{ar}), 124.6 (CH_{ar}), 124.9 (CH_{ar}), 125.9 (CH_{ar}), 126.5 (CH_{ar}), 127.0 (CH_{ar}), 127.5 (CH_{ar}), 128.1 (CH_{ar}), 128.4 (CH_{ar}), 128.7 (CH_{ar}), 130.7 ($C_{q,ar}$), 132.1 ($C_{q,ar}$), 147.1 ($C_{q,ar}$-NEt_2), 153.1 (CO).
HRMS (ESI) *m/z*: $C_{30}H_{41}N_2O_2$ ($M+H^+$) calcd. 461.3163
found 461.3159

(1*R*)-Menthyl 1-(5-morpholino-3-phenyl-4-(*p*-tolyl)-thien-2-yl)-1,2-dihydroisoquinoline-2-carboxylate (4m). 51 % yield of the product was obtained as colourless foam. R_f: 0.,23 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.53-2.10 (m, 18H, Menthyl), 2.15 (s, 3H, Ph-CH_3), 2.69 (m, 2H, 2x CH_2-N), 3.50 (t, *J* = 3.78 Hz, 2H, 2xCH_2-O), 4.47-4.78 (m, 1H, CH-O), 5.82 (d, *J* = 7.87 Hz, 1H, C<u>H</u>=CH-N), 6.16 (s, 1H, N-C<u>H</u>-C_q,Thiophen), 7.55-6.52 (m, 14H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.1 (CH_3), 21.2 (CH_3), 22.2 (CH_3), 23.1 (CH_2), 25.8 (CH), 31.6 (CH), 34.5 (CH_2), 45.0 (CH_2), 50.1 (CH), 52.8 (CH_2-N), 53.7 (CH), 66.7 (CH_2-O), 76.8 (CH), 107.8 (<u>C</u>H=CH-N), 124.7 (CH_{ar}), 126.2 (CH_{ar}), 126.8 (CH_{ar}), 127.5 (CH_{ar}), 128.3 (2xCH_{ar}), 129.9 (2xCH_{ar}), 132.6 ($C_{q,ar}$), 135.4 ($C_{q,ar}$), 136.6 ($C_{q,ar}$), 150.6 (CO).
HRMS (ESI) *m/z*: $C_{41}H_{46}N_2O_3S$ ($M+H^+$) calcd. 647.3312
found 647.3302

(1*R*)-Menthyl 4-bromo-1-(4-(diethylamino)phenyl)-1,2-dihydroisoquinoline-2-carboxylate (4n). 70 % yield of the product was obtained as colourless oil. R_f: 0.54 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.61-2.07 (m, 24H, Menthyl+ 2xCH_3), 3.20 (q, *J* = 7.03 Hz, 4H, 2xCH_2), 4.55-4.77 (m, 1H, CH-O), 6.42 (t, *J* = 8.45 Hz, 3H, CH_{ar}+N-C<u>H</u>), 6.83-7.08- (m, 3H, CH_{ar}), 7.20 (td, *J* = 14.37, 5.93 Hz, 3H, CH_{ar}), 7.46 (d, *J* = 7.60 Hz, 1H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 12.5 (CH_3), 16.2 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.3 (CH_2), 26.3 (CH), 31.4 (CH), 34.2 (CH_2), 41.3 (CH_2), 44.2 (CH_2), 47.2 (CH), 57.2 (CH), 77.1 (CH), 103.6 (C_q-Br), 111.1 (<u>C</u>H=CH-N), 124.6 (CH_{ar}), 125.7 (CH_{ar}), 127.0 (CH_{ar}), 127.8 (CH_{ar}), 128.1 (CH_{ar}), 128.4 (CH_{ar}), 128.6 (CH_{ar}), 129.9 ($C_{q,ar}$), 147.2 ($C_{q,ar}$-NEt_2), 152.4 (CO).
Elemental analysis: $C_{30}H_{39}N_2O$
calcd. C: 66.78 H: 7.29 N: 5.19
found C: 66.61 H: 7.49 N: 5.07

(1*R*)-Menthyl 4-bromo-1-(1*H*-indol-3-yl)-1,2-dihydroisoquinoline-2-carboxylate (4o). 93 % yield of the product was obtained as reddish foam. R_f: 0.62 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.56-2.04 (m, 18H, Menthyl), 4.73 (m, 1H, CH-O), 6.32, 6.50, 6.57 (3xs, together 1H, N-CH), 6.80 (d, *J* = 9.92 Hz, 1H, CH_{ar}), 7.05 (m, 4H, CH_{ar}), 7.15-7.36 (m, 3H, CH_{ar}), 7.51 (d, *J* = 7.58 Hz, 1H, CH_{ar}), 7.79 (d, *J* = 7.48 Hz, 1H, CH_{ar}), 7.91 (d, *J* = 12.53 Hz, 1H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 20.8 (CH_3), 22.0 (CH_3), 23.2 (CH_2), 26.1 (CH), 31.4 (CH), 34.1 (CH_2), 41.3 (CH_2), 47.1 (CH), 51.5 (CH), 76.9 (CH), 101.1 (C_q-Br), 107.8 (<u>C</u>$_{q,Indol}$-CH), 111.0 ($CH_{ar,Indol}$), 120.0 (CH_{ar}), 122.2 (CH_{ar}), 124.6 (CH_{ar}), 124.7 ($C_{q,ar}$), 125.5 ($C_{q,ar}$), 126.5 (CH_{ar}), 127.9 ($C_{q,ar}$), 128.0 (CH_{ar}), 128.4 (CH_{ar}).
Elemental analysis: $C_{30}H_{39}N_2O$
calcd. C: 66.27 H: 6.16 N: 5.52
found C: 65.95 H: 6.32 N: 5.28

(1*R*)-Menthyl 1-(1*H*-indol-3-yl)-4-phenyl-1,2-dihydroisoquinoline-2-carboxylate (4p). 82 % yield of the product was obtained as slightly yellow foam. R_f: 0.42 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.51-2.13 (m, 18H, Menthyl), 4.86-4.55 (m, 1H, CH-O), 6.78-6.46 (m, 2H, $CH_{ar.}$), 6.86 (t, *J* = 9.66 Hz, 1H, $CH_{ar.}$), 7.14 (ddq, *J* = 13.97, 8.69, 6.42 Hz, 8H, $CH_{ar.}$), 7.46-7.26 (m, 5H, $CH_{ar.}$), 7.99-7.82 (m, 2H, $CH_{ar.}$).
^{13}C-NMR ($CDCl_3$): δ = 16.6 (CH_3), 20.2 (CH), 20.4 (CH_3), 21.7 (CH_3), 22.9 (CH_2), 25.7 (CH), 31.0 (CH), 33.9 (CH_2), 41.0 (CH_2), 46.8 (CH), 51.2 (CH-N), 76.1 (CH-O), 110.6 (CH_{ar}), 117.0 ($C_{q,ar}$), 119.5 (C=CH-N), 120.0 (CH_{ar}), 121.7 (CH_{ar}), 122.8 (CH_{ar}), 123.6 (CH_{ar}), 124,1 (CH_{ar}), 126,5 ($C_{q,ar}$), 126.9(CH_{ar}), 127.0 (CH_{ar}), 128.2 (CH_{ar}), 128.8 (CH_{ar}), 132.6 ($C_{q,ar}$), 135.9 ($C_{q,ar}$), 137.3 ($C_{q,ar}$), 152.8 (CO).
HRMS (EI) *m/z*: $C_{34}H_{36}N_2O_2$ calcd. 504.27768
found 504.27767

(1*R*)-Menthyl 4-(4-chlorophenyl)-1-(1*H*-indol-3-yl)-1,2-dihydroisoquinoline-2-carboxylate (4q). 97 % of the product was obtained as brownish foam. R_f: 0.63 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.53-2.06 (m, 18H), 4.70 (tdd, *J* = 15.47, 10.96, 5.68 Hz, 1H, CH-O), 6.64 (s, 1H, CH-N), 6.83 (d, *J* = 8.97 Hz, 1H, $CH_{ar.}$), 6.93-7.12 (m, 3H, $CH_{ar.}$), 7.19 (dd, *J* = 10.21, 7.10 Hz, 4H, $CH_{ar.}$), 7.37-7.24 (m, 3H, $CH_{ar.}$), 7.38-7.64 (m, 1H, $CH_{ar.}$), 7.66-8.10 (m, 2H, $CH_{ar.}$).
^{13}C-NMR ($CDCl_3$): δ = 16.3 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.4 (CH_2), 26.3 (CH), 31.5 (CH), 34.2 (CH_2), 41.3 (CH_2), 47.2 (CH), 51.6 (CH), 76.7(CH-O), 111.0 ($CH_{ar,Indol}$), 119.9 (CH_{ar}), 120.3 (CH_{ar}), 122.2 (CH_{ar}), 123.3 (CH_{ar}), 123.7 (CH_{ar}), 124.4 (CH_{ar}), 125.8, 127.1 (CH_{ar}), 127.5 (CH_{ar}), 128.7 (CH_{ar}), 130.4 (CH_{ar}), 133.0 ($C_{q,ar}$), 136.1 ($C_{q,ar}$), 153.1(CO).
HRMS (EI) *m/z*: $C_{34}H_{35}ClN_2O_2$ calcd. 538.2387
found 538.2385

