Selective *N*-alkylation/α-arylation of *N*-heterocycles

Ph.D. Thesis

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"Research is to see what everybody else has seen, and to think what nobody else has thought."

Albert Szent-Györgyi

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PUBLICATIONS

Papers related to the thesis

I. István Szatmári, **Judit Sas**, Ferenc Fülöp
Catalyst-free coupling of indole derivatives with 3,4-dihydroisoquinoline and related compounds
Tetrahedron Lett., 2013, *54*, 5069-5071. DOI: 10.1016/j.tetlet.2013.07.039 **IF: 2.391**

II. **Judit Sas**, István Szatmári, Ferenc Fülöp
Selective *N*-alkylation of isoquinolines, benzazepines and thienopyridines with aromatic aldehydes and naphthols
Tetrahedron, 2015, *71*, 7216-7221. DOI: 10.1016/j.tet.2015.03.011 **IF: 2.641**

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One-pot α-arylation of β-carboline with indole and naphthol derivatives
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V. **Sas Judit**
Új indolilizokinolin- és indolilbenzazepin-származékok szintézise
XXXV. Kémiai Előadói Napok
Szeged, 2012. október 29-31. Absztr.: 205.

VI. **Sas Judit**, István Szatmári and Ferenc Fülöp
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MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2013. június 5-7.

VII. **Judit Sas**, István Szatmári and Ferenc Fülöp
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15th Blue Danube Symposium on Heterocyclic Chemistry
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VIII. **Judit Sas**, István Szatmári and Ferenc Fülöp
Catalyst-free coupling of partially unsaturated β-carboline with indole and naphthol derivatives
15th Tetrahedron Symposium, Challenges in Bioorganic and Organic Medicinal Chemistry
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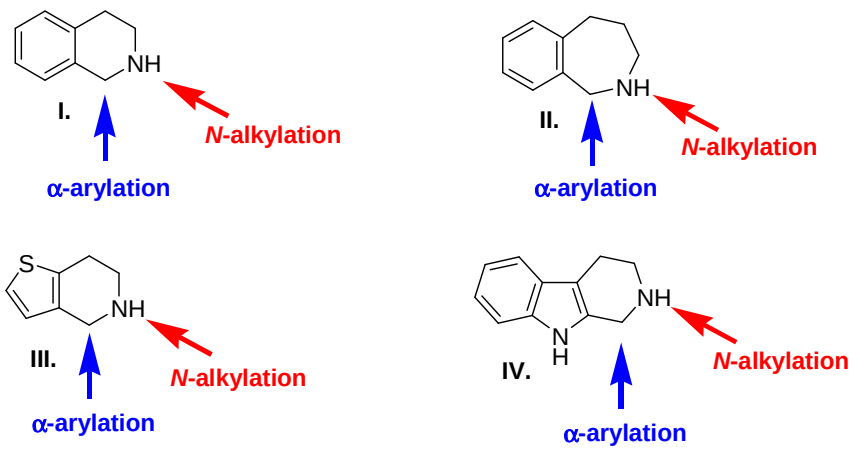
1. INTRODUCTION AND AIMS

The Mannich reaction[1] is an important reaction involving C–C bond formation that is widely used in the syntheses of secondary and tertiary amine derivatives and as a key step in the syntheses of many bioactive molecules and complex natural products.[2,3] More than one hundred years ago, Mario Betti reported a straightforward synthesis of 1-(α-aminobenzyl)-2-naphthol (the Betti base),[4-8] starting from 2-naphthol, benzaldehyde and ammonia. The Betti procedure can be interpreted as a modified Mannich reaction (mMR). The reaction conditions and the method for the isolation of the synthesized Mannich products are determined to a considerable extent by the character of the nitrogen source used (NH_3 or amine).[8]

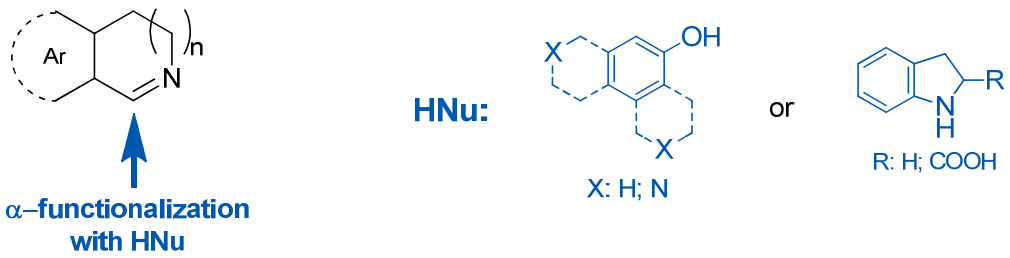
The importance of the aminonaphthols prepared via mMRs has recently increased because they have proved to be excellent model compounds for study of the α-arylation/*N*-alkylation of cyclic amines.[9-11] When pyrrolidine was aminoalkylated with electron-rich aromatic compounds in the presence of aromatic aldehydes, the two possible main products, i.e. α-arylated or *N*-alkylated, could be isolated only if the aldehyde component was added extremely slowly to the reaction mixture containing acid as catalyst. It was also demonstrated that 2-naphthol can be sufficiently acidic to promote the required tautomerization that determines the possibility of formation of the α-arylated/*N*-alkylated products.[10]

The primary aim of my PhD work was to investigate the application of 1,2,3,4-tetrahydroisoquinoline (**I**) and analogous secondary amines such as 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (**II**), 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**III**) and 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**IV**) in mMRs. A further aim was a systematic investigation of the α-arylation/*N*-alkylation process starting from tetrahydroisoquinoline, tetrahydrobenzazepine, tetrahydrothieno[3,2-*c*]pyridine or 2,3,4,9-tetrahydropyrido[3,4-*b*]indole by using 2- or 1-naphthol as nucleophile in the presence of benzaldehyde.



The reactions between electron-rich aromatic compounds such as 1- or 2-naphthol[8,12-14] and quinolinol or isoquinolinol[15] with 3,4-dihydroisoquinoline, first described by our group, can be interpreted as the aza-Friedel–Crafts alkylation of electron-rich aromatic compounds with cyclic amines containing a polarized double bond (C=N). Through the use of different reagents and/or substrates, the reactions were subsequently extended to the synthesis of 1-hydroxynaphthyl-substituted tetrahydroisoquinoline derivatives.[16-18] The modifications were mostly restricted to the use of 3,4-dihydroisoquinoline as cyclic imine, and the aim of my PhD work was therefore to investigate the possibility of the application of other partially saturated cyclic imines such as 4,6-dihydro-3*H*-benz[*c*]azepine, 6,7-dihydrothieno[2,3-*c*]pyridine and 4,9-dihydro-3*H*-β-carboline.

Another goal was to test the scope and limitations of this aza-Friedel–Crafts reaction starting from the above-mentioned cyclic imines and indole and its derivatives as electron-rich aromatic compounds.



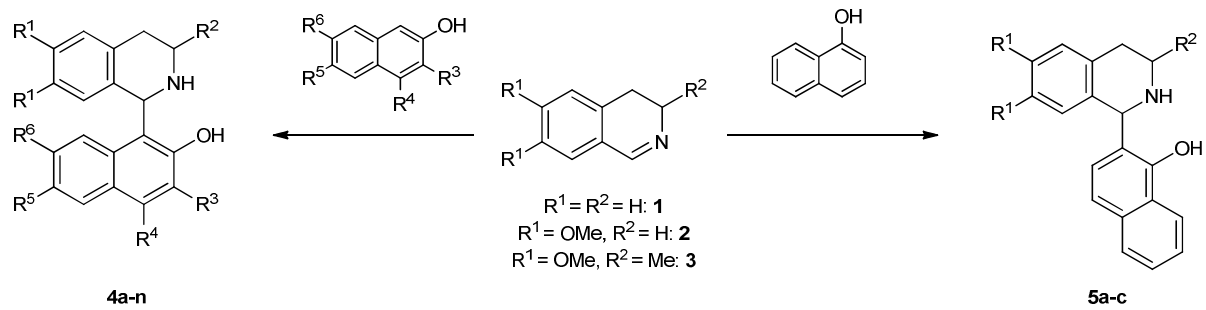
2. LITERATURE BACKGROUND

2.1. Aza-Friedel–Crafts alkylation of naphthol derivatives

Fülöp *et al.* reported the first syntheses of 1-(hydroxynaphthyl)-substituted 1,2,3,4-tetrahydroisoquinolines (**4a-c** and **5**, Table 1) in which 1- or 2-naphthol was reacted with 3,4-dihydroisoquinolines.[12,14,20,21] The moderate yields of the reactions performed at ambient temperature were significantly increased by applying solvent-free microwave (MW) heating (Table 1, entries 1, 3, 16, 18 and 19). The naphthol additions of 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline proved to be highly diastereoselective processes, resulting in the *cis* isomers as the main or the only products (Table 1, entries 4 and 19).[12]

A Canadian research group later published the syntheses of some 1-(hydroxynaphthyl)-substituted 1,2,3,4-tetrahydroisoquinoline derivatives by the same route, but with some modifications (Table 1, entries 2, 5-9 and 17).[19-21]

Table 1. Aza-Friedel–Crafts reaction between naphthols and dihydroisoquinolines

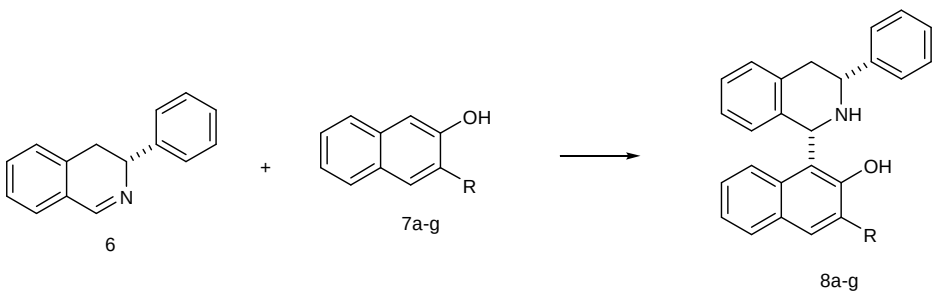


Entry	Product	R^{1-6}	Conditions	Isolated yield (%)	References
1	**4a**	-	Neat, MW, 90 °C, 20 min →70 °C, 30 min	65	12
2	**4a**	-	Neat, 70 °C, 16 h	87	14, 21
3	**4b**	R^1 = OMe	Neat, MW, 90 °C, 20 min →70 °C, 30 min	56	12
4	**4c**	R^1 = OMe R^2 = Me	Neat, MW, 90 °C, 10 min →70 °C, 30 min	61	12
5	**4c**	R^5 = OMe	Neat, 80 °C, overnight	89	14, 20, 21
6	**4e**	R^3 = OMe	Neat, 80 °C, overnight	100	14, 20, 21
7	**4f**	R^6 = OMe	Neat, 80 °C, overnight	95	14, 20, 21

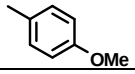
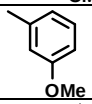
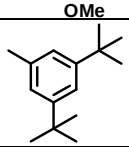
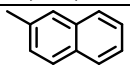
8	**4g**	R^5 = COPh	Neat, 80 °C, overnight	75	14, 20, 21
9	**4h**	R^5 = Br	Neat, 80 °C, overnight	85	14, 20, 21
10	**4i**	R^3 = COOH	Neat, 80 °C, overnight	83	20
11	**4j**	R^3 = CH_2OH	Neat, 80 °C, overnight	90	20
12	**4k**	R^3 = OH	Neat, 80 °C, overnight 2 equiv. DHI	89	20
13	**4l**	R^6 = OH	Neat, 80 °C, overnight	72	20
14	**4m**	R^4 = OH	Neat, 80 °C, overnight	86	20
15	**4n**	R^3 = Ph	Neat, 80 °C, overnight	71	20
16	**5a**	-	Neat, MW, 90 °C, 20 min →70 °C, 30 min	85	12
17	**5a**	-	Neat, 80 °C, overnight	96	14, 20, 21
18	**5b**	R^1 = OMe	Neat, MW, 100 °C, 20 min →80 °C, 40 min	72	12
19	**5c**	R^1 = OMe R^2 = Me	Neat, MW, 90 °C, 20 min →70 °C, 40 min	84	12

MacLeod *et al.* published the synthesis of **8a-g** in enantiomerically pure form, starting from 2-naphthol analogues and (*R*)-3-phenyl-3,4-dihydroisoquinoline. The arrangement of the naphthyl and phenyl substituents in **8a-g** was found to be *cis* (Table 2).[16] The isolated compounds were used as catalyst in the asymmetric addition of diethylzinc to aldehydes, but only modified enantiomeric excesses were found (57-92%). The isolated yields and optimum conditions are shown in Table 2.

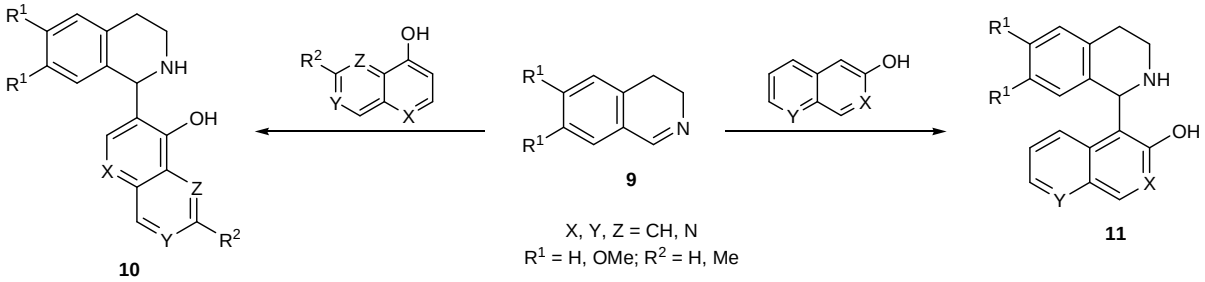
Table 2. Synthesis of non-racemic 1-(hydroxynaphthyl)-substituted 1,2,3,4-tetrahydroisoquinoline



Product	R	Conditions	Yield (%)
(1*S*,3*R*)-8a	H	H_2O, 80 °C, overnight	52
(1*S*,3*R*)-8b	$–CH_2–$ OH	H_2O, 80 °C, overnight	40

(1*S*,3*R*)-8c		H_2O, 80 °C, overnight	48
(1*S*,3*R*)-8d		H_2O, 80 °C, overnight	69
(1*S*,3*R*)-8e		H_2O, 80 °C, overnight	48
(1*S*,3*R*)-8f		H_2O, 80 °C, overnight	56
(1*S*,3*R*)-8g		H_2O, 80 °C, overnight	54

The solvent-free syntheses of 1-hydroxyquinolyl- and 1-hydroxyisoquinolyl-1,2,3,4-tetrahydroisoquinoline derivatives (**10** and **11**, Scheme 1) from *N*-containing 1-naphthol or 2-naphthol derivatives and 3,4-dihydroisoquinolines (**9**) were achieved through classical heating at 80-100 °C and MW agitation at the same temperature. Both reaction conditions yielded the products in good yields (57-92%), but the use of MW conditions allowed a decrease of the reaction time from 10-50 h to 1.5-3.5 h.[15]

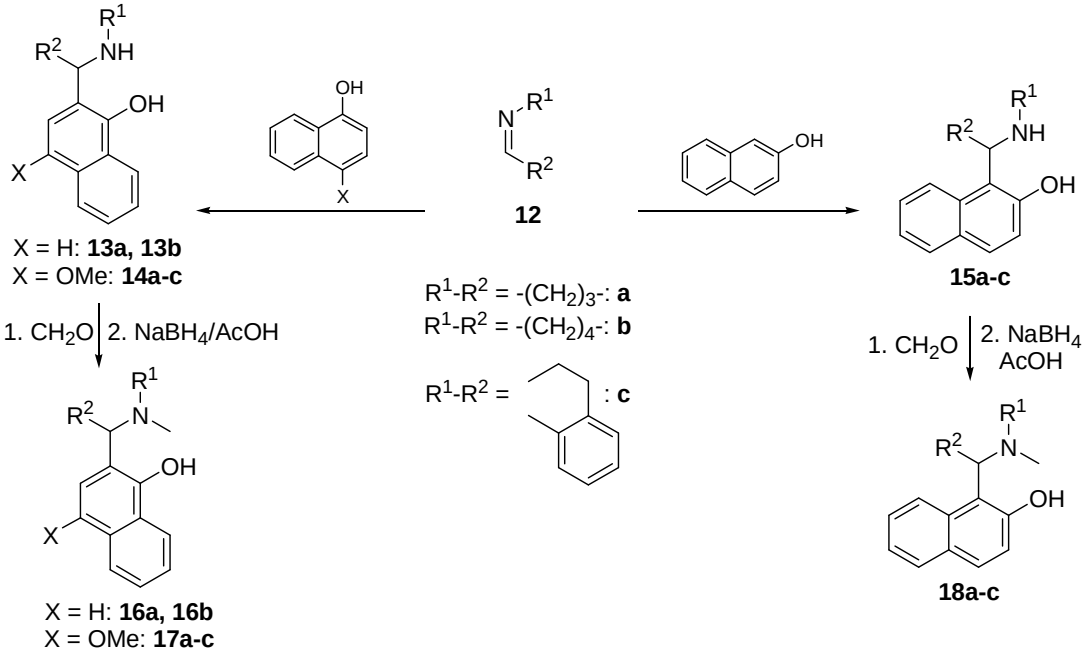


Scheme 1

Palmieri *et. al* published the aza-Friedel–Crafts reactions by using nitrogen-containing naphthol derivatives as starting compounds. The reaction was extended by starting from five- and six-membered cyclic imines (**12a** or **12b**) and 1- or 2-naphthol analogues to give **13a**,**b**-**15a**,**b**, or from 3,4-dihydroisoquinoline (**12c**) and 4-methoxy-1-naphthol or 2-naphthol to give **14c** and **15c** (Scheme 2).[18]

As an extension of the reaction, Palmieri *et al.* published the preparation of **13a**,**b**-**15a**,**b** from five- and six-membered cyclic imines (**12a**, **12b**) and 1- or 2-naphthol, and the synthesis of **14c** and **15c** by the reaction of 3,4-dihydroisoquinoline (**12c**) and 4-methoxy-1-naphthol or 2-naphthol (Scheme 2). The absolute configurations of **13a** and **13b** were ascertained by X-ray analysis and chiroptical methods (ECD) after resolution of the corresponding racemates with

(*R*,*R*)-tartaric acid. Additionally, all the prepared racemic compounds (**13-15**) were transformed to their *N*-methylated derivatives (**16-18**) by using formaldehyde, followed by reduction with $NaBH_4$.[18]



Scheme 2

2.2. C-3 substitution of indole derivatives

2.2.1. Oxidative coupling of indole derivatives with cyclic amines

Cross-dehydrogenative coupling (CDC) is one of the most powerful C-H activation processes for the construction of C-C bonds under oxidative conditions. In general, the oxidative protocol involves metal catalysts in the presence of oxygen or an organic oxidant. In essence, the oxidative coupling produces a new C-X bond from C-H and X-H fragments in the presence of a catalyst and a sacrificial oxidant. In contrast with traditional metal catalyst cross-coupling reactions, in the case of CDC the coupling partners do not require prefunctionalization, which helps to reduce waste and to streamline the synthesis (Fig. 1).

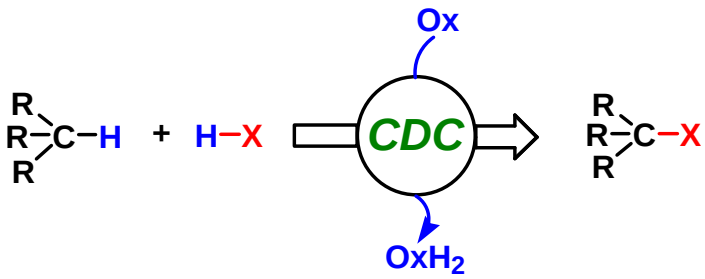


Fig. 1. Overall outline of CDC

Li *et al*. first synthesized **21aa** via the CuBr-catalysed indolation of tetrahydroisoquinoline. The highest yield was attained under neat conditions at 50 °C overnight with *tert*-butyl hydroperoxide (TBHP, 5-6 mol/L in *n*-decane) as oxidant. In this case, **21aa** was the only product and the intermediate 1-*tert*-butylperoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline was not detected (Table 3, entry 1).[22,23] Similar yields were observed by Chua and Quing with CuBr as catalyst and benzoyl peroxide (BPO) as oxidant (Table 3, entry 2).[24]

Wu *et al.* described the process of cross-dehydrogenative hydrogen evolution, in which no oxidant was used and only hydrogen was generated as a side-product. A combined eosin Y and graphene-supported RuO_2 nanocomposite (G-RuO_2) was applied as catalyst and photosensitizer (Table 3, entry 3).[25] Eosin Y was combined with $Co(dmgH)_2Cl_2$ (dmgH = dimethyilglyoximate) by Wu *et al*,[26] and **21aa** was isolated in similar yield. In this case, a mixture of MeCN and H_2O was used as solvent, the reaction mixture was deaerated by the bubbling of N_2 through it, and it was then irradiated by green LEDs (Table 3, entry 4).

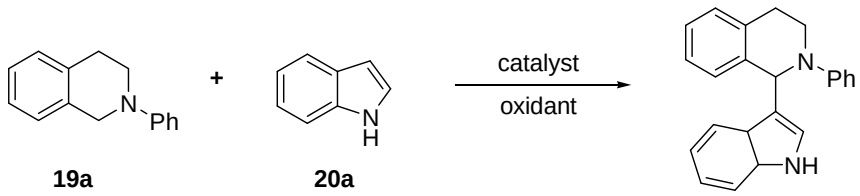
Some research groups have used different gold catalysts to transform *N*-substituted 1,2,3,4-tetrahydroisoquinolines (Table 3, entries 6 and 7).[28,29] Feng *et al*. achieved an excellent yield for the preparation of **21aa** (92%) by using $NaAuCl_4$ as catalyst with TBHP as oxidant at room temperature (Table 3, entry 7).[29]

The reaction time was dramatically decreased (30 min) when Su *et al.* made use of high-speed ball-milling in the presence of 2,3-dichloro-5,6-dicyanoquinone (DDQ) as oxidant. The reaction was catalysed efficiently by the application of two recoverable copper balls without any additional metal catalyst (Table 3, entry 9).[31]

The oxidative coupling of *N*-phenyltetrahydroisoquinoline with indole in the presence of catalytic amounts of a triarylaminium salt was reported by Huo *et al.* The highest yield (82%) was achieved with tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^+ \bullet SbCl_6^-$) as catalyst at room temperature in THF (Table 3, entry 11). However, when 2,2,6,6-tetramethylpiperidin-1-yloxyl was used as catalyst, only a low yield (25%) was observed.[33]

Iron(III) has been applied as another class of catalysts. Ratnikov *et al.* used iron(III) chloride catalysis in the aerobic oxidation of **19a** with 1*H*-indole (**20a**) as nucleophile to obtain **21aa** under mild conditions (without TBHP as oxidant), though after a relatively long reaction time (5 days) (Table 3, entry 14)[36], while Che *et al*. applied an SBA-15-supported iron terpyridyl complex as catalyst ($[Fe(terpy)_2]^{2+}$ (terpy = 2,2':6',2''-terpyridine)) with different oxidants for the synthesis of **21aa**. The optimum conditions are given in Table 3, entry 15.[37]

Table 3. Reaction conditions for the synthesis of 1-(3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21aa**)



19a **20a** **21aa**

Entry	Catalyst and/or oxidant, conditions	Yield (%)	Ref.	Entry	Catalyst and/or oxidant, conditions	Yield (%)	Ref.
1	CuBr, TBHP neat, 50 °C, overnight	79[a]	22,23	10	V_2O_5, O_2 H_2O, 100 °C, 24 h	71[a]	32
2	CuBr, BPO DCM, reflux, 5-10 h	79[a]	24	11	$TBPA^{+}\bullet SbCl_6^{-}$ THF, air, rt, 6 h	82[a]	33
3	eosin Y, G-RuO_2 irradiated by visible light (hν > 450nm), N_2, rt, 20 h	80[a]	25	12	2ClAQN, O_2 irradiated by visible light (hν > 450nm), MeOH, 40 h	31[a]	34
4	eosin Y, $Co(dmgH)_2Cl_2$ irradiated by green LEDs (hν = 525nm), N_2, H_2O:MeCN (4:1), 16-22 h	83[a]	26	13	$Ru(bpy)_3Cl_2$ irradiated by blue LEDs (hν = 435 nm), $BrCCl_3$, DMF, KO*t*Bu, 3 h	83[a]	35

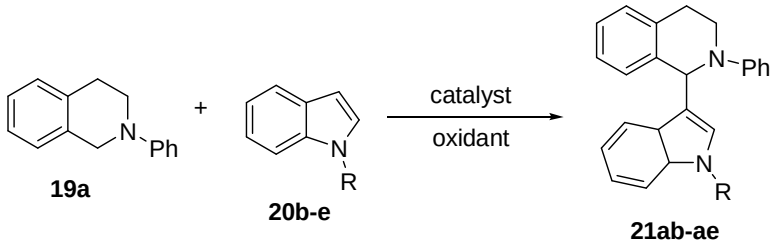
5	platinum(II) terpyridyl complex, $FeSO_4$ irradiated by blue LEDs (hν = 450nm), DMF, ambient air, 4 h	81[a]	27	14	$FeCl_3 \cdot 6H_2O$, O_2 EtOH, 40 °C, 5 days	56[a]	36
6	$CoCl_2$,dmgH irradiated by blue LEDs (hν = 450nm), H_2O, air, 24 h	83[a]	28	15	SBA-15 (mesoporous molecular sieves) supported, $[Fe(terpy)_2]^{2+}$ complex, TBHP toluene, reflux, 12 h	80[b]	37
7	$NaAuCl_4$, TBHP rt, 5 h	92[a]	29	16	$Fe(NO_3)_3 \cdot 9H_2O$, TBHP rt, 20 h	43[a]	38
8	AuNPs/C, O_2 bubbling toluene, 110 °C, 1 d	70[b]	30	17	$Fe(NO_3)_3 \cdot 9H_2O$, TBHP 50 °C, 15 h	65[a]	38
9	DDQ, ball-milling, copper balls silica gel, 30 min	77[a]	31	18	$CuCl_2 \cdot 2H_2O$, O_2 MeOH, rt, 22 h	86[a]	39

[a] isolated yield;
[b] yield based on conversion

1-(1-Methyl-3a,7a-dihydro-*1H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21ab**) has been produced by various research groups through the use of different catalysts and different reaction conditions (Scheme 3).[22,23,25-28,30,31,33,36,37,39-43] As an example, Tokuyama *et al.* reported the synthesis of **21ab** under metal-free conditions in an oxygen atmosphere in the presence of AcOH, which accelerated the reaction (78%).[41] Hou *et al.* applied $TBPA^{+}\bullet SbCl_6^{-}$ for the synthesis of 1-(1-benzyl-3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21ac**) in a yield of 83% from 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**19a**) and 1-benzyl-1H-indole (**20c**) in THF at only 40 °C.[33]

Che *et al*. published the functionalization of **19a** with 1-*p*-tolyl-1*H*-indole (**20d**) or 1-(4-methoxyphenyl)-1*H*-indole (**20e**) by the application of various ruthenium catalysts. The reaction was extended to the synthesis of indolyl tetrahydroisoquinoline derivatives bearing various aryl substituents on the indole skeleton nitrogen. The conditions included relatively high-temperature heating (110 °C) of the reaction mixture. The reaction usually needed a long reaction time (6 h) and resulted in the target compounds (**21ad** and **21ae**) in moderate yields (73-79%).[44]

The synthesis of 1-(2-methyl-3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21af**) has been reported independently by different research groups.[22,23,25-28,31-33,37] Wu *et al.* applied eosin Y and a graphene-supported RuO_2 nanocomposite[25] or eosin Y with $Co(dmgH)_2Cl_2$,[26] these conditions furnishing the desired product (**21af**) in excellent isolated yields (81% and 82%, respectively).[25,26] Huo *et al*. achieved a similarly high yield in the presence of $TBPA^+ \bullet SbCl_6^-$. They also investigated the reaction between **19a** and **20g** bearing an OH group at position 4 of the indole skeleton, when the target compound (**21ag**) was isolated in moderate yield (58%).[33]



R = Me: **20b**, **21ab**[22,23,25-28,30,31,33,36,37,39-43]; Bn: **20c**, **21ac**[33]; 4-MeC_6H_4: **20d**, **21ad**[44]; 4-$MeOC_6H_4$: **20e**, **21ae**[44]

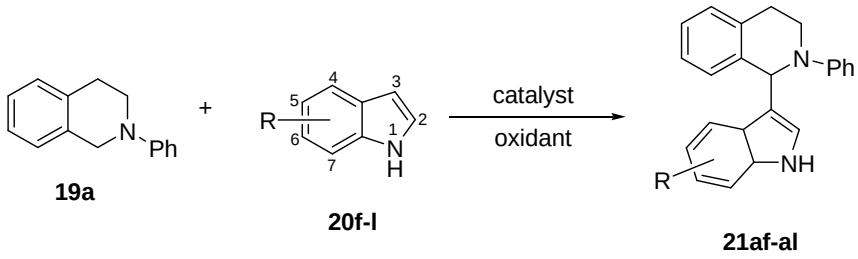
Scheme 3

1-(5-Methyl-3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21ah**) has been prepared by many research groups.[25-29,33] The best yield (86%) was attained by Feng *et al*. with a catalyst combination of $NaAuCl_4$ and TBHP (Table 4).[29]

Among the synthetic methods used to prepare **21ai**, the highest yield (87%; Table 4) was reported by Xie *et al.*, who applied $TBPA^+ \bullet SbCl_6^-$ as catalyst.[33] It should be mentioned that $TBPA^+ \bullet SbCl_6^-$ also proved most effective for the synthesis of 1-(5-bromo-3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21aj**).[33]

It is noteworthy that, when the starting indole contained an electron-withdrawing substituent such as –COOMe (**20k**) or $–NO_2$ (**20l**), the desired methyl 3-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-3a,7a-dihydro-1*H*-indole-5-carboxylate acid (**21ak**) and 1-(5-nitro-3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**21al**) could be isolated in only moderate yields (Table 4).[22,23,26-28,37]

Table 4. Reaction conditions for the synthesis of 1-(3a,7a-dihydro-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinolines (**21 af-al**)



19a **20f-l** **21af-al**

R = 2-Me: **20f**, **21af**; 4-OH: **20g**, **21ag**; 5-Me: **20h**, **21ah**; 5-OMe: **20i**, **21ai**; 5-Br: **20j**, **21aj**; 5-COOMe: **20k**, **21ak**; 5-NO_2: **20l**, **21al**

Product	**Catalyst and/or oxidant, conditions**	**Yield (%)**	**Ref.**	**Product**	**Catalyst and/or oxidant, conditions**	**Yield (%)**	**Ref.**
21af	CuBr, TBPH neat, 50 °C, overnight	61[a]	22, 23	**21ai**	DDQ, ball-milling, copper balls silica gel, 20 min	70[a]	31
21af	SBA-15-supported $[Fe(terpy)_2]^{2+}$, TBHP toluene, reflux, 12 h	73[b]	37	**21ai**	V_2O_5, O_2 H_2O, 100 °C, 24 h	50[a]	32
21af	DDQ, ball-milling, copper balls silica gel, 40 min	75[a]	31	**21ai**	$[Pt(terpy)_2]^{2+}$, $FeSO_4$ irradiated by blue LEDs (hν = 450 nm) DMF, ambient air , 12 h	76[a]	27
21af	V_2O_5, O_2 100 °C , H_2O, 24 h	50[a]	32	**21ai**	eosin Y, $Co(dmgH)_2Cl_2$ irradiated by green LEDs (hν = 525 nm), N_2, H_2O:MeCN (4:1), 16-22 h	80[a]	26
21af	eosin Y, G-RuO_2 irradiated by visible light (hν > 450 nm), N_2, rt, 20 h	81[a]	25	**21ai**	$TBPA^+ \bullet SbCl_6^-$ THF, ambient air, rt, 6-12 h	87[a]	33
21af	$[Pt(terpy)_2]^{2+}$, $FeSO_4$ irradiated by blue LEDs (hν = 450 nm), DMF, ambient air, 24 h	74[a]	27	**21ai**	$CoCl_2$, dmgH in H_2O irradiated by blue LEDs (hν = 450 nm), H_2O, air, 24 h	75[a]	28