Method B. General procedure
Anhydrous $AlCl_3$ (20 mol%) was added to a solution of (-)-*(R)*-menthyl chloroformate (2.00 mmol) in dry dichloromethane (50 ml) at -40 °C. After 5 min. a solution of the isoquinoline **1** (2.00 mmol) in dry dichloromethane (5 ml) was added slowly under the exclusion of humidity. After the solution had turned yellowish turbid (about 45 – 60 min.) it was cooled down to -78 °C. A solution of ArM (2.00 mmol) in THF or toluene (20 ml, Table 2) was added over a period of 45 min. After stirring overnight the mixture was allowed to warm up to rt. The mixture was quenched with satd. aqueous NH_4Cl (30 ml) and extracted with dichloromethane (3 x 40 ml). The combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography with dichloromethane.
(1*R*)-Menthyl 1-phenyl-1,2-dihydroisoquinoline-2-carboxylate (4r). Following method B using PhMgBr in THF 82 % yield (dr = 55:45) of the product was obtained as slightly yellow oil. With Ph_2Zn in THF and in toluene 76 % dr = 64:36) and 78 % yield (70:30), respectively, were obtained. R_f: 0.73 (DCM).

^{1}H-NMR ($CDCl_3$): δ = 0.70-2.20 (m, 18H, Menthyl); 4.65-4.80 (m, 1H, CH-O); 5.87 (m, 1H, N-CH=C<u>H</u>); 6.28, 6.30, 6.55 (s, together 1 H, ArCHN); 6.80-7.40 (m, 10H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.4 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.5 (CH_2), 26.5 (CH), 31.4 (CH), 34.2 (CH_2), 41.4 (CH_2), 47.4 (CH), 57.7 (<u>C</u>H-Ph), 76.9 (CH-O), 108.4 (N-CH=<u>C</u>H), 124.8 (CH_{ar}), 125.0 (CH_{ar}), 125.1 (CH_{ar}), 125.8 (CH_{ar}), 126.0 (CH_{ar}), 126.5 (CH_{ar}), 126.9 (CH_{ar}), 127.1 (CH_{ar}), 127.3 (CH_{ar}), 127.5 (CH_{ar}), 127.9 (CH_{ar}), 128.3 (CH_{ar}), 130.5 ($C_{q,ar}$), 131.4 ($C_{q,ar}$), 141.9 ($C_{q,ar}$), 146.8 ($C_{q,ar}$), 153.1 (CO).
HRMS (EI) *m/z*: $C_{26}H_{31}NO_2$ calcd. 389.23548
found 389.23554

(1*R*)-Menthyl 1-(4-bromophenyl)-1,2-dihydroisoquinoline-2-carboxylate (4s). Following method B using 4-BrPhMgBr in THF 62 % yield (dr = 1:1) of the product was obtained as yellow sticky oil. R_f : 0.66 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.42-2.06 (m, 18H, Menthyl), 4.64 (dt, *J* = 10.83, 4.25 Hz, 1H), 5.79 (dd, *J* = 13.73, 8.66 Hz, 1H, N-CH=C<u>H</u>), 6.16, 6.20, 6.43 (3xd, *J* =5.50, 6.79, 15.87 Hz, together 1H, Ph-CH-N), 6.78 (t, *J* = 8.09 Hz, 1H, CH_{ar}), 6.92-7.23 (m, 7H, CH_{ar}), 7.22-7.38 (m, 2H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.4 (CH_3), 20.8 (CH_3), 21.9 (CH_3), 23.5 (CH_2), 26.5 (CH), 31.4 (CH), 34.1 (CH_2), 41.3 (CH_2), 47.3 (CH), 57.1 (CH), 76.8 (CH-O), 108.0 (<u>C</u>H=CH-N), 121.5 ($C_{q,ar}$-Br), 124.9 (CH_{ar}), 125.8, 127.2 (CH_{ar}), 127.8 (CH_{ar}), 128.1 (CH_{ar}), 128.2 (CH_{ar}), 128.8 (CH_{ar}), 131.5 ($C_{q,ar}$), 140.9 ($C_{q,ar}$), 153.0 (CO).
HRMS (EI) *m/z*: $C_{26}H_{30}BrNO_2$ calcd. 467.14599
found 467.14598

(1*R*)-Menthyl 1-benzyl-1,2-dihydroisoquinoline-2-carboxylate (4t). Following method B using BnMgBr in THF 55 % yield (dr = 60:40) of the product was obtained as colourless oil. 87 % yield (dr = 60:40) was obtained when Bn_2Zn in THF was used. R_f: 0.82 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.6-2.2 (m, 18 H, Menthyl); 2.70-3.10 (m, 2 H, $ArCH_2$); 4.55-4.75 (m, 1H, CH-O), 5.27 (t, *J* = 6.99, 6.99 Hz, 0,4H) u. 5.46 (t, *J* = 7.11, 7.11 Hz, 0,6H)(together 1H, CH_2-C<u>H</u>-N), 5.73 (t, *J* = 7.41 Hz, 0.6H, CH_{ar}), 5.85 (t, *J* = 8.11 Hz, 0.4H, CH_{ar}), 6.54-6.66 (m, 1H, CH_{ar}), 6.69-6.82 (m, 1H, CH_{ar}), 6.83-7.03 (m, 4H, CH_{ar}), 7.04-7.33 (m, 5H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ = 16.7 (CH_3), 20.7 (CH_3), 22.1 (CH_3), 23.7 (CH_2), 26.3 (CH), 31.4 (CH), 34.3 (CH_2), 41.3 (CH_2), 47.3 (CH), 57.0 (Ar-CH-N), 76.3 (CH-O), 108.1 (<u>C</u>H-CH-N), 124.4 (CH_{ar}), 126.3 (CH_{ar}), 126.4 (CH_{ar}), 127.9 (CH_{ar}), 128.0 (CH_{ar}), 129.8 (CH_{ar}), 130.3 ($C_{q,ar}$), 131.8 ($C_{q,ar}$), 137.1 ($C_{q,ar}$), 153.1 (C=O).
HRMS (EI) *m/z*: $C_{27}H_{33}NO_2$ calcd. 403.25113
found 403.25116

α-Cbz-Aminoacid fluorides 2b. General procedure
Dry pyridine (2.5 mmol) was added to a suspension of the corresponding Cbz-protected amino acid in dichloromethane (50 ml) under the exclusion of humidity. After cooling the clear solution to – 10 °C, cyanuric fluoride (3.125 mmol) was added drop wise over a period of 30 min. The

mixture was stirred at 0 °C for 2-3 h while cyanuric acid precipitated. The reaction mixture was poured into ice/water (100 ml). The resulting layers were separated quickly. The aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried ($MgSO_4$). After removal of the solvent at a rotatory evaporator a colourless oil remained, which crystallized after a short time.

(2*S*)-2(*N*-Benzyloxycarbonyl)propionyl fluoride 2b (R^2 = Me). 98 % yield of the product was obtained as colourless oil.
^{1}H-NMR ($CDCl_3$): δ = 1.43 (d, 3H, *J* = 7.5, CH-C<u>H</u>$_3$), 4.45 (m, 1H, C<u>H</u>-CH$_3$), 5.05 (s, 2H, C<u>H</u>$_2$), 5.27 (d, 1H, *J* = 7.1, NH), 7.21-7.30 (m, 5H, CH $_{ar.}$).
^{13}C-NMR ($CDCl_3$): δ = 16.7 (CH-<u>C</u>H$_3$), 48.5 (d, *J* = 62.75 Hz, <u>C</u>H-CH$_3$), 67.1 (<u>C</u>H$_2$), 128.2 (<u>C</u>H$_{ar.}$), 128.4 (<u>C</u>H$_{ar.}$), 128.6 (<u>C</u>H$_{ar.}$), 135.6 (C$_{ar.}$), 155.6 (O-CO-N), 163.1 (d, *J* = 370.60 Hz, C(O)F).
^{19}F-NMR ($CDCl_3$): δ = 27.4 (COF).