21af	eosin Y, $Co(dmgH)_2Cl_2$ irradiated by green LEDs (hν = 525 nm) H_2O:MeCN, (4:1), N_2, 16-22 h	82[a]	26	**21aj**	DDQ, ball-milling, copper balls silica gel, 30 min	70[a]	31
21af	$TBPA^+•SbCl_6^-$ THF, ambient air, rt, 6-12 h	81[a]	33	**21aj**	V_2O_5, O_2 H_2O, 100 °C, 24 h	44[a]	32
21af	$CoCl_2$, dmgH in H_2O irradiated by blue LEDs (hν = 450 nm), air, H_2O, 24 h	80[a]	28	**21aj**	$TBPA^+•SbCl_6^-$ ambient air, 40 °C, 6-12 h	82[a]	33
21ag	$TBPA^+•SbCl_6^-$ THF, ambient air, 40 °C, 6-12 h	58[a]	33	**21aj**	eosin Y, $Co(dmgH)_2Cl_2$ irradiated by green LEDs (hν = 525 nm), N_2, H_2O:MeCN (4:1), 16-22 h	77[a]	26
21ah	$NaAuCl_4$, TBHP rt, 5-8 h	86[a]	29	**21aj**	$CoCl_2$, dmgH in H_2O irradiated by blue LEDs (hν = 450 nm), H_2O, air, 24 h	70[a]	28
21ah	eosin Y in H_2O, G-RuO_2 irradiated by blue LEDs (hν = 450 nm), N_2, rt, 20 h	78[a]	25	**21ak**	CuBr, TBPH neat, 50 °C, overnight	63[a]	22, 23
21ah	$[Pt(terpy)_2]^{2+}$, $FeSO_4$ irradiated by blue LEDs (hν = 450 nm), DMF, ambient air , 6 h	76[a]	27	**21ak**	$[Pt(terpy)_2]^{2+}$, $FeSO_4$ irradiated by blue LEDs (hν = 450 nm), DMF, ambient air, 6 h	63[a]	27
21ah	eosin Y, $Co(dmgH)_2Cl_2$ irradiated by green LEDs (hν = 525 nm), H_2O: MeCN (4:1), N_2, 16-22 h	73[a]	26	**21ak**	eosin Y, $Co(dmgH)_2Cl_2$ irradiated by green LEDs (hν = 525 nm), N_2, H_2O:MeCN (4:1), 16-22 h	52[a]	26

21ah	$TBPA^{+}•SbCl_6^{-}$ THF, ambient air, rt, 6-12 h	84[a]	33	**21ak**	$CoCl_2$, dmgH in H_2O irradiated by blue LEDs (hν = 450 nm), H_2O air, 24 h	60[a]	28
21ah	$CoCl_2$, dmgH in H_2O irradiated by blue LEDs (hν = 450 nm), air, H_2O, 24 h	82[a]	28	**21al**	CuBr, TBHP neat, 50 °C, overnight	85[a]	22, 23
21ai	CuBr, TBHP neat, 50 °C, overnight	57[a]	22, 23	**21al**	SBA-15-supported $[Fe(terpy)_2]^{2+}$,TBHP toluene, reflux, 12 h	69[b]	37
21ai	SBA-15-supported $[Fe(terpy)_2]^{2+}$, TBHP toluene, reflux, 12 h	72[b]	37	**21al**	$[Pt(terpy)_2]^{2+}$ $FeSO_4$ LEDs (hν = 450 nm) DMF, ambient air , 12 h	56[a]	27

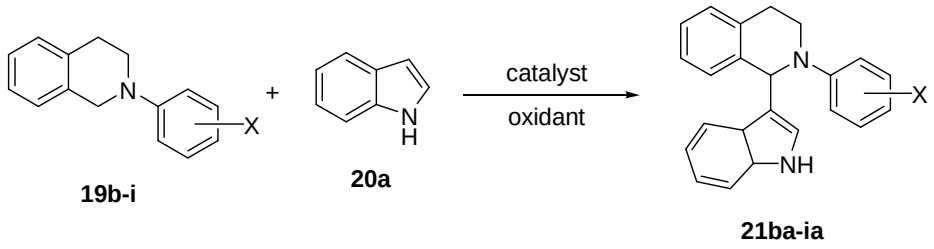
[a] isolated yield;
[b] yield based on conversion

The couplings between 2-aryltetrahydroisoquinolines and indole are shown in Scheme 4.

When 2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was used as starting compound, the isolated yields were only moderate (56-78%) regardless of the conditions applied.[25-28]

Many research groups have reported the reactions of 1-*H*-indole with tetrahydroisoquinolines containing halogenophenyl substituents at position 2. Feng *et al.* achieved the syntheses of **21fa** and **21ga** in excellent yields by applying $NaAuCl_4$ as catalyst at rt in a reaction time of 5-8 h.[29]

The syntheses of 1-(3a,7a-dihydro-1*H*-indol-3-yl)-2-(4-cyanophenyl)-1,2,3,4-tetrahydro-isoquinoline (**21ha**)[27] and 1-(3a,7a-dihydro-1*H*-indol-3-yl)-2-(4-nitrophenyl)-1,2,3,4-tetrahydro-isoquinoline (**21ia)**[28] have been described by only one research group. The yields were lowest when the phenyl group in the starting isoquinoline contained an electron-withdrawing substituent *e.g.* a nitrile or a nitro group.

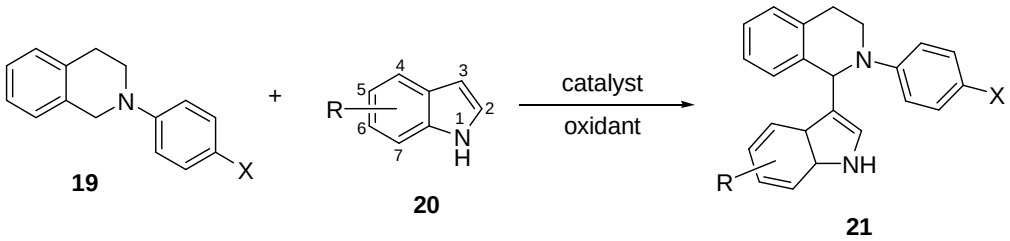


X = 4-Me: **19b**, **21ba**; 4-OMe: **19c**, **21ca**; 2-OMe: **19d**, **21da**; 4-F: **19e**, **21ea**; 4-Cl: **19f**, **21fa**; 4-Br: **19g**, **21ga**; 4-CN: **19h**, **21ha**; 4-NO_2: **19i**, **21ia**

Scheme 4

The scope and limitations of the reaction have been investigated by varying the substituents on the phenyl group in the starting isoquinoline and at positions 1, 2, 4 and 5 of the indole. The products, reaction conditions and yields are listed in Table 5. Schnürch *et al*. reported the synthesis of 1-(3a,7a-dihydro-1*H*-indol-3-yl)-2-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline from 2-pyridin-2-yl-1,2,3,4-tetrahydroisoquinoline and indole with $Cu(NO_3)_2 \cdot 3H_2O$ or CuBr as catalyst at 50 °C. In spite of the relatively long reaction time (15 h), the desired products could be isolated in only moderate yields.[46]

Table 5. Reaction conditions for the synthesis of substituted 1-(3a,7a-dihydro-1*H*-indol-3-yl)-2-aryl-1,2,3,4-tetrahydroisoquinolines (**21**)



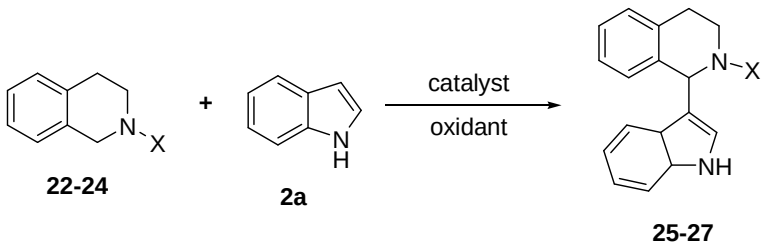
Entry	X	R	Product	Catalyst and/or oxidant	Conditions	Yield (%)	Ref.
1	OMe (**19c**)	1-Me (**20b**)	**21cb**	DDQ ball-milling, copper balls	silica gel, 40 min	71[a]	31
2	OMe (**19c**)	1-Me (**20b**)	**21cb**	AcOH O_2	DCM, 50 °C, 10.5 h	79[a]	41
3	Br (**19g**)	1-Me (**20b**)	**21gb**	I_2 O_2	MeOH, rt, 24 h	73[b]	40
4	Me (**19b**)	1-Me (**20b**)	**21bb**	AcOH O_2	DCM, 50 °C , 27 h	71[a]	41

5	OMe (**19c**)	2-Me (**20f**)	**21cf**	DDQ ball-milling, copper balls	silica gel, 40 min	70[a]	31
6	OMe (**19c**)	2-Me (**20f**)	**21cf**	V_2O_5 O_2	H_2O, 100 °C, 24 h	50[a]	32
7	Cl (**1f**)	2-Cl (**20m**)	**21fm**	$NaAuCl_4$ TBHP	rt, 5-8 h	92[a]	29
8	Br (**19g**)	2-Cl (**20m**)	**3gm**	$NaAuCl_4$ TBHP	rt, 5-8 h	93[a]	29
9	Me (**19b**)	2-Cl (**20m**)	**21bm**	$NaAuCl_4$ TBHP	rt, 5-8 h	75[a]	29
10	OMe (**19c**)	2-OMe **(20i)**	**21ci**	CuBr TBHP	neat, 50 °C, overnight	65[a]	22, 23
11	OMe (**19c**)	5-OMe (**20i**)	**21ci**	DDQ ball-milling, copper balls	silica gel, 40 min	65[a]	31
12	OMe (**19c**)	5-NO_2 (**20l**)	**21cl**	CuBr TBHP	neat, 50 °C, overnight	50[a]	22, 23
13	OMe (**19c**)	5-NO_2 (**20l**)	**21cl**	V_2O_5 O_2	H_2O, 100 °C, 24 h	58[a]	32
14	Cl (**19f**)	5-Me (**20h**)	**21fh**	$NaAuCl_4$ TBHP	rt, 5-8 h	90[a]	29
15	Br (**19g**)	5-Me (**20h**)	**21gh**	$NaAuCl_4$ TBHP	rt, 5-8 h	93[a]	29
16	Me (**19b**)	5-Me (**20h**)	**21bh**	$NaAuCl_4$ TBHP	rt, 5-8 h	79[a]	29
17	OMe (**19c**)	5-Me (**20h**)	**21ch**	$NaAuCl_4$ TBHP	rt, 5-8 h	80[a]	29
18	OMe (**19c**)	5-Br (**20k**)	**21ck**	V_2O_5 O_2	H_2O, 100 °C, 24 h	83[a]	32

[a] isolated yield;
[b] conversion

1-(3a,7a-Dihydro-1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline derivatives have also benn synthesized from *N*-protected 1,2,3,4-tetrahydroisoquinoline. In one group of products, the nitrogen of the isoquinoline skeleton forms amide bonds. Table 6 contains the reaction conditions and yields. Schnürch *et al.* investigated the syntheses of **25-27** on compounds of iron[38] or copper[45] as catalyst. In all cases, the reported yields were rather low (10-54%). When 2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline was used as starting compound, the desired product was detected only in traces.[45]

Table 6. Reaction conditions for the synthesis of *N*-acyl 1-(3a,7a-dihydro-1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline derivatives (**25-27**)



X = Ac: **22**, **25**; Piv: **23**, **26**; Bz: **24**, **27**

Entry	**X**	**Product**	**Catalyst and/or oxidant**	**Conditions**	**Isolated yield (%)**	**Ref.**
1	Ac	**25**	$Cu(NO_3)_2 \cdot 3H_2O$ TBHP	50 °C, 15 h	54	45
2	Ac	**25**	CuBr TBHP	50 °C, 15 h	47	45
3	Piv	**26**	$Cu(NO_3)_2 \cdot 3H_2O$ TBHP	50 °C, 15 h	26	45
4	Piv	**26**	CuBr TBHP	50 °C, 15 h	21	45
5	Bz	**27**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	22	38
6	Bz	**27**	$Cu(NO_3)_2 \cdot 3H_2O$ TBHP	50 °C, 15 h	40	45
7	Bz	**27**	CuBr TBHP	50 °C, 15 h	10	45

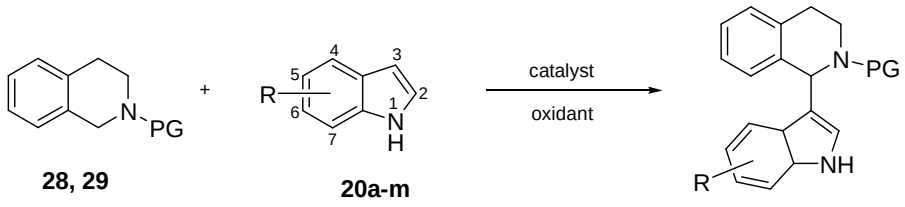
Ac: acetyl;
Piv: pivaloyl;
Bz: benzoyl

Syntheses from 2-carbamato-1,2,3,4-tetrahydroisoquinolines have also been investigated. Schnürch *et al*. studied the reactions of indole derivatives and Boc-protected 1,2,3,4-tetrahydroisoquinoline with numerous catalysts. The conditions and isolated yields are listed in Table 7 (entries 1-13).[38] The coupling of Boc-protected isoquinolines with various substituted indole derivatives was reported by the same research group, who used a number of transition metal salts as catalysts. The lowest yields were obtained when the indole contained a methyl ester or amino function at position 5[38] or a 4-methoxyphenyl substituent at position 2[46] (Table 7, entries 7, 10 and 17).

In most cases, the Boc group could be removed by using TMSCl in MeOH at room temperature (**30**, **30f**, **30i**, **30l**, **30p**, **30q** and **30r**). In the case of **30b**, the removal was achieved by MW heating at 250 °C in ethyleneglycol for 30 s.[38]

When Cbz-protected 1,2,3,4-tetrahydroisoquinoline was applied as starting compound, the desired product (**31**) could be isolated in only moderate yields.[38,45,47,48] The best yield (69%) was reported by Lou *et al.* when triphenylcarbenium perchlorate (Ph_3CClO_4) was used as catalyst.[48]

Table 7. Reaction conditions for the synthesis of *N*-protected 1-(3a,7a-dihydro-1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinolines (**30,31**)



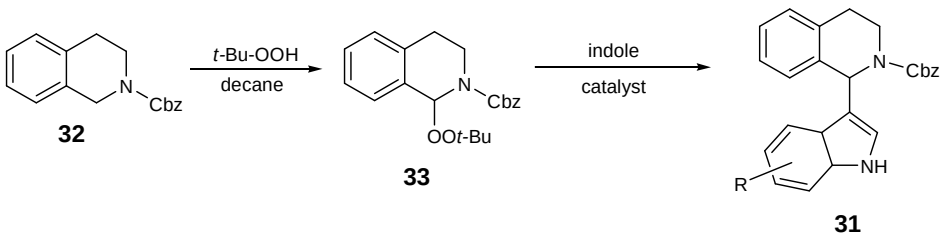
28, 29 **20a-m** **30, 31**

PG = Boc: **28**, **30**; Cbz: **29**, **31**

Entry	R	Boc-protected products	Catalyst and/or oxidant	Conditions	Isolated yield (%)	Ref.
1	-	**30**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	54	38
2	-	**30**	$FeCl_2 \cdot 4H_2O$ TBHP	50 °C, 15 h	53	38
3	-	**30**	$FeCl_3 \cdot 6H_2O$ TBHP	50 °C, 15 h	50	38
4	-	**30**	$FeBr_3$ TBHP	50 °C, 15 h	36	38
5	1-Me (**20b**)	**30b**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	65	38
6	2-Me (**20f**)	**30f**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	23	38
7	5-NH_2 (**20o**)	**30o**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	16	38
8	5-OMe (**20i**)	**30i**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	43	38
9	5-NO_2 (**20l**)	**30l**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	66	38
10	5-COOMe (**20j**)	**30j**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	5	38
11	5-Cl (**20p**)	**30p**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	72	38
12	6-Cl (**20q**)	**30q**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	56	38
13	7-NO_2 (**20r**)	**30r**	$Fe(NO_3)_3 \cdot 9H_2O$ TBHP	50 °C, 15 h	70	38
14	2-Ph (**20s**)	**30s**	$Cu(NO_3)_2$ TBHP	50 °C, 48 h	44	46
15	2-Ph	**30s**	$Fe(NO_3)_3$	50 °C, 48 h	56	46

	(**20s**)		TBHP			
16	2-(4-MeC_6H_4) (**20t**)	**30t**	$Fe(NO_3)_3$ TBHP	50 °C, 48 h	20	46
17	2-(4-$MeOC_6H_4$) (**20u**)	**30u**	$Fe(NO_3)_3$ TBHP	50 °C, 48 h	14	46
18	1-Ph (**20v**)	**30v**	$Cu(NO_3)_2$ TBHP	50 °C, 24 h	83	46
19	1-Ph (**20v**)	**30v**	$Fe(NO_3)_3$ TBHP	50 °C, 24 h	49	46
20	1-(4-$MeOC_6H_4$) (**20w**)	**30w**	$Cu(NO_3)_2$ TBHP	50 °C, 24 h	69	46
21	1-(4-$MeOC_6H_4$) (**20w**)	**30w**	$Fe(NO_3)_3$ TBHP	50 °C, 24 h	40	46
22	1-(2-thienyl) (**20x**)	**30x**	$Cu(NO_3)_2$ TBHP	50 °C, 24 h	78	46
23	1-(4-FC_6H_4) (**20y**)	**30y**	$Cu(NO_3)_2$ TBHP	50 °C, 24 h	65	46
24	1-(4-$NO_2C_6H_4$) (**20z**)	**30z**	$Cu(NO_3)_2$ TBHP	80 °C, 2d	45	46
25	-	**30**	$Cu(NO_3)_2 \cdot 3H_2O$	50 °C, 15 h	79	45
26	-	**30**	CuBr	50 °C, 15 h	72	45

Klussmann and Schweitzer-Chaput reported the synthesis of **31** in good yields (86-95%). Moreover, the previously postulated intermediate amino *tert*-butyl peroxide (**33**) was isolated and transformed in the presence of methanesulfonic acid (MsOH) to Cbz-protected isoquinoline derivatives **31a-i** (Scheme 5).[49]

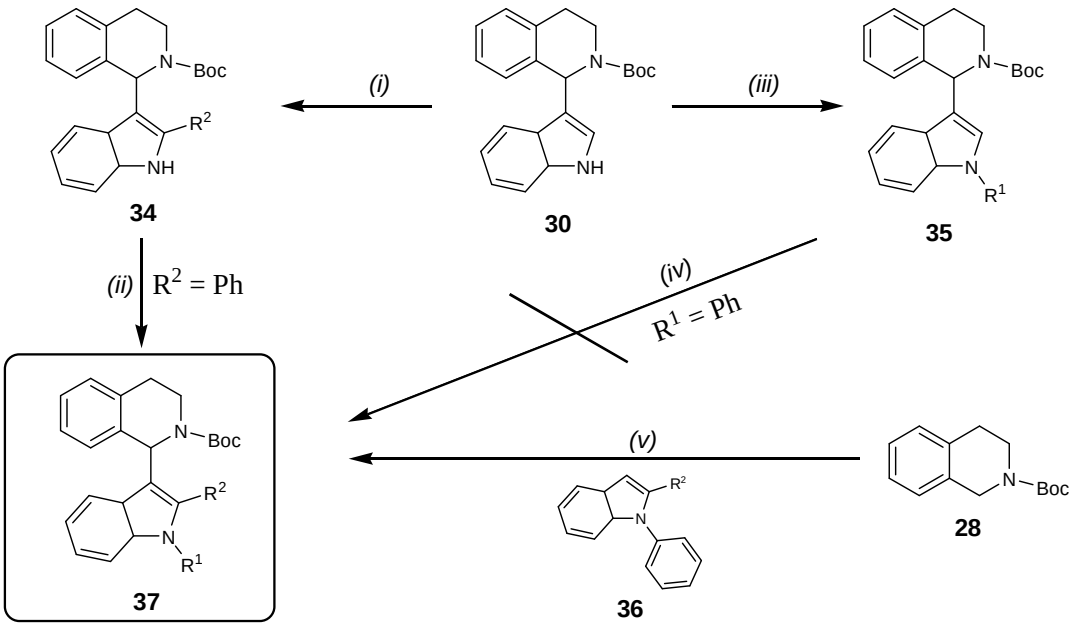


R = H: **31a**; 1-Me: **31b**; 2-Me: **31f**; 5-Br: **31k**; 5-CN: **31n**; 5-NO_2: **31l**; 5-OMe: **31i**

Scheme 5

Diarylindoles have been found to be oestrogen receptor ligands with potential in the treatment of Alzheimer's disease, and Schnürch *et al*. reported the synthesis of **37** via different pathways: arylation of the indole skeleton with arylboronic acids, and *N*-arylation of intermediate **34** with different iodobenzenes, leading to the diarylindole derivative **37**; in the inverse arylation

protocol, the first step led to the desired *N*-arylated compound **35**, but insertion of an additional aryl group at position 2 of the indole skeleton failed; as a third method, direct coupling of diarylindoles **36** with **28** led to the desired diarylated **37** (Scheme 6).[46]



R^1 = Ph; 4-$MeOC_6H_4$; 2-thienyl; 4-FC_6H_4;4-$NO_2C_6H_4$; 2-fluoropyridin-3-yl
R^2 = Ph; 4-MeC_6H_4; 4-$MeOC_6H_4$; 4-$NO_2C_6H_4$; 1-naphthyl

Reagents and conditions: (i) $R^2B(OH)_2$, $Pd(OAc)_2$, $Cu(OAc)_2$ AcOH, O_2, rt, 24 h ; *(ii)* R^1I, CuI, dimethylethylenediamine, K_3PO_4, toluene, 135 °C, 24 h; *(iii)* R^1I, dimethylethylenediamine, $FeCl_3$, K_3PO_4, toluene, 135 °C; *(iv)* $PhB(OH)_2$, $Pd(OAc)_2$, $Cu(OAc)_2$ AcOH, O_2, rt, 24 h; *(v)* $Cu(NO_3)_2$, TBHP, 50 °C, 2 d.

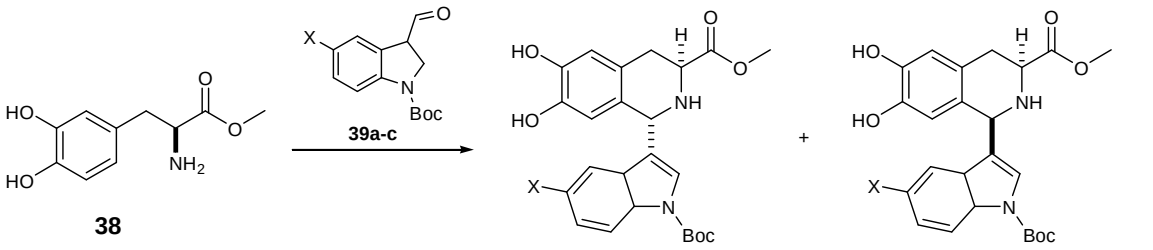
Scheme 6

Despite the large numbers of compounds and/or reaction conditions employed, few examples are to be found where the starting saturated isoquinoline has no substituent on the nitrogen. Schnürch *et al.* described the functionalization of unprotected 1,2,3,4-tetrahydroisoquinoline with substituted indole derivatives, using $Cu(NO_3)_2$ as catalyst.[45] In view of the wide-ranging yields, clear-cut conclusions concerning a generalization of the synthesis of unsubstituted 1-(1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline derivatives are not possible.

2.2.2. Miscellaneous synthetic pathways

Sterner *et al.* developed a protocol for Pictet–Spengler condensation between the methyl ester of L-DOPA (**38**) and various *N*-Boc-protected 1*H*-indole-3-carbaldehydes (**39a-c**) that gave C-1 indolyl-substituted tetrahydroisoquinolines **40a-c** and **41a-c** in moderate isolated yields (66-

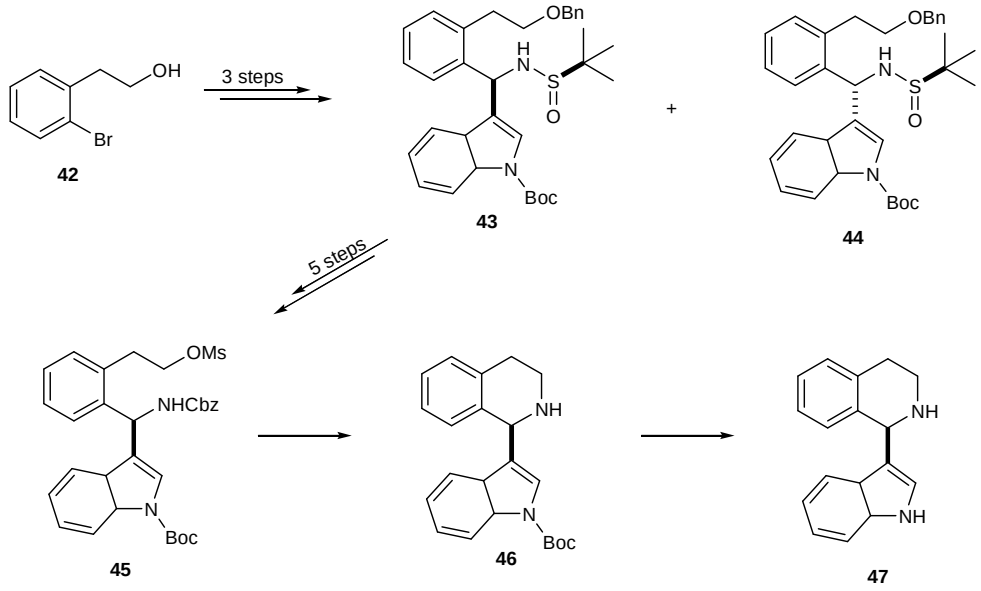
72%). In all cases the *cis* epimer was found to be the major product. The ratios are given in Scheme 7.[50]



X = H: **a**; Cl: **b**; OMe: **c**

Scheme 7

Chamberlin *et al.* devised a stereoselective route for the synthesis of optically pure *N*-benzylsulfonylindol-3-yltetrahydroisoquinoline as a new type of IBR2 analogue (Scheme 8). The pathway involved contained indol-3-yltetrahydroisoquinoline (**47**) in enantiopure form as intermediate. 2-(2-Bromophenyl)ethanol (**42**) was transformed to the sulfinimine diastereomers **43** and **44,** which were then separated. Through 5 steps, **43** led to the orthogonally protected mesylate derivative **45**. The isoquinoline ring (**46**) was formed by catalytic (Pd/C) reduction (H_2, 1 atm., EtOH, rt). On removal of the protecting group, the desired indol-3-yltetrahydroisoqinoline (**47**) was obtained in non-racemic form.[51]

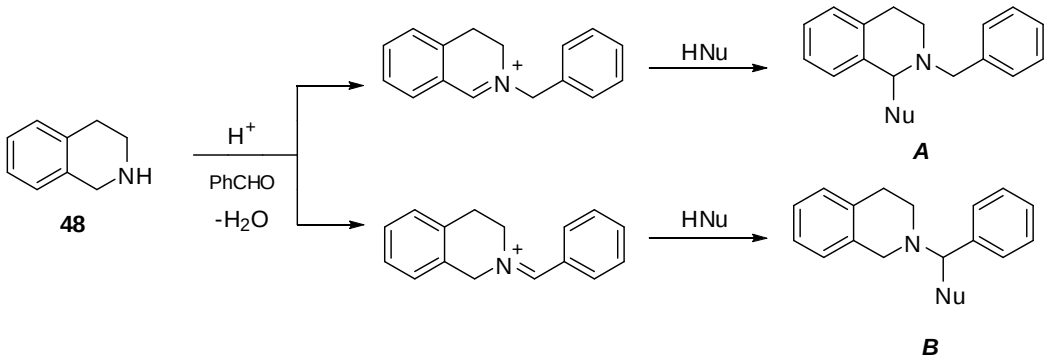


Scheme 8

3. RESULTS AND DISCUSSION

3.1. *N-Alkylation of cyclic amines with 2-, or 1-naphthol [II], [III]*

The importance of the aminonaphthols prepared *via* the mMR has recently increased because they have proved to be excellent model compounds for studies of the α-arylation/*N*-alkylation of cyclic amines.[9-11] It was pointed out by Seidel's group that, through the aminoalkylation of pyrrolidine with electron-rich aromatic compounds in the presence of aromatic aldehydes, the two possible main products *i.e.* α-arylated or *N*-alkylated, could be isolated only on the extremely slow addition of the aldehyde component to the reaction mixture containing acids as catalysts. It was also proved that 2-naphthol can be sufficiently acidic to promote the required tautomerization.[10] This process, starting from 1,2,3,4-tetrahydroisoquinoline as substrate, can theoretically lead to the formation of the regioisomeric tertiary aminonaphthols (***A*** or ***B***) according to Scheme 9, where HNu is an electron-rich aromatic compound such as 2- or 1-naphthol. The direct functionalization of 1,2,3,4-tetrahydroisoquinolines with indoles in the presence of aromatic aldehydes was recently developed. It was concluded that, under CuBr and acid catalysis, the α-arylation took place and aminoindole type ***A*** was isolated as a single product.[52]

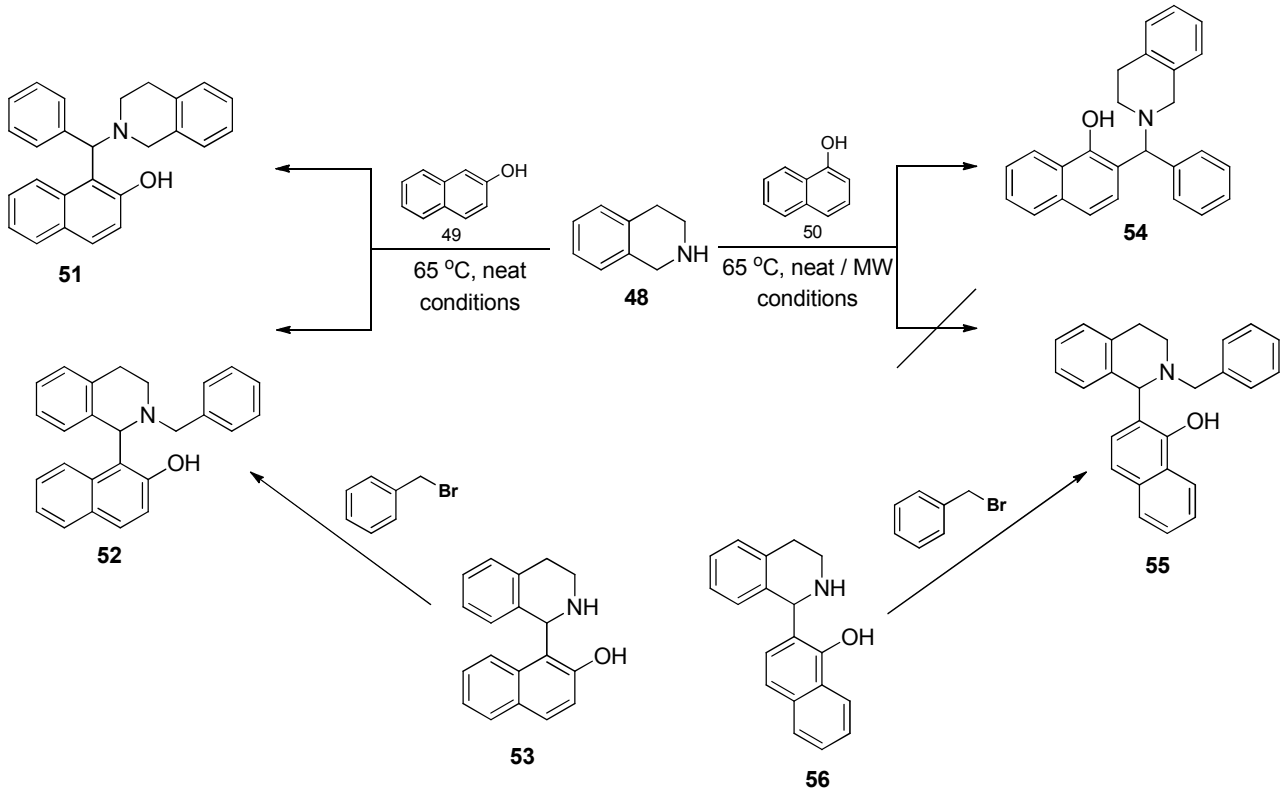


Scheme 9

Our present main aim was to develop the possibility of the application of 1,2,3,4-tetrahydroisoquinoline and analogue secondary amines such as 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine in the mMR. A further aim was the systematic investigation of the α-arylation/*N*-alkylation process starting from tetrahydroisoquinoline, tetrahydrobenzazepine and tetrahydrothieno[3,2-*c*]pyridine by using 2- or 1-naphthol as nucleophile in the presence of benzaldehyde.