(2*S*)-2(*N*-Benzyloxycarbonyl)-3-phenylpropionyl fluoride 2b (R^2 = Benzyl). 93 % yield of the product was obtained as colourless oil.
^{1}H-NMR ($CDCl_3$): δ = 3.09 (m, 2H, CH-C<u>H</u>$_2$), 4.74 (m, 1H, C<u>H</u>-CH$_2$), 5.02 (s, 2H, OC<u>H</u>$_2$-Ph), 7.05-7.26 (m, 11H, 10 CH $_{ar.}$ and NH).
^{13}C-NMR ($CDCl_3$): δ = 36.8 (CH-<u>C</u>H$_2$), 53.8 (d, *J* = 60.05 Hz <u>C</u>H-CH$_2$), 67.5 (O<u>C</u>H$_2$-Ph), 127.8 (CH$_{ar.}$), 128.2 (CH$_{ar.}$), 128.6 (2CH$_{ar.}$), 129.1 (2CH$_{ar.}$), 129.2 (2CH$_{ar.}$), 129.4 (2CH$_{ar.}$) 134.2 (OCH$_2$- <u>C</u>$_{ar.}$), 135.6 (C$_{ar.}$), 155.6 (O-CO), 161.9 (d, *J* = 369.88 Hz, COF).
^{19}F-NMR ($CDCl_3$): δ = 30.5 (COF).
Elemental analysis: $C_{17}H_{16}FNO_3$
calcd. C: 67.76 H: 5.35 N: 4.65
found C: 67.64 H: 5.68 N: 4.92

2-(α-Cbz-aminoacyl)-1-aryl-1,2-dihydroisoquinolines 5 (R^1 = H) and Imidazoisoquinolines 6 (R^1 = H)
Method C. General procedure
$AlCl_3$ (20 mmol) was added to a solution of the aminoacid fluoride **2b** (1.00 mmol) in dry dichloromethane (50 ml) at -20 °C. After 30 min a solution of isoquinoline (1.00 mmol) in dry dichloromethane (5 ml) was added slowly under argon maintaining – 20°C. After stirring for 3 h the mixture was allowed to warm up to 0 °C. After the solution had turned red it was cooled to – 78 °C and a solution of Ar-H (1.00 mmol) in dichloromethane (20 ml) was added over a period of 45 min. The mixture was stirred overnight while it slowly warmed up to rt. Saturated aqueous $NaHCO_3$ (20 ml) was added, the layers were separated and the aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), the solvent removed and the residue was purified by column chromatography.

(*S*)-2-(*N*-Benzyloxycarbonyl-2-aminopropionyl)-1-(4-(*N,N*-diethylamino)phenyl)-1,2-dihydroisoquinoline (5a). 21 % yield of the product was obtained as slightly yellow oil. dr = 82:18, R_f : 0.21 (c-Hex/AcOEt, 8:2).

^{1}H-NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.07 Hz, 6H, 2x CH_3), 1.39 (d, *J* = 6.84 Hz, 3H, CH-C<u>H</u>$_3$), 3.39 (q, *J* = 7.06 Hz, 4H, 2x CH_2), 4.33 (dq, *J* = 6.65, 1.86 Hz, 1H, C<u>H</u>-CH_3), 5.14 (s, 2H, CH_2-Ph), 6.34 (d, *J* = 7.37 Hz, 1H, C<u>H</u>=CH-N), 6.53 (d, *J* = 8.23 Hz, 1H, CH_{ar}), 6.79-6.67 (m, 2H, CH_{ar}), 6.92 (d, *J* = 7.34 Hz, 1H, CH=C<u>H</u>-N), 7.50-7.13 (m, 11H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 12.5 (2x CH_3), 19.3 (CH_3), 44.2 (2x CH_2), 47.9 (<u>C</u>H-CH_3), 55.7 (CH), 66.7 (O-CH_2), 112.4 (<u>C</u>H=CH-N), 116.5 (2x$CH_{ar.}$), 121.0 (<u>C</u>H_{ar}), 123.4 (<u>C</u>H_{ar}), 125.4 (<u>C</u>H_{ar}), 128.0 (<u>C</u>H_{ar}), 128.4 (<u>C</u>H_{ar}), 128.6 (<u>C</u>H_{ar}), 128.7 (<u>C</u>H_{ar}), 129.3 (<u>C</u>H_{ar}), 129.9 ($C_{q,ar}$), 130.7 ($C_{q,ar}$), 135.4 ($C_{q,ar}$), 136.5 ($C_{q,ar}$), 155.4 (CO_2-Bn), 168.6 (CON).

HRMS (ESI) *m/z*: $C_{30}H_{34}N_3O_3$ ($M+H^+$) calcd. 484.2600
found 484.2595

(*S*)-2-(*N*-Benzyloxycarbonyl-2-amino-3-phenylpropionyl)-1-(4-(*N,N*-diethylamino)phenyl)-1,2-dihydroisoquinoline (5b). 21 % yield of the product was obtained as slightly yellow oil. dr = 72:28, R_f = 0.21 (C-Hex/AcOEt, 8:2).

^{1}H-NMR ($CDCl_3$): δ = 1.12 (t, *J* = 7.22 Hz, 6H, 2x CH_3), 3.11-2.95 (m, 2H, CH_2), 3.28 (dd, *J* = 13.49, 6.57 Hz, 4H, 2x CH_2), 5.03 (dd, *J* = 14.24, 6.34 Hz, 1H, C<u>H</u>-CH_2-Ph), 5.12 (d, *J* = 2.92 Hz, 2H, O-CH_2-Ph), 5.82 (d, *J* = 8.06 Hz, 1H, CH_{ar}), 6.00 (d, *J* = 7.80 Hz, 1H, C<u>H</u>=CH-N), 6.50 (d, *J* = 6.91 Hz, 2H, CH_{ar}), 6.65 (s, 1H, CH_{ar}), 6.91-7.41 (m, 16H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 12.5 (2x CH_3), 39.2 (CH-<u>C</u>H_2-Ph), 44.3 (2x CH_2), 53.0 (<u>C</u>H-CH_2-Ph), 56.0 (CH-Ph), 66.8 (CH_2-O), 110.9 (<u>C</u>H=CH-N), 112.9 (2x$CH_{ar.}$), 123.3 (<u>C</u>H_{ar}), 125.1 (<u>C</u>H_{ar}), 126.8 (<u>C</u>H_{ar}), 127.2 (<u>C</u>H_{ar}), 128.0 (<u>C</u>H_{ar}), 128.2 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 129.3 (<u>C</u>H_{ar}), 129.6, 130.0 (<u>C</u>H_{ar}), 135.4 ($C_{q,ar}$), 136.3 ($C_{q,ar}$), 147.2 ($C_{q,ar}$), 155.5 (CO_2-Bn), 166.8 (CON).

HRMS (ESI) *m/z*: $C_{36}H_{38}N_3O_3$ ($M+H^+$) calcd. 560.2913
found 560.2908

(*S*)-2-(*N*-Benzyloxycarbonyl-2-amino-3-phenylpropionyl)-1-(4-(*N,N*-dimethylamino) phenyl) -1,2-dihydroisoquinoline (5c). 44 % yield of the product was obtained as slightly yellow oil. dr = 78:22, R_f = 0.19 ($CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ = 2.89 (s, 3H, CH_3), 2.96 (s, 2H, CH_2), 2.99 (s, 3H, CH_3), 4.93-5.08 (m, 1H, C<u>H</u>-CH_2), 5.13 (d, *J* = 3.40 Hz, 2H, CH_2-O), 5.85 (d, *J* = 8.17 Hz, 1H, CH_{ar}), 6.01 (d, *J* = 7.82 Hz, 1H, C<u>H</u>=CH-N), 6.59 (d, *J* = 8.83 Hz, 1H, CH_{ar}), 6.65 (dd, *J* = 7.07, 5.19 Hz, 2H, CH_{ar}), 6.76-7.42 (m, 16H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 39.2 (CH-<u>C</u>H_2-Ph), 40.5 (2x CH_3), 53.0 (CH-Ph), 56.0 (<u>C</u>H-CH_2), 66.8 (CH_2-O), 112.1 (<u>C</u>H=CH-N), 112.9 (2x<u>C</u>H_{ar}), 115.8 (<u>C</u>H_{ar}), 123.3 (<u>C</u>H_{ar}), 125.0 (<u>C</u>H_{ar}), 125.2 (<u>C</u>H_{ar}), 126.9 (<u>C</u>H_{ar}), 127.2 (<u>C</u>H_{ar}), 127.6 (<u>C</u>H_{ar}), 128.0 (<u>C</u>H_{ar}), 128.1 (<u>C</u>H_{ar}), 128.3 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 128.9 (<u>C</u>H_{ar}), 129.1 (<u>C</u>H_{ar}), 129.3 (<u>C</u>H_{ar}), 129.5 (<u>C</u>H_{ar}), 129.9 (<u>C</u>H_{ar}), 133.0 ($C_{q,ar}$), 135.1 ($C_{q,ar}$), 135.4 ($C_{q,ar}$), 136.4 ($C_{q,ar}$), 149.8 ($C_{q,ar}$), 155.5 (CO_2-Bn), 169.6 (CON).