In our first experiment, 1,2,3,4-tetrahydroisoquinoline (**48**), 2-naphthol (**49**) and benzaldehyde were reacted under neat conditions at 80 °C. After a reaction time of 4 h, the desired 1-[(3,4-dihydro-1*H*-isoquinolin-2-yl)phenylmethyl]naphthalen-2-ol (**51**) was isolated by crystallization with MeOH. Since the yield of the reaction was only 28%, the reaction was repeated under MW irradiation at 65 °C. Siurprisingly, after a relatively long reaction time (1.5 h), the ^{1}H NMR spectra of the crude reaction mixture did not reveal the formation of **51**. The synthesis of **51** was earlier performed by refluxing **49**, 1,2,3,4-tetrahydroisoquinoline (**48**) and benzaldehyde in ethanol for 12 h. Under these conditions, **51** was isolated as a "yellow gummy" in a yield of 78%.[53] When we attempted to repeat this under the same reaction conditions, the ^{1}H NMR spectra of the crude product indicated that the desired product **51** was formed in only trace amounts.

In the above experiments, the possibility of formation of the α-arylated product **52** was not taken into account. For a systematic investigation of this reaction, **52** was synthetized from 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol (**53**)[12] and benzyl bromide on the basis of the literature process.[16] 2-Naphthol (**49**), 1,2,3,4-tetrahydroisoquinoline (**48**) and benzaldehyde were reacted under neat conditions at 65 °C. The formation of the possible products (**51** and **52**) and the conversion of the reaction were followed by ^{1}H NMR spectroscopy for different reaction times up to 20 h. The ratio of the products formed, **51**:**52**, was determined by comparing the relative intensities of the characteristic signals of 2-naphthol (9.73 ppm), **51** (5.51 ppm) and **52** (5.75 ppm). Under the optimum conditions (65 °C, neat), an average ratio of 4:1 for **51**:**52** could be assumed (Table 8, entries 1-7). After a relatively long (20 h) reaction time, the conversion was only 85% (which could not be increased even by using a longer reaction time).



Scheme 10

To extend this mMR, 1-naphthol (**50**) was reacted with 1,2,3,4-tetrahydroisoquinoline (**48**) in the presence of benzaldehyde, where the possible products obtained by α-arylation/*N*-alkylation of **48** were **54** and **55** (Scheme 10). For a systematic study of this reaction, the *N*-alkylated product 2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol (**55)** was synthesized from 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol (**56**)[12] and benzyl bromide. 1-Naphthol (**50**), 1,2,3,4-tetrahydroisoquinoline (**48**) and benzaldehyde were reacted under neat conditions by heating at 65 °C or under MW irradiation at the same temperature. The presence of the possible products (**54** and **55**) was followed by comparing the relative intensities of the characteristic signals of benzaldehyde (10.03 ppm), **54** (s, 5.00 ppm) and **55** (s 5.07 ppm) from the crude product. The characteristic singlets of the CH_2 in **54** and **55** were found to be near each other: at 3.77 ppm (2H, dd, J = 14.8; 47.3 Hz) in **54** and at 3.71 ppm (2H, dd, J = 13.7; 200 Hz) in **55** (Table 8, entries 8-11).

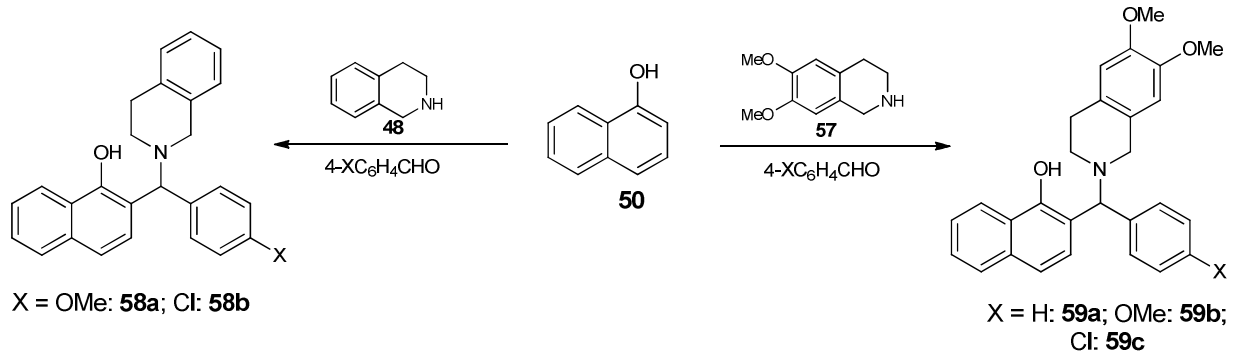
Table 8. Systematic study of the formation of products **51**, **52** and **54**, **55**

Entry	Products	Reaction conditions	Reaction time	Ratios of 51[a]:52[b] or 54[a]:55[b]	Conversion (%)
1	**51; 52**	Classical heating; 65 °C	0.5 h	78:22	42
2	**51; 52**	Classical heating; 65 °C	1h	81:19	45
3	**51; 52**	Classical heating; 65 °C	1.5 h	71:29	55
4	**51; 52**	Classical heating; 65 °C	2 h	82:18	56
5	**51; 52**	Classical heating; 65 °C	5 h	80:20	57
6	**51; 52**	Classical heating; 65 °C	10 h	82:18	60
7	**51; 52**	Classical heating; 65 °C	20 h	81:19	85
8	**54; 55**	Classical heating; 65 °C	0.5 h	100:0	91
9	**54; 55**	Classical heating; 65 °C	1.5 h	100:0	96
10	**54; 55**	MW; 65 °C	0.5 h	100:0	98
11	**54; 55**	MW; 65 °C	1 h	100:0	100

[a] *N*-alkylated product;
[b] α-arylated product

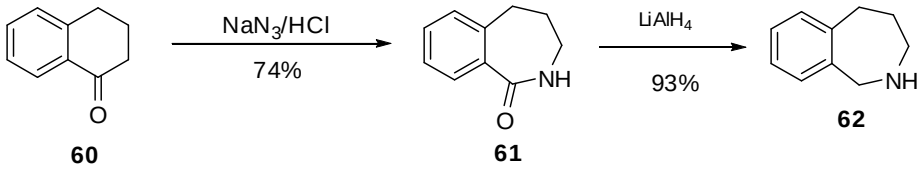
Interestingly, in contrast with our expectations, the signals of the crude product indicated only the formation of **54** when classical heating was applied at 65 °C (Table 8, entries 8 and 9). This tendency seemed to be independent of the reaction conditions (classical or MW heating): even after relatively short reaction times (1.5 h under classical heating or 0.5 h under MW; Table 8, entries 8-11), both conditions led to the formation of **54** in excellent yields.

The series of 2-substituted 1-naphthol analogues was extended by using different 4-substituted benzaldehydes such as 4-methoxybenzaldehyde or 4-chlorobenzaldehyde, leading to **58a** and **58b** (Scheme 11), while 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**57**) was tested as substrate with 1-naphthol and benzaldehyde or 4-substituted benzaldehydes, leading to **59a-c** (Scheme 11). The reaction conditions and yields are listed in Table 9.



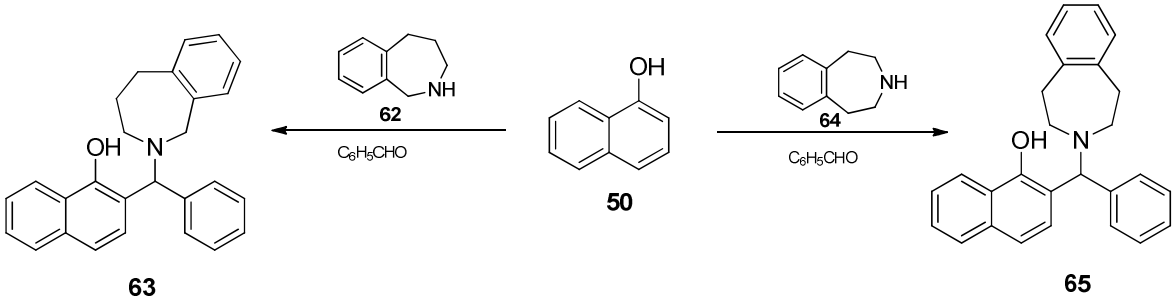
Scheme 11

To test the scope and limitations of the reaction, 1-naphthol was reacted with other secondary cyclic amines, such as 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (**62**), 2,3,4,5-tetrahydro-1*H*-benz[*d*]azepine (**64**) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**66**). Compound **64** is a commercially available secondary amine, while **62** was prepared from α-tetralone with NaN_3 in HCl medium followed by the reduction of cyclic amide (**61**) with $LiAlH_4$ (Scheme 12).[54]



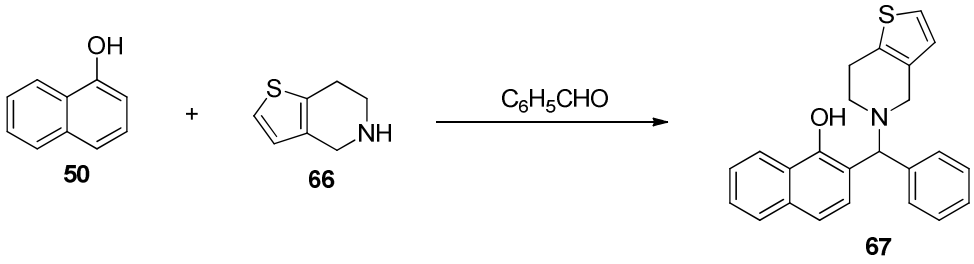
Scheme 12

In the case of **66**, the known Pictet–Spengler cyclization[55] was applied and optimized as follows to obtain the desired cyclic amine **66**. Thiophen-2-yl-ethylamine was mixed with formalin to obtain the imine intermediate. The second ring closure was performed in the presence of HCl/EtOH at 100 ºC under MW conditions. These conditions led to the formation of **66** in a yield of 63%.



Scheme 13

As the next step, 1-naphthol was reacted with secondary cyclic amines **62**, **64** and **66** in the presence of benzaldehyde, leading to the formation of 2-((4,5-dihydro-1*H*-benz[*c*]azepin-2(3*H*)-yl)(phenyl)methyl)naphthalen-1-ol (**63**), 2-((4,5-dihydro-1*H*-benz[*d*]azepin-3(2*H*)-yl)(phenyl)-methyl)naphthalen-1-ol (**65**) and 2-((6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)(phenyl)methyl)-naphthalen-1-ol (**67**) (Schemes 13 and 14). The reaction conditions and yields are given in Table 9.



Scheme 14

As concerns the aldehyde substrates, the highest yields were obtained with 4-chlorobenzaldehyde, when shorter reaction times too were needed (Table 9). The yields of the 1-naphthol derivatives pointed to the lower reactivity of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**66**) vs. the 1,2,3,4-tetrahydroisoquinolines (**48** and **57**) or the 2,3,4,5-tetrahydro-1*H*-benzazepines (**62** and **64**). When MW irradiation was applied, the reaction times were in all cases shorter, while the yields were improved.

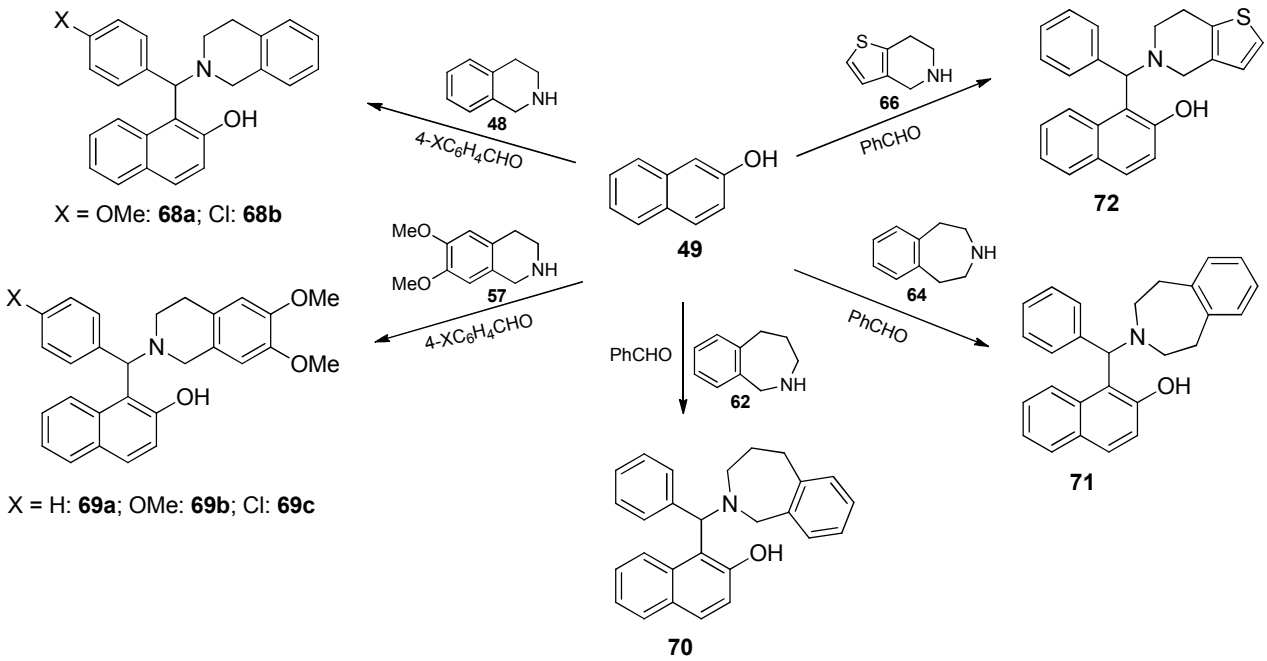
Since the solvent-free heating of 1-naphthol with different cyclic amine substrates in the presence of the above aldehydes (either by classical heating or by MW agitation) led to the formation of the desired aminonaphthols (**51**, **68a-b**, **69a-c**, **70**, **71** and **72**) in good yields, our attention turned back to the aminoalkylation of 2-naphthol (Table 10). Thus, tetrahydroisoquinoline (**48**) was reacted with 2-naphthol (**49**) and 4-methoxybenzaldehyde or 4-chlorobenzaldehyde under neat conditions. The reaction was then extended by applying the above cyclic amines, such as 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**57**), 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (**62**), 2,3,4,5-tetrahydro-1*H*-benz[*d*]azepine (**64**) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**66**).