HRMS (ESI) *m/z*: $C_{34}H_{34}N_3O_3$ ($M+H^+$) calcd.532.2595
found 532.2603

(*S*)-2-(*N*-Benzyloxycarbonyl-2-aminopropionyl)-1-(1*H*-pyrrol-2-yl)-1,2-dihydroisoquinoline (5e). 32% yield of the major diastereomer and 14% of the minor diastereomer was obtained as slightly yellow oil.
Major diastereomer: R_f = 0.21 (DCM +1% acetone).
^{1}H-NMR ($CDCl_3$): δ = 1.40 (d, *J* = 6.97 Hz, 3H, CH_3), 4.82 (p, *J* = 6.91 Hz, 1H, C<u>H</u>-CH_3), 5.16 (s, 2H, CH_2-O), 5.45 (s, 1H, CH_{ar}), 5.89 (d, *J* = 6.55 Hz, 1H, CH_{ar}), 5.99 (dd, *J* = 5.76, 2.89 Hz, 1H, CH_{ar}), 6.09 (d, *J* = 7.74 Hz, 1H, C<u>H</u>=CH-N), 6.61 (d, *J* = 7.69 Hz, 1H, CH=C<u>H</u>-N), 6.72 (d, *J* = 1.47 Hz, 1H, CH_{ar}), 6.79 (s, 1H, CH_{ar}), 7.14-7.50 (m, 8H, CH_{ar}), 8.82 (s, 1H, NH).
^{13}C-NMR ($CDCl_3$): δ = 19.1 (CH_3), 47.9 (<u>C</u>H-$C_{q,Pyrrol}$), 51.3 (<u>C</u>H-CH_3), 67.0 (CH_2-O), 107.5 (<u>C</u>$H_{ar,Pyrrol}$), 108.5 (<u>C</u>H=CH-N), 112.0 (<u>C</u>$H_{ar,Pyrrol}$), 116.0 (<u>C</u>$H_{ar,Pyrrol}$), 118.3 (<u>C</u>H_{ar}), 122.4 (<u>C</u>H_{ar}), 125.1 (<u>C</u>H_{ar}), 125.3 (<u>C</u>H_{ar}), 127.6 (<u>C</u>H_{ar}), 127.7 (<u>C</u>H_{ar}), 128.1 (<u>C</u>H_{ar}), 128.2 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 128.7 (<u>C</u>H_{ar}), 130.0 ($C_{q,ar}$), 130.5 ($C_{q,ar}$), 131.6 ($C_{q,ar}$), 155.5 (CO_2-Bn), 172.5 (CON).
HRMS (ESI) *m/z*: $C_{24}H_{24}N_3O_3$ ($M+H^+$) calcd. 402.1818
found 402.1812
Minor diastereomer: R_f = 0.13 (DCM +1% acetone)
^{1}H-NMR ($CDCl_3$): δ = 1.39 (d, *J* = 6.81 Hz, 1H, CH_3), 4.74-4.93- (m, 1H, C<u>H</u>-CH_3), 5.13 (s, 2H, CH_2-O), 5.51 (s, 1H, CH_{ar}), 5.90-6.08 (m, 3H, CH_{ar} u. C<u>H</u>=CH-N), 6.53 (d, *J* = 7.77 Hz, 1H, CH=C<u>H</u>-N), 6.71 (dd, *J* = 4.06, 2.49 Hz, 1H, CH_{ar}), 6.87 (s, 1H, CH_{ar}), 7.09-7.47 (m, 8H, CH_{ar}), 8.81 (s, 1H).
^{13}C-NMR ($CDCl_3$): δ = 18.5 (CH_3), 47.2 (<u>C</u>H-$C_{q,Pyrrol}$), 50.7 (<u>C</u>H-CH_3), 66.9 (CH_2-O), 107.6 (<u>C</u>$H_{ar,Pyrrol}$), 108.3 (<u>C</u>H=CH-N), 111.8 (<u>C</u>$H_{ar,Pyrrol}$), 118.2 (<u>C</u>$H_{ar,Pyrrol}$), 122.1 (<u>C</u>H_{ar}), 125.1 (<u>C</u>H_{ar}), 125.5 (<u>C</u>H_{ar}),127.6 (<u>C</u>H_{ar}), 128.1 (<u>C</u>H_{ar}), 128.3 (<u>C</u>H_{ar}), 128.6 (<u>C</u>H_{ar}), 129.8 ($C_{q,ar}$), 130.3 ($C_{q,ar}$), 131.9 ($C_{q,ar}$), 136.3 ($C_{q,ar}$), 155.5 (CO_2-Bn), 172.0 (CON).

(*S*)-2-(*N*-Benzyloxycarbonyl-2-amino-3-phenylpropionyl)-1-(1*H*-indol-3-yl)-1,2-dihydro-isoquinoline (5f). 63 % yield of the product was obtained as slightly yellow oil. dr = 2:1, R_f = 0.23 (DCM +1,5% acetone).
^{1}H-NMR ($CDCl_3$): δ = 2.84-3.25 (m, 2H, CH-C<u>H</u>$_2$-Ph), 4.96-5.22 (m, 3H, C<u>H</u>-CH_2-Ph, CH_2-O), 6.09 (d, *J* = 7.55 Hz, 1H, C<u>H</u>=CH-N), 6.55 (s, 1H, N-CH), 6.82 (dd, *J* = 18.64, 7.14 Hz, 1H, CH_{ar}), 6.96-7.32 (m, 1H, CH_{ar}), 7.32-7.51 (m, 12H, CH_{ar}), 7.94 (t, *J* = 7.91 Hz, 5H, CH_{ar}), 8.46 (s, 1H, NH).
^{13}C-NMR ($CDCl_3$): δ = 39.1 (CH-<u>C</u>H_2-Ph), 50.2 (CH-N), 53.2 (<u>C</u>H-CH_2-Ph), 66.9 (CH_2-O), 111.2 (<u>C</u>H=CH-N), 113.7 (<u>C</u>H_{ar}), 115.8,119.9 (<u>C</u>H_{ar}), 120.2 (<u>C</u>H_{ar}), 122.1 (<u>C</u>H_{ar}), 123.3 (<u>C</u>H_{ar}), 125.2 (<u>C</u>H_{ar}), 128.0 (<u>C</u>H_{ar}), 128.3 (<u>C</u>H_{ar}), 128.5v, 129.4 (<u>C</u>H_{ar}), 130.0 ($C_{q,ar}$), 133.4 ($C_{q,ar}$), 135.4 ($C_{q,ar}$), 136.2 ($C_{q,ar}$), 136.4 ($C_{q,ar}$), 155.6 (CO_2-Bn), 169.4 (CON).
HRMS (ESI) *m/z*: $C_{34}H_{30}N_3O_3$ ($M+H^+$) calcd. 528,2282
found 528.2292

(*S*)-2-(*N*-Benzyloxycarbonyl-2-aminopropionyl)-1-(1*H*-indol-3-yl)-1,2-dihydroiso- quinoline (5g). 56 % yield of the product was obtained as slightly yellow oil. dr = 2:1. R_f = 0.23 (DCM +1.5% acetone).

^{1}H-NMR ($CDCl_3$): δ = 1.40 (d, *J* = 6.82 Hz, 3H, CH_3), 4.76 (p, *J* = 6.84, 6.84, 6.83, 6.83 Hz, 1H, CH-CH_3), 5.11 (d, *J* = 2.76 Hz, 2H, CH_2-O), 6.12 (d, *J* = 7.52 Hz, 1H, C<u>H</u>=CH-N), 6.16 (d, *J* = 7.61 Hz, 1H, CH_{ar}), 6.57 (d, *J* = 7.48 Hz, 1H, CH=C<u>H</u>-N), 6.62 (d, *J* = 2.30 Hz, 1H, CH_{ar}), 7.33-7.06 (m, 9H, CH_{ar}), 7.49-7.34 (m, 5H, CH_{ar}), 7.91 (d, *J* = 7.32 Hz, 1H, CH_{ar}), 8.48 (s, 1H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 19.2 (CH_3), 48.0 (CH-N), 50.1 (CH-CH_3), 66.8 (CH_2-O), 111.2 (<u>C</u>H_{ar}), 113.2 (<u>C</u>H=CH-N), 116.2 (<u>C</u>$_{q,Indol}$-CH-N), 119.9 (<u>C</u>H_{ar}), 120.2 (<u>C</u>H_{ar}), 122.2 (<u>C</u>H_{ar}), 123.4 (<u>C</u>H_{ar}), 125.1 (<u>C</u>H_{ar}), 125.5($C_{q,ar}$), 127.0 (<u>C</u>H_{ar}), 128.0 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 129.9($C_{q,ar}$), 133.6 ($C_{q,ar}$), 136.2 ($C_{q,ar}$), 136.3 ($C_{q,ar}$), 155.5 (CO_2-Bn), 170.8 (CON).

HRMS (ESI) *m/z*: $C_{28}H_{26}N_3O_3$ ($M+H^+$) calcd. 452.1969
found 452.1979

(2S,10b*R*)-Benzyl-2-methyl-3-oxo-2,3-dihydroimidazo[2,1-a]isoquinoline-1(10b*H*)-carboxylate (6). 35-72 % yield was obtained depending on ArH of the product as slightly yellow oil. dr 1:1 – 95:5. R_f = 0.22 (DCM +1% acetone).

^{1}H-NMR ($CDCl_3$): δ = 1.48 (d, *J* = 6.89 Hz, 3H, CH_3), 4.52 (d, *J* = 6.35 Hz, 1H, C<u>H</u>-CH_3), 5,32 (s, 2H, CH_2-O), 6.22 (s, 1H, CH-N), 6.29 (d, *J* = 7.43 Hz, 1H, C<u>H</u>=CH-N), 6.90 (d, *J* = 7.40 Hz, 1H, CH=C<u>H</u>-N), 7.21-7.09 (m, 1H, CH_{ar}), 7.34-7.25 (m, 3H, CH_{ar}), 7.63-7.34 (m, 6H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 19.2 (CH_3), 56.1 (CH-CH_3), 68.0 (CH_2-O), 70.8 (CH-N), 115.9 (<u>C</u>H=CH-N), 120.9 (<u>C</u>H_{ar}), 123.7 (<u>C</u>H_{ar}), 125.3 (<u>C</u>H_{ar}), 128.4 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 128.6 (<u>C</u>H_{ar}), 130.3 ($C_{q,ar}$), 130.8 ($C_{q,ar}$), 135.6 ($C_{q,ar}$), 148.7 ($C_{q,ar}$), 149.4 (CO_2-Bn), 168.9 (CON).

HRMS (ESI) $C_{20}H_{19}N_2O_3$ ($M+H^+$) *m/z*: calcd. 335.1396
found 335.1395

Method D. General procedure

Anhydrous $AlCl_3$ (20 mol%) was added to a solution of aminoacid fluoride **2b** (1.00 mmol) in dry dichloromethane (50 ml) at -20 °C under exclusion of humidity. After 30 min, a solution of isoquinoline (1.00 mmol) in dry dichloromethane (5 ml) was added slowly at -20 °C. The resulting mixture was stirred for 3 h and was then allowed to warm to 0 °C. After the solution had turned to orange-red colour it was cooled to -78 °C. A solution of the Grignard reagent (1.10 mmol) in diethyl ether/dichloromethane (20 ml) was added over a period of 45 min. The mixture was stirred overnight while it warmed up to rt. Aqueous saturated $NaHCO_3$ was added and the further work up followed method C.

Benzyl-(S)-1-oxo-1-(*(R)*-1-phenylisoquinoline-2(1*H*)-yl)propan-2-ylcarbamate (5h). 50 % yield of the product was obtained as slightly brownish oil. dr = 73:27. R_f = 0.43 (DCM +2% acetone).
^{1}H-NMR ($CDCl_3$): δ =1.47 (d, *J* = 7.06 Hz, 3H, CH_3), 5.17 (d, *J* = 9.95 Hz, 2H, CH_2-O), 5.64 (br. s, 1H, C<u>H</u>-CH3), 6.09 (dd, *J* = 17.97, 7.69 Hz, 1H, C<u>H</u>=CH-N), 6.92 (dd, *J* = 11.06, 4.22 Hz, 1H, CH_{ar}), 7.07-7.45 (m, 13H, CH_{ar}), 7.75-7.46 (m, 2H, CH_{ar}), 8.00 (d, *J* = 7.67 Hz, 1H, CH=C<u>H</u>-N).
^{13}C-NMR ($CDCl_3$): δ = 19.9 (CH_3), 47.9 (<u>C</u>H-CH_3), 56.6 (CH-N), 67.0 (CH_2-O), 112.7 (C<u>H</u>=CH-N), 120.1 (<u>C</u>H_{ar}), 125.5 (<u>C</u>H_{ar}), 125.8 (<u>C</u>H_{ar}), 126.9 (<u>C</u>H_{ar}), 127.3 (<u>C</u>H_{ar}), 128.1 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 128.9 (<u>C</u>H_{ar}), 129.5 (<u>C</u>H_{ar}), 129.8 ($C_{q,ar}$), 132.5 ($C_{q,ar}$), 133.9 ($C_{q,ar}$), 135.3 ($C_{q,ar}$), 136.3 ($C_{q,ar}$), 140.6 ($C_{q,ar}$), 145.0 ($C_{q,ar}$), 155.9 (CO_2-Bn), 171.4 (CON).
HRMS (ESI) $C_{26}H_{25}N_2O_3$ ($M+H^+$) *m/z*: calcd. 413.1865
found 415.1871

Benzyl-(S)-1-(*(R)*-1-benzylisoquinoline-2(1*H*)-yl)-1-oxopropan-2-ylcarbamate (5i). 69 % yield of the product was obtained as slightly yellow oil. dr = 2:1. R_f = 0.51 (DCM +2% acetone).
^{1}H-NMR ($CDCl_3$): δ = 1.47 (d, *J* = 7.21 Hz, 3H, C<u>H</u>$_3$-CH)), 2.97 (s, 2H, CH_2-Ph), 5.16 (d, *J* = 0.74 Hz, 2H, O-CH_2), 5.41-5.52 (m, 1H, CH_{ar}), 6.05 (dd, *J* = 7.68, 1.82 Hz, 1H, C<u>H</u>=CH-N), 6.62 (dd, *J* = 7.61, 3.29 Hz, 1H, CH=C<u>H</u>-N), 6.82 (dd, *J* = 8.63, 2.45 Hz, 1H, CH_{ar}), 7.15-7.45 (m, 13H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ =18.6 (CH_3), 37.9 (CH-<u>C</u>H_2-Ph), 47.4 (<u>C</u>H-CH_3), 55.9 (CH-N), 67.1 (CH_2-O), 111.8(C<u>H</u>=CH-N), 112.4 (<u>C</u>H_{ar}), 123.1 (<u>C</u>H_{ar}), 124.9 (<u>C</u>H_{ar}), 125.0 (<u>C</u>H_{ar}), 126.5 (<u>C</u>H_{ar}), 126.6 (<u>C</u>H_{ar}), 126.9 (<u>C</u>H_{ar}), 127.8 (<u>C</u>H_{ar}), 128.0 (<u>C</u>H_{ar}), 128.2 (<u>C</u>H_{ar}), 128.4 (<u>C</u>H_{ar}), 128.5 (<u>C</u>H_{ar}), 128.6 (<u>C</u>H_{ar}), 129.9 (<u>C</u>H_{ar}), 132.3 ($C_{q,ar}$), 135.3 ($C_{q,ar}$), 136.9 ($C_{q,ar}$), 141.8 ($C_{q,ar}$), 155.6 (CO_2-Bn), 170.6 (CON).
HRMS (ESI) $C_{27}H_{27}N_2O_3$ ($M+H^+$) *m/z*: calcd. 427.2022
found 427.2025

Tetrahydroisoquinolines 7. General procedure
The dihydroisoquinoline **4** (1.5 mmol) was dissolved in MeOH (50 ml, eventually some dichloromethane had to be added). After the addition of 20% Pd/C (about 80 mg) the mixture was put under H_2 at atmospheric pressure. After stirring for 4 h the solution was filtered and the filtrate concentrated under vacuum to 1/10 of its volume. The residue was dissolved in dichloromethane (20 ml) and dried ($MgSO_4$). Removing the solvent under vacuum gives the product which eventually was purified by column chromatography.