Table 9. Optimized reaction conditions for the syntheses of **54**, **58, 59**, **63**, **65** and **67**

Product	Classical heating	Yield (%)	MW agitation	Yield (%)
54	70 °C, 12 h	58[a]	65 °C, 0.5 h	78[a]
58a	70 °C, 8 h	53[a]	65 °C, 0.5 h	72[a]
58b	70 °C, 5 h	57[a]	65 °C, 0.5 h	74[a]
59a	70 °C, 12 h	52[b]	65 °C, 1 h	73[b]
59b	70 °C, 7 h	60[b]	65 °C, 0.5 h	77[b]
59c	70 °C, 5 h	61[b]	65 °C, 0.5 h	81[b]
63	60 °C, 64 h	53[c]	55 °C, 1.5 h	57[c]
65	60 °C, 64 h	45[c]	55 °C, 1.5 h	55[c]
67	65 °C, 45 h	37[d]	60 °C, 1,5 h	48[d]

[a] recrystallized from *i*Pr_2O:MeOH (1:1);
[b] recrystallized from MeOH;
[c] recrystallized from *i*Pr_2O:MeOH (2:1);
[d] recrystallized from *i*Pr_2O:MeOH (4:1)

On the use of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**57**), the aldehyde substrates were benzaldehyde, 4-methoxybenzaldehyde and 4-chlorobenzaldehyde. The structures of the tertiary aminonaphthol products **68a-b**, **69a-c** and **70-72** are shown in Scheme 15, while the reaction conditions and yields are listed in Table 10.



Scheme 15

When tetrahydroisoquinoline **48** was reacted with 2-naphthol in the presence of 4-methoxybenzaldehyde or 4-chlorobenzaldehyde, relatively long reaction times (classical heating: 20 h, MW agitation: 2.5 h) were needed. In all cases, the isolated yields were sufficiently high to allow the conclusion that other α-arylated by-products were absent. When 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**57**) was applied as starting material, a higher temperature (75 °C) was needed; a faster reaction as compared with **51** and **68a-b** can be assumed.

Table 10. Optimized reaction conditions for the syntheses of **51** and **68-72**

Product	Classical heating	Yield (%)	MW agitation	Yield (%)
51	80 °C, 4 h	46[a]	65 °C, 1.5 h	-
68a	70 °C, 5 h	48[c]	65 °C, 0.5 h	71[c]
68b	70 °C, 5 h	50[c]	65 °C, 0.5 h	77[c]
69a	75 °C, 8 h	55[b]	70 °C, 1 h	82[b]
69b	75 °C, 8 h	57[b]	70 °C, 1 h	84[b]
69c	75 °C, 3.5 h	65[b]	70 °C, 0.5 h	87[b]
70	60 °C, 56 h	62[d]	60 °C, 1.5 h	70[d]
71	60 °C, 64h	58[a]	60 °C, 2 h	67[a]
72	75 °C, 56 h	28[a]	70 °C, 1.5 h	41[a]

[a] recrystallized from *i*Pr$_2$O:MeOH (4:1);
[b] recrystallized from MeOH;
[c] recrystallized from *i*Pr$_2$O:MeOH (1:1);
[d] recrystallized from *i*Pr$_2$O:MeOH (2:1)

A consideration of the yields of all the product aminonaphthols (except **51** and **52**) revealed the lowest yields for those whose synthesis started from 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine (**62**). This might be due to the lower stability of the benzazepine ring system at higher temperature, or to the formation of two regioisomers (*N*-alkylation or α-substitution) during the reaction. To check on this, the syntheses of **63** and **70** were repeated and the conversion of the starting compounds was systematically followed via the NMR spectra of the crude products (Table 11). The desired aminonaphthols **63** and **70** were found to be single products, independently of the reaction conditions (classical or MW heating), suggesting that the lower yields observed for **63** and **70** were due to the lower stability of the starting benzazepine (**62**).

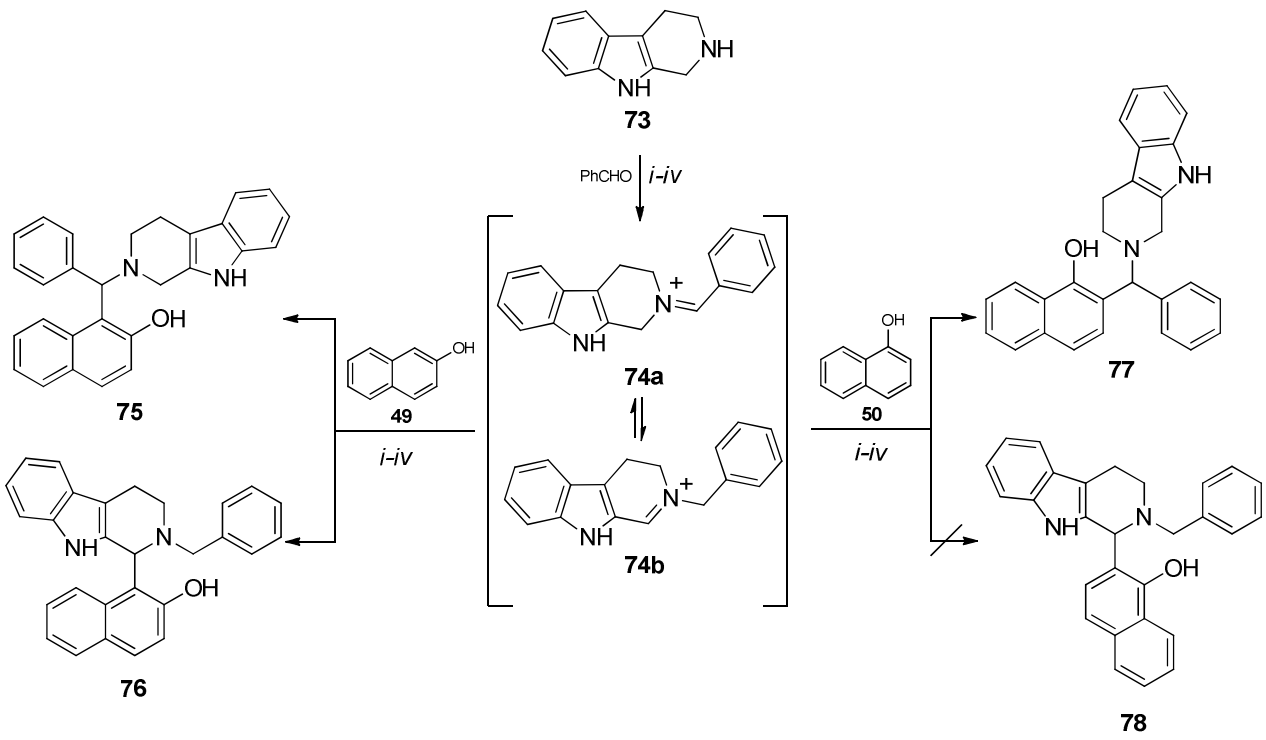
Table 11. Systematic study of the formation of products **63**[a] and **70**[a]

Entry	Product	Reaction conditions	Reaction time	Conversion (%)
1	**63**[b]	Classical heating; 65 °C	0.5 h	80
2	**63**[b]	Classical heating; 65 °C	2 h	95
3	**63**[b]	MW; 65 °C	0.5 h	100
4	**70**[b]	Classical heating; 65 °C	0.5 h	32
5	**70**[b]	Classical heating; 65 °C	1 h	44
6	**70**[b]	Classical heating; 65 °C	2 h	54
7	**70**[b]	Classical heating; 65 °C	5 h	63
8	**70**[b]	Classical heating; 65 °C	10 h	66
9	**70**[b]	Classical heating; 65 °C	20 h	58
10	**70**[b]	MW; 65 °C	0.5 h	37
11	**70**[b]	MW; 65 °C	1 h	38
12	**70**[b]	MW; 65 °C	2 h	48
13	**70**[b]	MW; 65 °C	3 h	50
14	**70**[b]	MW; 65 °C	4 h	71
15	**70**[b]	MW; 65 °C	6h	69

[a] *N*-alkylated product;
[b] single product

The β-carboline skeleton is present in numerous naturally occurring alkaloids, which often exhibit biological activity. Natural β-carboline-containing compounds, such as the harman family, have attracted interest because of their potent psychoactive and hallucinogenic abilities.[56-58] Moreover, synthetic β-carbolines display antimalarial[59], antiparasitic[59] and antineoplasic[60] activity, while certain β-carbolines inhibit TNF-α[61] or MK2.[62] Tricyclic β-carboline derivatives have been found to be $mGluR_1$ antagonists[63], and bromo-substituted tetrahydro-β-carbolines have been described as neurotoxic agents.[64] The production of these compounds demands efficient synthetic methodologies, for the construction of the heterocyclic system and its functionalization. The strategies for the synthesis of condensed β-carbolines mainly start from the partially saturated β-carbolines through 1,3-dipolar cycloaddition,[65] coupling with isatoic anhydride[66], reaction with Mannich bases[67], the inverse-electron-demand imino Diels–Alder reaction with chromone-derived dienes[68], or reaction with salicyl chloride.[69-71]

Our results on the aminoalkylation of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde showed that it led to the parallel *N*-alkylation and redox α-arylation of the tetrahydroisoquinoline in a ratio of 4:1. Hence, our attention focused on the possibility of aminoalkylation of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**73**) as cyclic secondary amine with 1- or 2-naphthol as nucleophile in the presence of benzaldehyde.



Reaction conditions: *i*) 60 °C, neat; *ii*) 80 °C, neat; *iii*) 60°C, neat, MW; *iv*) 80 °C, neat, MW

Scheme 16

The selected starting amine **73** was synthesized according to a literature process, via Pictet–Spengler cyclization of tryptamine. [72,73]

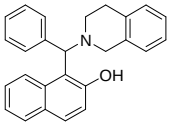
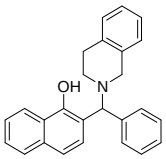
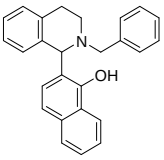
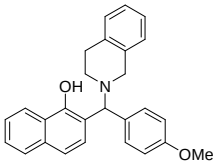
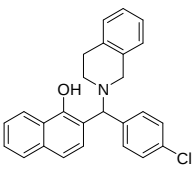
2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole (**73**), 2-naphthol (**49**) and benzaldehyde were reacted (Scheme 15) neat under different reaction conditions (*i*: 60 °C, classical heating; *ii*: 80 °C, classical heating; *iii*: 60 °C, MW; *iv*: 80 °C, MW). For the systematic investigation of this reaction, the possible α-arylated product **76** was synthesized from 1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-2-ol and benzyl bromide. The formation of the possible products (**75** and **76**) and the conversions of the reactions (*i*-*iv*) were followed by NMR spectroscopy, comparing the relative intensities of the characteristic signals of 2-naphthol (9.73 ppm), **75** (5.70) and **76** (5.85 ppm). The reactions were found to be complete after 7 h (*i*), 5 h (*ii*) and 3 h (*iii* and *iv*), respectively. The crude reaction mixture in all cases indicated the presence of both possible

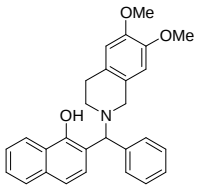
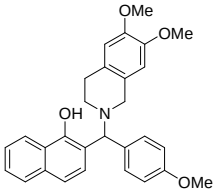
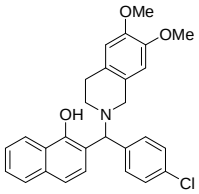
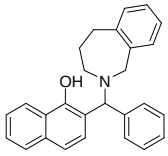
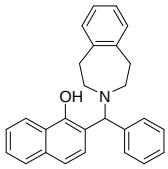
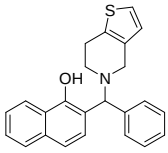
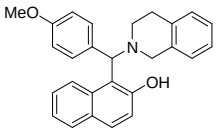
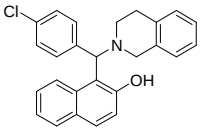
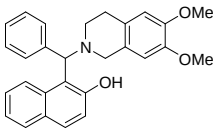
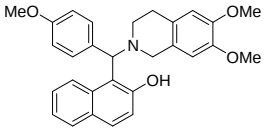
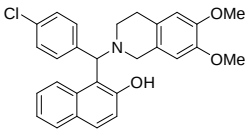
products **75** and **76**. The ratio **75**:**76** was found to be 4:1 for *i* and *iii*, and 2:1 for *ii*. In the case of *iv* (80 °C, MW), the ratio was not constant during the reaction. After 0.5 h it was 1:0.8, and at the end of the reaction (3 h) a ratio of 1:2.5 was assumed. This means that the formation of **74a** is more preferable at 80 °C than at 60 °C. It can also be assumed that the product ratio depends on the heating technique: classical heating or MW agitation.

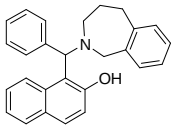
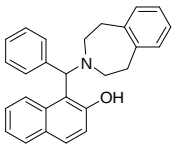
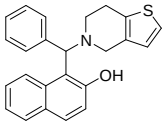
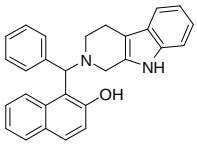
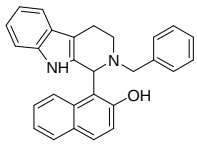
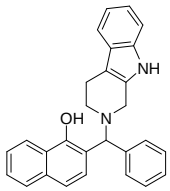
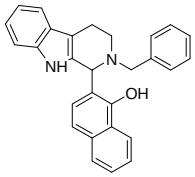
To examine the behaviour of 1-naphthol in this reaction, **50** was reacted with 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**73**) in the presence of benzaldehyde, when the possible products obtained through the α-arylation/*N*-alkylation of **73** were **77** and **78** (Scheme 16). For a systematic study of this reaction, the α-arylated product was prepared by the reaction of 2-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-1-ol and benzyl bromide.

By using reaction conditions *i*-*iv*, 1-naphthol (**50**), 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**73**) and benzaldehyde were reacted. Interestingly, the signals of the crude products indicated only the formation of **77**. This was found to be independent of the temperature (60 °C or 80 °C) and of the reaction conditions (classical or MW heating).