(1*R*)-Menthyl 1-(1*H*-indol-3-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7a). 84% yield of the product was obtained as reddish foam. R_f = 0.34 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.54 - 2.16 (m, 18H, Menthyl), 2.68 (ddd, *J* = 11.59, 6.06, 3.03 Hz, 1H, C<u>H</u>$_2$-CH_2-N), 2.82-3.03 (m, 1H, C<u>H</u>$_2$-CH_2-N), 3.11 (dd, *J* = 12.01, 8.82 Hz, 1H, CH_2-C<u>H</u>$_2$-N),

3.82-4.07 (m, 1H, CH_2-C<u>H</u>$_2$-N), 4.39-4.87 (m, 1H, CH-O), 6.53 (m, 1H, $C_{q,Indol}$-C<u>H</u>-N), 6.72 (s, 1H, CH_{ar}), 7.00-7.21 (m, 6H, CH_{ar}), 7.27 (d, *J* = 8.15 Hz, 1H, CH_{ar}), 7.73 (s, 1H, CH_{ar}), 7.96 (s, 1H, NH).

^{13}C-NMR ($CDCl_3$): δ = 20.7 (CH_3), 22.1 (CH_3), 23.7 (CH_2), 26.3 (CH), 28.7 (CH_2), 31.4 (CH), 34.4 (CH_2), 37.3 (CH_2), 41.6 (CH_2), 47.6 (CH), 51.3 (CH), 75.0 (CH-O), 110.9 ($CH_{ar,Indol}$), 119.7 (CH_{ar}), 122.3 (CH_{ar}), 125.7 (CH_{ar}), 126.6 (CH_{ar}), 128.4 ($C_{q,ar}$), 129.0 (CH_{ar}), 130.6 ($C_{q,ar}$), 134.8 ($C_{q,ar}$), 136.3 ($C_{q,ar}$), 155.0 (CO).

Elemental analysis: $C_{28}H_{34}N_2O_2$

calcd.	C: 78.10	H: 7.74	N: 6.51
found	C: 77.59	H: 8.15	N: 6.66

(1*R*)-Menthyl 1-(4-(*N*,*N*-diethylanilino)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7b). 83% yield of the product was obtained as yellow oil. R_f = 0.4 (DCM).

^{1}H-NMR ($CDCl_3$): δ = 0.71-2.14 (M, 24H, Menthyl + 2x CH_3) 2.67-2.84 (m, 1H, C<u>H</u>$_2$-CH_2-N), 2.85-3.08 (m, 1H, C<u>H</u>$_2$-CH_2-N), 3.31 (q, *J* = 7.01 Hz, 4H, 2xC<u>H</u>$_2$-CH_3), 3.22 (ddd, *J* = 13.22, 11.24, 4.35 Hz, 1H, CH_2-C<u>H</u>$_2$-N), 3.83-4.25 (m, 1H, CH_2-C<u>H</u>$_2$-N), 4.65 (dt, *J* = 10.67, 3.92 Hz, 1H, CH-O), 6.31 (2 x s, together. 1H, CH-$C_{q,ar}$), 6.56 (d, *J* = 8.18 Hz, 2H, CH_{ar}), 7.04 (m, 3H, CH_{ar}), 7.09-7.29 (m, 3H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 12.6 (2x CH_3), 16.5 (CH_3), 20.8 (CH_3), 22.1 (CH_3), 23.6 (CH_2), 26.4 (CH), 28.5 (<u>C</u>H_2-CH_2-N), 31.4 (CH), 34.4 (CH_2), 37.6 (CH_2), 41.7 (CH_2-<u>C</u>H_2-N), 44.3 (2xCH_2), 47.5 (CH), 57.0 (<u>C</u>H-$C_{q,ar}$), 75.0 (CH-O), 111.0 (CH_{ar}), 125.8 (CH_{ar}), 125.9 (CH_{ar}), 126.6 (CH_{ar}), 128.8 (CH_{ar}), 129.5 (CH_{ar}), 135.0 ($C_{q,ar}$), 136.2 ($C_{q,ar}$), 146.9 ($C_{q,ar}$-N), 155.1 (CO).

Elemental analysis: $C_{30}H_{42}N_2O_2$

calcd.	C: 77.88	H: 9.15	N: 6.05
found	C: 77.41	H: 9.46	N: 5.86

(1*R*)-Menthyl 1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7c). 54% yield of the product was obtained as colourless oil. R_f = 0.67 (DCM).

^{1}H-NMR ($CDCl_3$): δ = 0.65-2.11 (m, 18H, Menthyl), 2.56-2.77 (m, 1H, C<u>H</u>$_2$-CH_2-N), 2.76-3.00 (m, 1H, C<u>H</u>$_2$-CH_2-N), 3.03-3.31 (m, 1H, CH_2-C<u>H</u>$_2$-N), 3.78-4.23 (m, 1H, CH_2-C<u>H</u>$_2$-N), 4.58 (dt, *J* = 10.84, 4.29 Hz, 1H, CH-O), 6.16, 6.40 (2xs, together 1H, CH-$C_{q,Ph}$), 6.97 (d, *J* = 6.85 Hz, 1H, CH_{ar}), 7.03-7.28 (m, 8H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ = 16.6 (CH_3), 20.9 (CH_3), 22.1 (CH_3), 23.7 (CH_2), 26.5 (CH), 28.5 (CH_2), 31.4 (CH), 34.4 (CH_2), 38.2 (CH_2), 41.7 (CH_2), 47.6 (CH), 57.5 (CH-$C_{q,Ph}$), 75.3 (CH-O), 126.1 (CH_{ar}), 126.4 (CH_{ar}), 127.0 (CH_{ar}), 127.3 (CH_{ar}), 128.2 (CH_{ar}), 128.9 (CH_{ar}), 135.1 ($C_{q,ar}$), 135.5 ($C_{q,ar}$), 142.9 ($C_{q,ar}$), 155.3 (CO).

HRMS (EI) $C_{26}H_{33}NO_2$ *m/z*: calcd. 391.2511
found 391.2512

(1*R*)-Menthyl 1-(3-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7d). 98% yield of the product was obtained as colourless sticky oil. R_f = 0.62 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.64-2.18 (m, 18H), 2.65-2.89 (m, 1H), 2.88-3.14 (m, 1H), 3.30 (ddd, *J* = 13.17, 10.26, 4.61 Hz, 1H), 3.78 (s, 3H), 3.93-4.27 (m, 1H), 4.71 (dt, *J* = 10.84, 4.33 Hz, 1H), 6.27 u..6.48 (2xs, together 1H), 6.80 (td, *J* = 9.18, 5.96, 5.96 Hz, 3H), 7.05-7.33 (m, 5H).
^{13}C-NMR ($CDCl_3$): δ = 16.6 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.7 (CH_2), 26.5 (CH), 28.4 (CH_2), 31.4 (CH), 34.4 (CH_2), 38.2 (CH_2), 41.6 (CH_2), 47.5 (CH), 55.1 (O-CH_3), 57.6 (CH), 75.3 (CH-O), 112.7 (CH_{ar}), 114.3 (CH_{ar}), 120.6 (CH_{ar}), 126.0 (CH_{ar}), 127.0 (CH_{ar}), 128.6 (CH_{ar}), 128.8 (CH_{ar}), 129.0 (CH_{ar}), 129.1 ($C_{q,ar}$), 135.4 ($C_{q,ar}$), 144.4 ($C_{q,ar}$), 155.3 (CO), 159.5 ($C_{q,ar}$).
Elemental analysis: $C_{27}H_{35}NO_3$
calcd. C: 76,92 H: 8,37 N: 3,32
found C: 76,50 H: 8,56 N: 3,30