Table 12. Characteristic NMR chemical shifts (Nph-C*H*-Ph or Nph-*C*H-Ph) and melting points of the synthesized tertiary aminonaphthol derivatives presented in this chapter

Products	Structures	$\delta_{C\text{-}H}$ (ppm)	$\delta_{C\text{-}H}$ (ppm)	M.p.
51		5.57	70.2	151-152
54		5.00	74.0	138-140
55		5.07	67.1	148-149
58a		4.92	73.6	178-179
58b		5.05	72.6	180-182

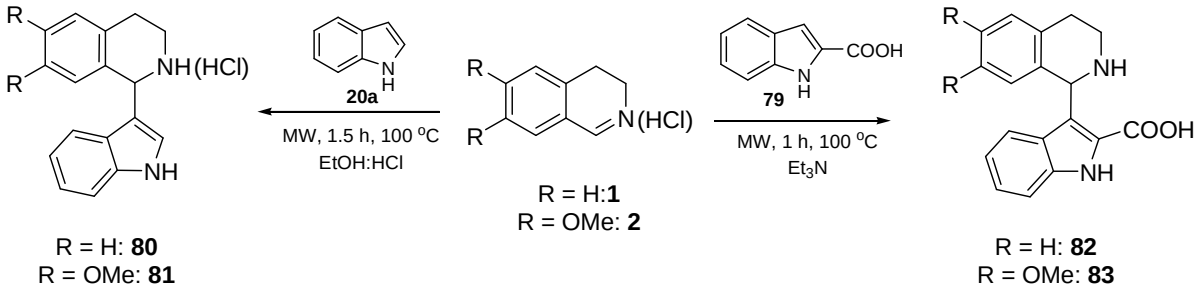
59a		4.96	74.3	164-166
59b		4.90	73.8	121-123
59c		5.01	73.0	132-133
63		4.89	71.6	79-81
65		5.13	74.3	153-155
67		5.05	73.4	161-162
68a		5.51	69.6	176-178
68b		5.61	69.1	180-181
69a		5.54	70.3	193-195
69b		5.48	69.7	207-209
69c		5.59	69.3	209-211

70		5.56	69.9	158-160
71		5.45	68.1	201-203
72		5.62	69.7	142-143
75		5.70	69.7	203-205
76		5.85	58.1	198-199
77		5.12	73.6	196-198
78		5.22	63.5	179-181

3.2. Aza–Friedel Crafts alkylation of partially saturated cyclic imines with electron-rich aromatic compounds [I], [III]

3.2.1. α-Arylation of 3,4-dihydroisoquinoline with indole derivatives [I]

In previous works, the aza-Friedel–Crafts alkylations of electron-rich aromatic compounds such as 2- or 1-naphthol[12] and quinolinol or isoquinolinol[15] with 3,4-dihydroisoquinoline were achieved, and were extended by using different reagents and/or substrates to the synthesis of 1-substituted tetrahydroisoquinoline derivatives.[8,18-20] Our aim was to develop a new approach for the preparation of 1-(3-indolyl)-1,2,3,4-tetrahydroisoqinolines from 3,4-dihydroisoquinoline and indole as electron-rich aromatic compound, and as a further aim to examine the scope and limitations of this reaction by using different cyclic imines and/or different indole derivatives.



Scheme 17

The reaction between indole (**20a**) and 3,4-dihydroisoquinoline (**1**) in MeCN at 80 °C was examined first (Table 13, entry 1), the conversion of the reactants being monitored by TLC analysis. After a reaction time of 6 h, TLC showed only the presence of the starting materials. Thus, the reaction was repeated by using MW agitation (Table 13, entry 2). Even after a reaction time of 4 h reaction time TLC showed only the unreacted starting compounds (Scheme 17). The reaction was then repeated under neat conditions, first by using classical heating. At 60 °C, after a relative long reaction time (10 h) the desired product **80**[74] was isolated in a yield of 37% as a yellow oil, and column chromatography was needed for the purification (Table 13, entry 3). When the temperature was increased (85 °C), a somewhat shorter reaction time was needed (8 h), and the yield was still only 48%. Even on the use of MW agitation the yield could not be improved (43% and 40%, respectively); only the reaction times were decreased (3 h and 2 h, respectively, Table 13, entries 5 and 6). The reaction was then repeated from 3,4-dihydroisoquinoline-hydrochloride (**1.HCl**). After a reaction time of 12 h at 80 °C, on the addition of DCM, beige crystals started to

separate out. After filtration and recrystallization, these were identified as the hydrochloride of the desired 3-tetrahydroisoquinolylindole (**80**). This was surprising, because 2 equiv. of Et_3N was used for the *in situ* basification of the starting 3,4-dihydroisoquinoline. In spite of this, **80.HCl** was isolated, which can be explained by the stronger basicity of **80** than Et_3N. The yield was found to be 62% (Table 13, entry 7). Similar yields were obtained by increasing the temperature to 100 ºC or by using MW heating at 80 ºC (Table 13, entries 8 and 9). To test the role of HCl, the reaction was repeated by starting from **1.HCl** and indole (**20a**) in DCM and 2 drops of EtOH:HCl were used as additive. The reaction was performed at 100 ºC under MW conditions. After a reaction time of 1.5 h the separated crystals were filtered off. The yield excellent (94%, Table 13, entry 10).

To examine the possibility of the extension possibility of this reaction, 6,7-dimethoxy-3,4-dihydroisoquinoline (**2**) was tested as substrate. We started our experiments by applying the best conditions for the synthesis of **80**. **2.HCl** and indole (**20a**) were reacted in DCM by using EtOH:HCl as additive, under MW agitation. Unfortunately, the TLC showed only the decomposition of the starting 6,7-dimethoxy-3,4-dihydroisoquinoline (**2.HCl**) (Table 13, entry 11). When **2.HCl** was reacted with **20a** under neat conditions, using classical heating and 2 equiv. of Et_3N for *in situ* basification, the hydrochloride of the desired product (**81.HCl**) was isolated in only 40% yield (Table 13, entry 12). Increase of the temperature by using either classical heating or MW irradiation led to the decomposition of **2.HCl** (Table 13, entries 13 and 14). We therefore decided to start the reaction from the free base (**2**). By classical heating at 80 ºC, after a long reaction time (55 h) the desired 3-(6,7-dimethoxy-tetrahydroisoquinolyl)indole (**81**) was isolated in a yield of 70% (Table 13, entry 15). The yield was improved to 73% and the reaction time decreased (4 h + 2.5 h) by using a two-step MW reaction (Table 13, entry 16). Further increase of the temperature (110 ºC) under MW conditions led to the formation of **81** in a yield of only 45% (Table 13, entry 17).

Table 13. Reaction conditions for the synthesis of 1-(indol-3-yl)-1,2,3,4-tetrahydroisoquinolines **80** and **81**.

Entry	Reagent/solvent/ additive	Products	Conditions	Yields (%)
1	**1**/MeCN/-	**80**	80 °C, 6 h[a]	[c]
2	**1**/MeCN/-	**80**	80 °C, 4 h[b]	[c]
3	**1**/neat/-	**80**	60 °C, 10 h[a]	37
4	**1**/neat/-	**80**	85 °C, 8 h[a]	48

5	**1**/neat/-	**80**	60 °C, 3 h[b]	43
6	**1**/neat/-	**80**	85 °C, 2 h[b]	40
7	**1-HCl**/neat/2 equiv. Et_3N	**80.HCl**	80 °C, 12 h[a]	62
8	**1-HCl**/neat/2 equiv. Et_3N	**80.HCl**	100 °C, 4 h[a]	68
9	**1-HCl**/neat/2 equiv. Et_3N	**80.HCl**	80 °C, 2 h[b]	60
10	**1-HCl**/DCM/EtOH:HCl	**80.HCl**	100 °C, 1.5 h[b]	94
11	**2-HCl**/DCM/EtOH:HCl	**80.HCl**	100 °C, 1.5 h[b]	[d]
12	**2-HCl**/neat/2 equiv. Et_3N	**81**	80 °C, 4 h[a]	40
13	**2-HCl**/neat/2 equiv. Et_3N	**81**	120 °C, 2 h[a]	[d]
14	**2-HCl**/neat/2 equiv. Et_3N	**81**	100 °C, 4 h[b]	[d]
15	**2**/neat/-	**81**	80 °C, 55 h[a]	70
16	**2**/neat/-	**81**	80 °C, 4 h→100 °C, 2.5 h[b]	73
17	**2**/neat/-	**81**	110 °C, 5 h[b]	45

[a] classical heating;
[b] MW agitation;
[c] no reaction;
[d] decomposition

To test the scope and limitations of this aza-Friedel–Crafts aminoalkylation of indole, indole-2-carboxylic acid (**79**) was reacted with 3,4-dihydroisoquinoline-hydrochloride (**1.HCl**). In our first experiment, DCM was used as solvent and 2 drops of EtOH:HCl as additive. By using MW heating, after a reaction time of 1.5 h only the presence of the starting compounds could be detected by TLC (Table 14, entry 1). Change of the solvent (DCM→EtOH) and the use of 2 equiv. of Et_3N for *in situ* basification did not lead to the formation of the desired product. Thus, the reaction was repeated under neat conditions, and by using 8 equiv. of Et_3N under MW agitation. A relatively high amount of Et_3N was needed to support the homogeneous medium of the reaction. The synthesized new γ-aminoacid (**82**) was isolated by crystallization with DCM (Table 14, entry 3). These reaction conditions could be successfully applied for the preparation of 3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)indole-2-carboxylic acid (**83**). It should be mentioned that a somewhat higher temperature and a somewhat longer reaction time were needed for the synthesis of **83** as compared with **82** (Table 14, entry 4).

Table 14. Reaction conditions for the syntheses of **82** and **83**

Entry	Reagent/solvent/ additive	Products	Conditions	Yields (%)
1	**1**/DCM/EtOH:HCl	**82**	100 °C, 1.5 h[a]	[b]
2	**1**/EtOH/2 equiv. Et_3N	**82**	110 °C, 8 h[a]	[b]
3	**1**/neat/8 equiv. Et_3N	**82**	100 °C, 1 h[a]	79
4	**2**/neat/8 equiv. Et_3N	**83**	110 °C, 3 h[a]	77

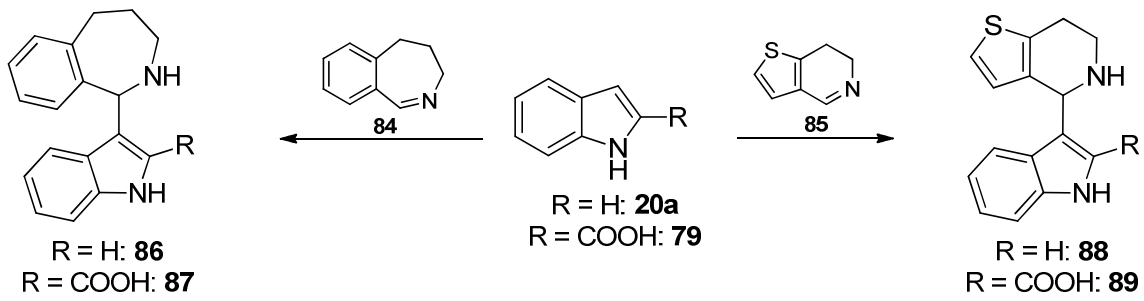
[a] MW agitation;
[b] no reaction

3.2.2. α-Arylation of 6,7-dihydrothieno[2,3-c]pyridine and 4,6-dihydro-3H-benz[c]azepine with indole derivatives [I]

The possibility of extentsion of the reaction was tested by applying different other cyclic imines. These partially saturated heterocycles were selected to have characteristic differences as compared with the dihydroisoquinoline skeleton. Our attention therefore focused on the application of 4,6-dihydro-3*H*-benz[*c*]azepine (**84**) and 6,7-dihydrothieno[2,3-*c*]pyridine (**85**). Two synthetic pathways were applied to achieve the desired starting compounds. In the case of **84**, **62** was reacted with *N*-chlorosuccinimide followed by elimination promoted by KOH.[75,76] 6,7-Dihydrothieno[2,3-*c*]pyridine (**85**) was prepared by a literature process, via Bischler–Napieralski cyclization of 2-(thiophen-2-yl)ethanamine.[77]

When the unsaturated benz[*c*]azepine (**84**) was reacted with indole (**20a**) at 80 ºC for a relatively long reaction time, the desired 3-benzazepinylindole (**86**) was isolated in a yield of 62% after purification by column chromatography (Table 15, entry 1). Possibly because of the decomposition of **84**, increase of the temperature (110 ºC) led to the formation of **86** in lower yield (37%, Table 15, entry 2). The best conditions for the synthesis of **86** were found to be 85 ºC under MW condition, but it should be mentioned that a relatively long reaction time (5 h) was needed (Table 15, entry 3). On further increase of the temperature under MW conditions, the yields could not be improved (Table 15, entries 4 and 5).

Table 15. Reaction conditions for the synthesis of 3-substituted-indole (**86**, **88**) and 3-substituted-indole-2-carboxylic acid (**87**, **89**) derivatives.



R = H: **86**
R = COOH: **87**

R = H: **20a**
R = COOH: **79**

R = H: **88**
R = COOH: **89**

Entry	R	Products	Conditions	Yields (%)
1	**H**	**86**	80 °C, 34 h[a]	62
2	**H**	**86**	110 °C, 2.5 h[a]	37
3	**H**	**86**	85 °C, 5 h[b]	76
4	**H**	**86**	100°C, 1.5 h[b]	40
5	**H**	**86**	120 °C, 0.5 h[b]	-[c]
6	**COOH**	**87**	80 °C, 44 h[a]	65
7	**COOH**	**87**	80 °C, 6 h→90 °C, 2 h[b]	78
8	**H**	**88**	80 °C, 7 h[a]	57
9	**H**	**88**	80 °C, 2 h[b]	68
10	**COOH**	**89**	80 °C, 1.5 h[a]	65
11	**COOH**	**89**	80 °C, 0.5 h→90 °C, 0.5 h[b]	72

[a] classical heating;
[b] MW agitation;
[c] decomposition

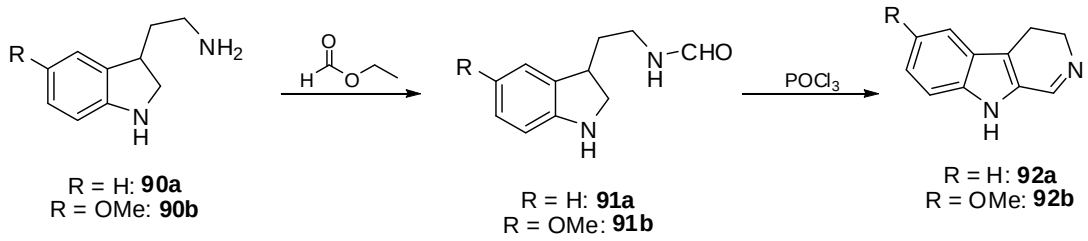
For the synthesis of 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole-2-carboxylic acid (**87**), both classical heating and MW agitation were tested. Table 15 shows that by applying two-step MW conditions, the final product (**87**) was isolated in somewhat higher yield (Table 15, entries 6 and 7), when 6,7-dihydrothieno[3,2-*c*]pyridine (**85**) was reacted either with **20a** or with **79**. From the results in Table 15 (entries 8-11), it can be concluded that **85** has a higher reactivity with indolederivatives as compared with 4,6-dihydro-3*H*-benz[*c*]azepine (**84**).

3.2.3. α-Arylation of 4,9-dihydro-3H-β-carboline with indole or naphthol derivatives [III]

3.2.3.1. α-Arylation of 4,9-dihydro-3H-β-carboline with indole derivatives

A vast number of natural and synthetic indoles have found applications as pharmaceuticals,[78] *e.g.* through the catalyst-free coupling of indoles and cyclic imines we have prepared numerous 3-substituted indoles and our attention focused on the reactions between the previously applied indoles and β-carboline derivatives.

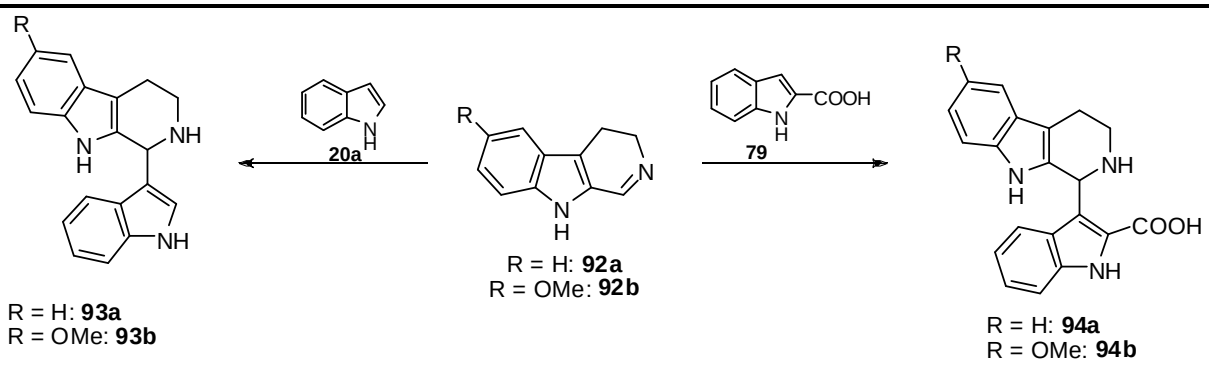
The selected starting imines **92a,b** were synthesized from tryptamine (**90a**) or 5-methoxytryptamine (**90b**) by Bischler–Napieralski cyclization (Scheme 18).[79-81]



Scheme 18

When indole (**20a**) was reacted under solvent-free conditions with the partially unsaturated β-carboline (**92a**) at 80 °C, 3-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)indole (**93a**) was isolated in a yield of 35%. When the reaction was repeated under MW agitation at 100 °C, the reaction time could be decreased from 4 h to 30 min (Table 16). The synthesis of **93a** was earlier achieved[82-84] from 1*H*-indole-3-ethanamine and 1*H*-indole-3-carboxaldehyde via Pictet–Spengler condensation. The main advantage of our method is the application of indole derivatives instead of indole-3-carboxaldehyde, the direct α-arylation of partially saturated β-carbolines with electron-rich aromatic compounds opening up new areas of diversity for this reaction. To prove this, the reaction between **92a** and indole-2-carboxylic acid (**79**) was examined. In this case the optimum reaction conditions were found to be 80 °C with 4 h classical heating, or 100 °C with 20 min under MW irradiation. The desired new indole-γ-amino acid **94a** was isolated in a yield of 73% (classical heating) or 91% (MW agitation). The reaction was then extended by using **92b** as cyclic imine and indole (**20a**) or indole-2-carboxylic acid (**79**) as electron-rich aromatic compound, leading to the desired 3-(6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)indole derivatives (**93b** and **94b**) in good yields (see Table 16).

Table 16. Reaction conditions for the synthesis of **93a**, **93b**, **94a**, and **94b** from indole or indole-2-carboxylic acid

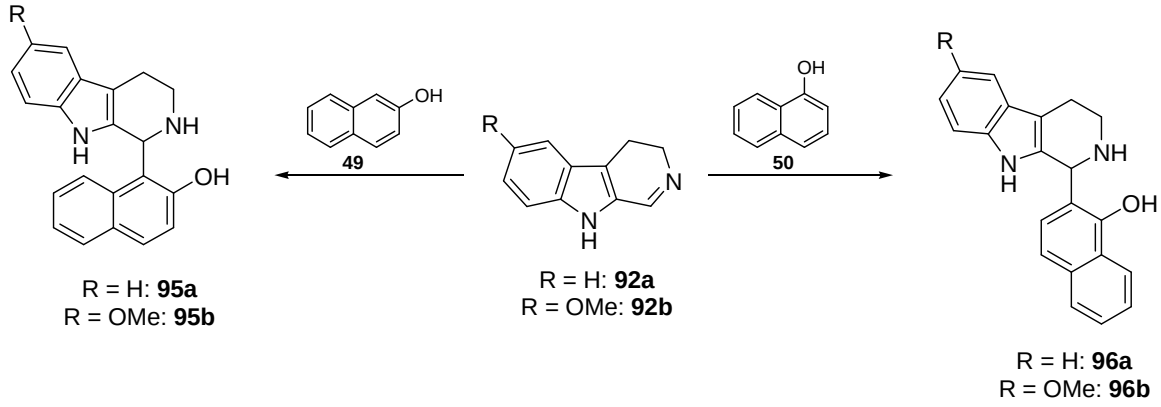


Product	Neat conditions	Yield (%)	MW agitation	Yield (%)
93a	80 °C, 4 h	35	100 °C, 30 min	83
93b	80 °C, 6 h	31	100 °C, 1 h	77
94a	80 °C, 4 h	73	100 °C, 20 min	91
94b	80 °C, 5 h	54	100 °C, 0.5 h	87

3.2.3.2. α-Arylation of 4,9-dihydro-3H-β-carboline with naphthol analogues

In our first experiments, the reaction between 4,9-dihydro-3*H*-β-carboline (**92a**) and 2-naphthol (**49**) was examined under neat conditions at 80 °C. After 10 h, the desired product **95a** was isolated in a yield of 48% (Table 17). When the temperature was increased (100 °C) and/or a longer reaction time was applied, decomposition of the starting compounds was assumed. Thus, the reaction was then repeated by using MW agitation. In this case after 2 h at 100 °C, the addition of diethylether led to the isolation of 1-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-2-ol (**95aa**) in a yield of 75% (Table 17).

To test the scope and limitations of the reaction, **92a** was reacted with 1-naphthol (**50**). After 8 h at 80 °C, the desired 2-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)naphthalen-1-ol (**96a**) was isolated in a yield of 61%. By using MW irradiation, the reaction could be accelerated (reaction time 1.5 h), while the yield at 100 °C was improved to 80% (Table 17).



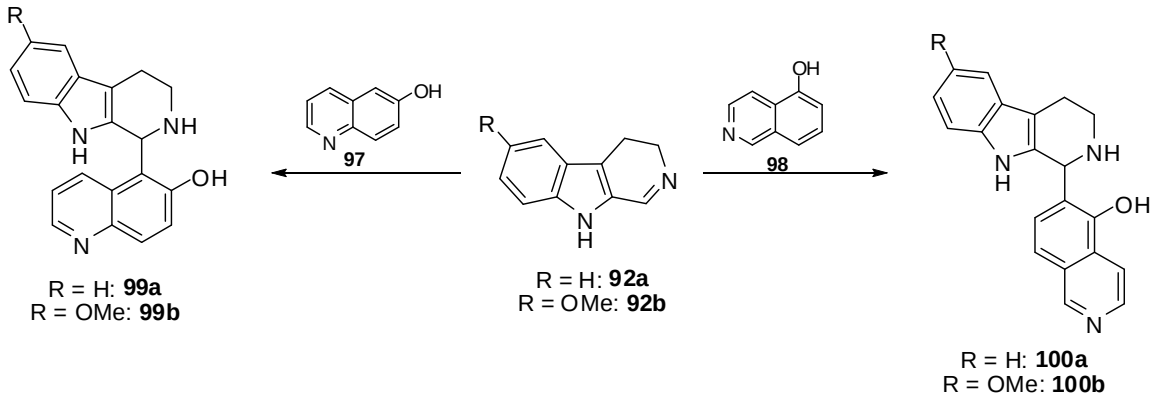
R = H: **95a**
R = OMe: **95b**

R = H: **92a**
R = OMe: **92b**

R = H: **96a**
R = OMe: **96b**

Scheme 19

Recent developments highlighted that *N*-containing naphthol analogues can be successfully applied as electron-rich aromatic compounds in the mMR[8] and in the aza-Friedel–Crafts reaction.[15] Two representative *N*-containing naphthol analogues (6-hydroxyquinoline as 2-naphthol, and 5-hydroxyisoquinoline as 1-naphthol analogue) were selected to examine their reactivities toward 4,9-dihydro-3*H*-β-carboline (**92a**). When **92a** and 6-hydroxyquinoline (**97b**) or 5-hydroxyisoquinoline (**98b**) were subjected to classical heating under neat conditions, the desired 5-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol (**99a**) and 6-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)isoquinolin-5-ol (**100a**) were isolated in moderate yields (57% for **99a**, 43% for **100a**, Table 17). On the use of MW agitation, the reaction times were decreased, but the yields could not be improved significantly (68% for **99a**, 63% for **100a**, Table 17).



R = H: **99a**
R = OMe: **99b**

R = H: **92a**
R = OMe: **92b**

R = H: **100a**
R = OMe: **100b**

Scheme 20

To generalize the application of β-carboline in this reaction, 6-methoxy-β-carboline (**92b**) was examined. When naphthol derivatives (**49, 50, 97** and **98**) were reacted with **92b** the desired

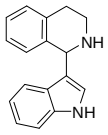
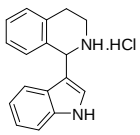
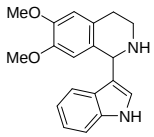
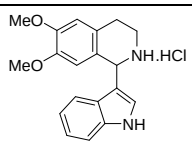
aminonaphthols (**95b, 96b, 99b, 100b**) were isolated. The reaction conditions and yields are given in Table 17.

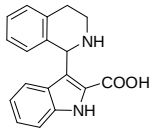
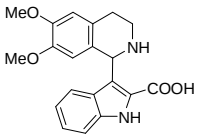
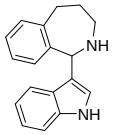
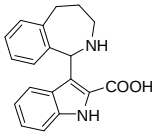
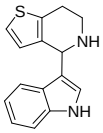
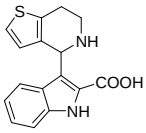
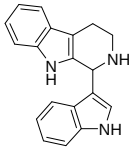
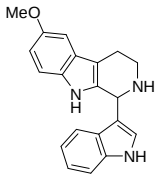
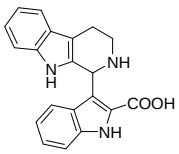
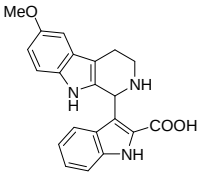
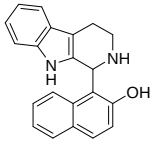
Table 17. Reaction conditions for the synthesis of **95a**, **95b**, **96a**, **96b**, **99a**, **99b**, **100a** and **100b** from 1- or 2-naphthol or their *N*-containing analogues.

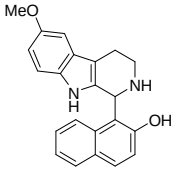
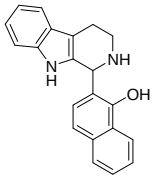
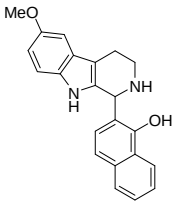
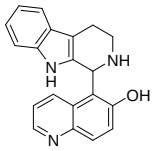
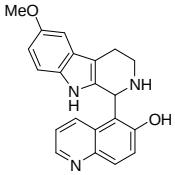
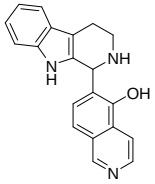
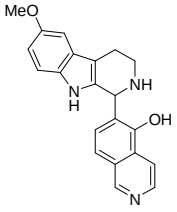
Product	Neat conditions	Yield (%)	MW agitation	Yield (%)
95a	80 °C, 10 h	48	100 °C, 2 h	75
95b	80 °C, 12 h	39	100 °C, 3 h	65
96a	80 °C, 5 h	57	100 °C, 0.5 h	68
96b	80 °C, 10 h	43	100 °C, 2 h	56
99a	80 °C, 8 h	61	100 °C, 1.5 h	80
99b	80 °C, 12 h	41	100 °C, 2 h	64
100a	80 °C, 6 h	43	100 °C, 1.5 h	63
100b	80 °C, 4 h	63	100 °C, 1 h	82

The formation of the α-arylated products was followed by comparing the NMR chemical shifts of the α-protons and/or α-carbons, the characteristic values of which are presented in Table 18.

Table 18. Characteristic NMR chemical shifts (NH-C*H*-Ar or NH-*C*H-Ar) and melting points of the synthesized α-arylated cyclic amines presented in this chapter.

Products	Structures	$\delta_{C\text{-}H}$ (ppm)	$\delta_{C\text{-}H}$ (ppm)	M.p.
80		5.30	54.7	oil
80.HCl		6.07	52.4	245-247
81		5.23	56.4	142-143
81.HCl		5.98	56.5	188-189

82		5.96	53.5	247-248
83		5.87	56.4	241-243
86		5.34	60.3	137-139
87		6.10	55.6	272-273
88		5.25	52.7	148-149
89		5.89	50.6	282-284
93a		5.97	49.9	145-147
93b		5.39	56.3	224-225
94a		6.07	49.1	276-277
94b		6.14	56.3	230-231
95a		6.17	52.6	191-192

95b		6.13	55.4	175-176
96a		5.49	56.8	200-201
96b		6.89	55.4	189-190
99a		6.14	52.2	239-240
99b		6.91	56.2	221-222
100a		5.55	56.6	229-230
100b		5.54	56.7	222-223

4. SUMMARY

1. Selective *N*-alkylations of tetrahydroisoquinolines, tetrahydrobenz[*d*]azepine, tetrahydrobenz[*c*]azepine and tetrahydrothieno[3,2-*c*]pyridine were achieved by using 1-naphthol and aromatic aldehydes under neat conditions to obtain tertiary aminonaphthols **54**, **58a**, **58b**, **59a-c**, **63**, **65** and **67**. The reactions were extended to the synthesis of 1-aminoalkylated 2-naphthol derivatives (**51**, **68a**, **68b**, **69a-c**, and **70-72**) by mixing 2-naphthol, aromatic aldehydes and the corresponding cyclic amines **48**, **57**, **62**, **64** and **66**. The yields were found to be good with the exception of **51**, where it was only 46%. We conceived that the moderate yield for **51** can be explained by parallel *N*-alkylation and redox α-arylation, and to prove this a systematic investigation was performed with the reaction of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde at 65 °C. The reaction was followed by comparing the characteristic singlets from the ^{1}H NMR, and it was found that the ratio of **51:52** is 4:1 during the reaction time (10 h) is 4:1. In contrast, the reaction of 1-naphthol with 1,2,3,4-tetrahydroisoquinoline led to the formation of the *N*-alkylated compound (**54**) as a single product. Starting from 2,3,4,5-tetrahydro-1*H*-benz[*c*]azepine, benzaldehyde and 2- or 1-naphthol at 65 °C, formation of the *N*-alkylated product was assumed in each case.

2. The reaction of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole as secondary cyclic amine with 2- or 1-naphthol as nucleophile in the presence of benzaldehyde led to the formation of 1-((3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methyl)naphthalen-2-ol (**75**) and 2-((3,4-dihydro-1*H*-pyrido[3,4-*b*]indol-2(9*H*)-yl)(phenyl)methyl)naphthalen-1-ol (**77**). The reaction of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole with 1-naphthol as nucleophile in the presence of benzaldehyde proved to be regioselective for the formation of the *N*-alkylated derivative **77** as a single product. With 2-naphthol as nucleophile, both of the possible *N*-alkylated and α-arylated products **75** and **76** were detected; the ratio was found to depend on the temperature and the heating technique.

3. A simple synthesis of 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)indole (**80**) and 3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)indole (**81**) has been developed, involving the reaction of 3,4-dihydroisoquinoline or 6,7-dimethoxy-3,4-dihydroisoquinoline and indole. The reaction was tested by starting from the latter cyclic imines and indole-2-carboxylic acid. The new γ-amino acids (**82**, **83**) prepared in this way were obtained in good yields.

4. The synthetic applicability of this aza-Friedel–Crafts reaction was extended to the preparation of 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole (**86**), 3-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-4-yl)indole (**88**), 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole-2-carboxylic acid (**87**) and 3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-4-yl)indole-2-carboxylic acid (**89**) from cyclic imines such as 4,6-dihydro-3*H*-benz[*c*]azepine and 6,7-dihydrothieno[2,3-*c*]pyridine. All the reactions could be accelerated dramatically by using microwave irradiation.

5. 4,9-Dihydro-3*H*-β-carboline and 6-methoxy-4,9-dihydro-3*H*-β-carboline were subjected to catalyst-free one-pot α-arylation with indole or indole-2-carboxylic acid to prepare 1-(1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**93a**), 1-(1*H*-indol-3-yl)-6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**93b**), 3-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1*H*-indole-2-carboxylic acid (**94a**) and 3-(6-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1*H*-indole-2-carboxylic acid (**94b**) in good yields. The reactions were performed under neat conditions, using microwave agitation.

6. A simple synthesis of 1-hydroxynaphthyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles (**95a**, **95b**, **96a** and **96b**) has been developed, involving the reaction of **92a**, **92b** and 2- or 1-naphthol. The synthetic pathway was extended to the preparation of 5-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)quinolin-6-ol and 6-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)isoquinolin-5-ol derivatives (**99a**, **99b**, **100a** and **100b**) from *N*-containing naphthol analogues (6-quinolinol or 5-isoquinolinol). The yields of the reactions were improved by the use of microwave irradiation, and the reactions were accelerated.

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