Tetrahydroisoquinolines 8 by cleavage of carbamate
Method E. General procedure
The carbamate **7** (2.00 mmol) and trifluoroacetic acid (15 ml) were put into a pressure glass container, sealed and heated to 110 °C for 6 h. After cooling down to rt the container was opened with caution and the mixture was adjusted to pH 9 by addition of aqueous 10M NaOH. The solution was extracted with AcOEt (3 x 30 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography

4-*N,N*-Diethylanilino-1,2,3,4-tetrahydroisoquinoline (8a). 69% yield of the product was obtained as brownish solid. R_f = 0.09, (DCM/acetone, 1:1).
^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (t, *J* = 7.07 Hz, 6H, 2x CH_3), 2.53-2.85 (m, 2H, C$\underline{H}_2$$CH_2$-N), 2.87-3.08 (m, 2H, CH_2C$\underline{H}_2$-N), 3.25 (q, *J* = 7.05 Hz, 4H, 2x CH_2), 4.94 (s, 1H, $\underline{C}$H-$C_{q,ar}$), 6.54 (d, *J* = 8.76 Hz, 2H, CH_{ar}), 6.76 (d, *J* = 7.54 Hz, 1H, CH_{ar}), 6.90-7.08 (m, 5H, CH_{ar}).
^{13}C-NMR ($CDCl_3$): δ (ppm) = 12.6 (2xCH_3), 29.6 ($\underline{C}H_2CH_2$-N), 41.9 ($CH_2\underline{C}H_2$-N), 44.3 (2xCH_2), 61.2 (CH-$C_{q,ar}$), 111.4 ($\underline{C}H_{ar}$), 125.5 ($\underline{C}H_{ar}$), 126.0 ($\underline{C}H_{ar}$), 128.2 ($\underline{C}H_{ar}$), 128.8 ($\underline{C}H_{ar}$), 129.9 ($\underline{C}H_{ar}$), 131.1 ($C_{q,ar}$), 135.2 ($C_{q,ar}$), 138.6 ($C_{q,ar}$), 147.1 ($C_{q,ar}$).
HRMS (EI) $C_{19}H_{24}N_2$ *m/z*: calcd. 280.1939
found 280.1934

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (8b). 90% yield of the product was obtained as colourless solid R_f = 0.14 (DCM/acetone, 1:1).
^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.89 (td, *J* = 9.09, 5.70 Hz, 1H, C$\underline{H}_2$$CH_2$-N), 2.96-3.17 (m, 2H, C$\underline{H}_2$$CH_2$-N, CH_2C$\underline{H}_2$-N), 3.24 (dd, *J* = 12.79, 7.57 Hz, 1H, CH_2C$\underline{H}_2$-N), 5.15 (s, 1H, CH-N), 6.74 (d, *J* = 7.56 Hz, 1H, CH_{ar}), 7.05 (dt, *J* = 8.60, 4.23 Hz, 1H, CH_{ar}), 7.16 (d, *J* = 3.86 Hz, 2H, CH_{ar}), 7.21 (dd, *J* = 7.61, 1.84 Hz, 2H, CH_{ar}), 7.25-7.37 (m, 3H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ (ppm) = 26.6 ($\underline{C}H_2CH_2$-N), 39.5 ($CH_2\underline{C}H_2$-N), 59.9 (CH-N), 126.6 ($\underline{C}H_{ar}$), 127.6 ($\underline{C}H_{ar}$), 128.2 ($\underline{C}H_{ar}$), 128.8 ($\underline{C}H_{ar}$), 128.9 ($\underline{C}H_{ar}$), 129.5 ($\underline{C}H_{ar}$), 132.9 ($C_{q,ar}$), 133.0 ($C_{q,ar}$), 138.9 ($C_{q,ar}$).

Elemental analysis: $C_{15}H_{15}N$

calcd.	C: 86.08	H: 7.22	N: 6.69
found	C: 85.88	H: 7.41	N: 6.67

1-(3-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (8c). 96% yield of the product was obtained as brownish oil. R_f = 0.29 (DCM/acetone, 1:1).

^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.85 (td, *J* = 8.54, 6.35 Hz, 1H, $C\underline{H}_2CH_2$-N), 3.00-3.17 (m, 2H, $C\underline{H}_2CH_2$-N u. $CH_2C\underline{H}_2$-N), 3.31 (td, *J* = 15.66, 6.97 Hz, 1H, $CH_2C\underline{H}_2$-N), 3.80 (s, 3H, O-CH_3), 5.11 (s, 1H, C<u>H</u>-NH), 6.73-6.94 (m, 4H, CH_{ar}), 6.98-7.13 (m, 1H, CH_{ar}), 7.17 (d, *J* = 3.84 Hz, 2H, CH_{ar}), 7.22-7.34 (m, 1H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ (ppm) = 29.7 ($\underline{C}H_2CH_2$-N), 42.2 ($CH_2\underline{C}H_2$-N), 55.2 (O-CH_3), 62.0 (CH-NH), 112.8 ($\underline{C}H_{ar}$), 114.6 ($\underline{C}H_{ar}$), 121.4 ($\underline{C}H_{ar}$), 125.6 ($\underline{C}H_{ar}$), 126.3 ($\underline{C}H_{ar}$), 128.0 ($\underline{C}H_{ar}$), 129.0 ($\underline{C}H_{ar}$), 129.3 ($\underline{C}H_{ar}$), 135.3 ($C_{q,ar}$), 138.0 ($C_{q,ar}$), 146.4 ($C_{q,ar}$), 159.6 ($C_{q,ar}$).

HRMS (EI) $C_{16}H_{17}NO$ *m/z*: calcd. 239.1310
found 239.1310

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (8d). 59% yield of the product was obtained as brownish oil. R_f = 0.14 (C-Hex/AcOEt, 1:1).

^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.79-2.91 (m, 1H, $C\underline{H}_2CH_2$-N), 2.97-3.16 (m, 2H, $C\underline{H}_2CH_2$-N, $CH_2C\underline{H}_2$-N), 3.23-3.36 (m, 1H, $CH_2C\underline{H}_2$-N), 3.81 (s, 1H, OCH_3), 5.09 (s, 1H, CH-N), 6.77 (d, *J* = 7.62 Hz, 1H, CH_{ar}), 6.83-6.91 (m, 2H, CH_{ar}), 7.06 (td, *J* = 8.55, 3.99 Hz, 1H, CH_{ar}), 7.15 (d, *J* = 3.86 Hz, 2H, CH_{ar}), 7.17-7.24 (m, 3H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ (ppm) = 29.2 ($\underline{C}H_2CH_2$-N), 42.1 ($CH_2\underline{C}H_2$-N), 55.2 (O-CH_3), 61.3 (CH-N), 113.7 2x($\underline{C}H_{ar}$), 125.6 ($\underline{C}H_{ar}$), 126.2 ($\underline{C}H_{ar}$), 128.0 ($\underline{C}H_{ar}$), 128.9 ($\underline{C}H_{ar}$), 130.0 2x($\underline{C}H_{ar}$), 135.3 ($C_{q,ar}$), 136.8 ($C_{q,ar}$), 138.3 ($C_{q,ar}$), 158.9 ($C_{q,ar}$).

HRMS (EI) $C_{16}H_{17}NO$ *m/z*: calcd. 239.1310
found 239.1310

2-Methyltetrahydroisoquinolines 9

1-(3-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (9a)

Method F

A solution of 3.5 M Red-Al® in toluene (3 ml, 10 mmol) was added drop wise to a solution of the carbamate **7d** (185 mg, 0.47 mmol) in dry toluene (20 ml). The mixture was refluxed for 4 h and after cooling to rt quenched by the addition of saturated aqueous NH_4Cl (20 ml). The organic layer was separated and the aqueous layer extracted with AcOEt (3 x 20 ml). The combined organic layers were dried ($NaSO_4$) and concentrated under vacuum. The brown residue was

purified by column chromatography affording 53 mg (45%) of the product as brownish oil. R_f = 0.18 (DCM/acetone, 97.5:2.5).

^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.17 (s, 3H, N-CH_3), 2.71-2.85- (m, 1H, C$\underline{H}_2$CH_2-N), 2.99 (td, *J* = 11.72, 5.72 Hz, 1H, C$\underline{H}_2$CH_2-N), 3.25-3.51 (m, 2H, CH_2C$\underline{H}_2$-N), 3.78 (s, 3H, O-CH_3), 4.87 (s, 1H, $\underline{C}$H-$C_{q,ar}$), 6.80 (dd, *J* = 7.96, 2.34 Hz, 1H, CH_{ar}), 6.90 (d, *J* = 7.57 Hz, 1H, CH_{ar}), 6.99 (s, 1H, CH_{ar}), 7.11-7.29 (m, 4H, CH_{ar}), 7.30-7.40 (m, 1H, CH_{ar}).

^{13}C-NMR ($CDCl_3$): δ (ppm) = 29.3 ($\underline{C}H_2CH_2$-N), 44.3 (N-CH_3), 52.2 ($CH_2\underline{C}H_2$-N), 55.2 (O-CH_3), 65.1 ($\underline{C}$H-$C_{q,ar}$), 112.8 ($\underline{C}H_{ar}$), 115.2 ($\underline{C}H_{ar}$), 122.2 ($\underline{C}H_{ar}$), 126.0 ($\underline{C}H_{ar}$), 127.5 ($\underline{C}H_{ar}$), 128.3 ($\underline{C}H_{ar}$), 129.2 ($\underline{C}H_{ar}$), 134.1 ($C_{q,ar}$), 138.2 ($C_{q,ar}$), 141.0 ($C_{q,ar}$), 145.2 ($C_{q,ar}$), 159.6 ($C_{q,ar}$).

HRMS (EI) $C_{17}H_{19}NO$ *m/z*: calcd. 253.1467
found 253.1468

1-(1*H*-Indol-3-yl)-2-methyl-1,2,3,4-tetrahydroisoquinoline 9b

Method G

A solution of carbamate **7a** (352 mg, 0.81 mmol) in dry THF (5 ml) was added drop wise under stirring to a suspension of $LiAlH_4$ (650 mg, 17.1 mmol) in dry THF (50 ml). The resulting suspension was stirred at rt for 3 d and then quenched by adding saturated aqueous NH_4Cl (20 ml). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 x 20 ml). The combined organic layers were dried ($NaSO_4$). After removal of the solvent the brown residue was purified by column chromatography affording 85 mg (40%) yield of the product as slightly brown oil. R_f = 0.11 (DCM/acetone, 1:1).

^{1}H-NMR ($CDCl_3$): δ (ppm) =1H 2.37 (s, 3H, N_CH_3), 2.73 (m, 1H, C$\underline{H}_2$CH_2-N), 2.90-3.11 (m, 1H, C$\underline{H}_2$CH_2-N), 3.17-3.44 (m, 2H, CH_2C$\underline{H}_2$-N), 4.76 (s, 1H, $\underline{C}$H-$C_{q,Indol}$), 7.01 (m, 4H, CH_{ar}), 7.19 (m, 3H, CH_{ar}), 7.30 (d, *J* = 8.12 Hz, 1H, CH_{ar}), 7.51 (d, *J* = 7.91 Hz, 1H, CH_{ar}), 8.77 (s, 1H, NH).

^{13}C-NMR ($CDCl_3$): δ (ppm) = 29.2 ($\underline{C}H_2CH_2$-N), 44.3 (N-CH_3), 51.8 ($CH_2\underline{C}H_2$-N), 62.8 ($\underline{C}$H-$C_{q,ar}$), 111.2 ($CH_{ar,Indol}$), 117.3 (CH-$\underline{C}_{q,Indol}$), 119.4 ($\underline{C}H_{ar}$), 120.0 ($\underline{C}H_{ar}$), 121.8 ($\underline{C}H_{ar}$), 124.7 ($\underline{C}H_{ar}$), 125.7 ($\underline{C}H_{ar}$), 126.0 ($\underline{C}H_{ar}$), 127.2 ($C_{q,ar}$), 128.2 ($\underline{C}H_{ar}$), 134.1 ($C_{q,ar}$), 136.5 ($C_{q,ar}$), 138.6 ($C_{q,ar}$).

HRMS (EI) $C_{16}H_{17}NO$ *m/z*: calcd. 262.1470
found 262.1470

4-Aryldihydroisoquinolines 10 by Suzuki coupling. General procedure

The boronic acid $ArB(OH)_2$ (6.25 mmol) was added to a solution of the bromoisoquinoline **4** (R^1 = Br) (5 mmol) in dimethoxyethane (20 ml). After stirring for 10 min PPh_3 (230 mg, 0.88 mmol), Na_2CO_3 (2.10 g, 18.75 mmol) and 20% Pd/C/52% water (250 mg) were added in this sequence and the resulting suspension was diluted with water (10 ml). The mixture was heated in a reflux setup with an oil bath (90 °C) under stirring. After cooling to rt the mixture was filtered and the filtrate was extracted with AcOEt (3 x 40 ml). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography.

(1*R*)-Menthyl 1-(1*H*-indol-3-yl)-4-phenylisoquinoline-2(1*H*)-carboxylate (10a). General procedure afforded 383 mg (96%) of the product as yellow foam. R_f: 0.42 (DCM).
^{1}H-NMR ($CDCl_3$): δ =1H 0.51-2.13 (m, 18H, Menthyl), 4.86-4.55 (m, 1H, CH-O), 6.78-6.46 (m, 2H, $CH_{ar.}$), 6.86 (t, *J* = 9.66 Hz, 1H, $CH_{ar.}$), 7.14 (m, 8H, $CH_{ar.}$), 7.46-7.26 (m, 5H, $CH_{ar.}$), 7.99-7.82 (m, 2H, $CH_{ar.}$).
^{13}C-NMR ($CDCl_3$): δ = 16.6 (CH_3), 20.2 (CH), 20.4 (CH_3), 21.7 (CH_3), 22.9 (CH_2), 25.7 (CH), 31.0 (CH), 33.9 (CH_2), 41.0 (CH_2), 46.8 (CH), 51.2 (CH-N), 76.1 (CH-O), 110.6 (CH_{ar}), 117.0 ($C_{q,ar}$), 119.5 (C=CH-N), 120.0 (CH_{ar}), 121.7 (CH_{ar}), 122.8 (CH_{ar}), 123.6 (CH_{ar}), 124.1 (CH_{ar}), 126.5 ($C_{q,ar}$), 126.9(CH_{ar}), 127.0 (CH_{ar}), 128.2 (CH_{ar}), 128.8 (CH_{ar}), 132.6 ($C_{q,ar}$), 135.9 ($C_{q,ar}$), 137.3 ($C_{q,ar}$), 152.8 (CO).
HRMS (EI) *m/z*: $C_{34}H_{36}N_2O_2$ calcd. 504.2777
found 504.2777

(1*R*)-Menthyl 4-(4-acetylphenyl)-1-(4-(diethylanilino)-isoquinoline-2(1*H*)-carboxylate (10b). General procedure afforded 344mg (81%) of the product as slightly yellow foam. R_f: 0.375 (DCM).
^{1}H-NMR ($CDCl_3$): δ = 0.53-2.10 (m, 24H, Menthyl+2xCH_3), 2.56 (s, 3H, CH_3), 3.21 (q, *J* = 7.02 Hz, 4H, 2x CH_2), 4.69 (m, 1H, CH-O), 6.45 (d, *J* = 8.54 Hz, 2H, $CH_{ar.}$), 7.17-6.97 (m, 6H, $CH_{ar.}$), 7.47 (t, *J* = 7.59 Hz, 2H, $CH_{ar.}$),7.93 (dd, *J* = 8.24, 1.30 Hz, 2H, $CH_{ar.}$), 7.65, 7.99 (d, *J* = 8.53 Hz, 1H, $CH_{ar.}$).
^{13}C-NMR ($CDCl_3$): δ = 12.6 (CH_3), 20.8 (CH), 22.0 (CH_3), 26.6 (CH_3), 31.5 (CH_3), 34.2 (CH_2), 41.4 (CH_2), 44.2 (CH_2), 47.3 (CH), 57.4(CH), 111.1 (CH_{ar}), 123.8 (CH_{ar}), 127.3 (CH_{ar}), 127.4 (CH_{ar}), 127.5 (CH_{ar}), 127.7(CH_{ar}), 128.2 (CH_{ar}), 128.5 (CH_{ar}), 128.7 (CH_{ar}), 129.0 (CH_{ar}), 129.1 (CH_{ar}), 135.8, 136.6 ($C_{q,ar}$), 142.9 ($C_{q,ar}$), 144.3 ($C_{q,ar}$), 147.2 ($C_{q,ar}$), 153.7 (CO_2), 197.7(CO).
HRMS (EI) *m/z*: $C_{38}H_{46}N_2O_3$ calcd. 578.3508
found 578.3508

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