Enantioselective Synthesis of 3,3-Disubstituted Indolines via Asymmetric Intramolecular Carbolithiation in the Presence of (–)-Sparteine[1]

Ulrich Groth,* Peter Köttgen, Philipp Langenbach, Andreas Lindenmaier, Thorben Schütz, Matthias Wiegand

Fachbereich Chemie, Universität Konstanz, Postfach M-720, Universitätsstr. 10, 78457 Konstanz, Germany
Fax +49(7531)884155; E-mail: Ulrich.groth@uni-konstanz.de

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Abstract: The functionalized *N*-benzyl-protected bromoanilines underwent an asymmetric intramolecular carbolithiation in the presence of *t*-BuLi and (–)-sparteine yielding 3,3-disubstituted indolines.

Key words: asymmetric synthesis, indolines, lithiations, natural products, sparteine

3,3-Disubstituted indolines are incorporated in many biologically active compounds and natural products such as (–)-physostigmin,[2] (–)-horsfilin[3,4] (Figure 1) and the spirotryprostatins.[5] In the past few years these and other alkaloids have been interesting and challenging targets for chemical synthesis.[6,7]

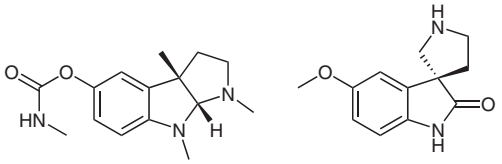


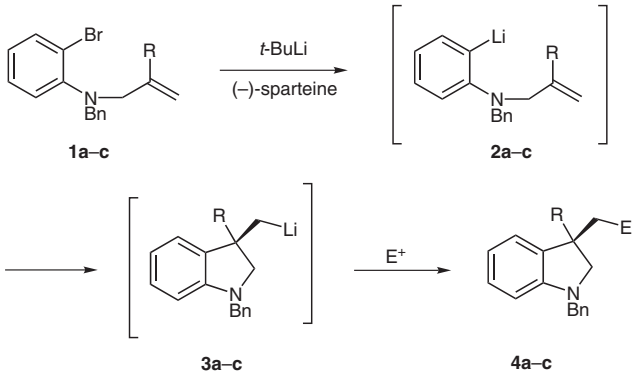
Figure 1 (–)-Physostigmin and (–)-horsfilin

Fu et al. presented a new method for generating the quaternary stereocenter in the 3-position of the heterocycle by enantioselective rearrangement of O-acylated indoles.[8] In 2004 Wood et al. used a SmI_2-mediated reductive coupling of acrylates with isocyanates to create the stereocenter in the 3-position.[9]

Herein we wish to report the first direct and highly enantioselective synthesis of 3,3-disubstituted indolines via a (–)-sparteine-mediated asymmetric intramolecular carbolithiation process. In the year 2000 we and others described the enantioselective synthesis of 3-substituted indolines via a (–)-sparteine-mediated asymmetric intramolecular carbolithiation process.[1,10,11] (–)-Sparteine is a chiral bidentate ligand with broad applicability.[12] Hoppe was the first to use a mixture of alkyllithium and (–)-sparteine for very effective asymmetric deprotonations.[13] Beak examined enantioselective deprotonations of *N*-Boc-pyrrolidines and *N*-Boc-allylamines.[14]

Consequently, we were interested if this strategy could be employed for the construction of 3,3-disubstituted indolines using sterically demanding and highly functionalized disubstituted olefins as precursors.[11,15]

The benzyl-protected *N*-methallyl-*N*-benzyl-2-bromoaniline (**1a**) was selected as the model for optimization of the reaction conditions (Scheme 1, R = Me).



Scheme 1

Since it has been demonstrated that sparteine shows the most pronounced effect in nonpolar solvents such as toluene, special attention was given to the reaction temperature and reaction time. The best results regarding chemical yields were obtained, when after bromine–lithium exchange at –80 °C the reaction mixture was allowed to warm to room temperature. After standard aqueous NH_4Cl workup the *N*-benzyl-3,3-dimethylindoline (**4a**) was obtained in 75% yield (Table 1, entry 1). As byproduct (18%) the *N*-benzyl-*N*-methallylaniline was observed presumably through competitive protonation by the solvent or after workup. In order to determine the enantioselectivity, the organolithium derivative **3a** was allowed to react with DMF. Under these reaction conditions the corresponding (1-benzyl-3-methylindolin-3-yl)acetaldehyde was obtained in 70% chemical yield with 72% ee (Table 1, entry 1). Next, the intramolecular carbolithiation of *N*-benzyl-*N*-isopropylallyl-2-bromoaniline (**1b**) was investigated. Under optimized reaction conditions the indoline **4b** was obtained in 69% yield with 80% ee (Table 1, entry 2). The enantiomeric excess was significantly higher, most probably due to the higher steric demand of an isopropyl group compared to a methyl group. The corresponding phenyl derivative **1c** did not undergo an intramolecular carbolithiation at all (Table 1, entry 3).

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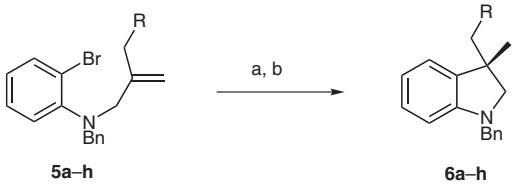
Table 1 Carbon-Substituted Indolines

Entry	**1**, R	Temp (°C)	Time (h)	Yield of **4** (%)	ee of **4** (%)
1	**1a**, Me	25	3	75	72[a]
2	**1b**, *i*-Pr	25	14	69	80
3	**1c**, Ph	25	10	0	–

[a] Yield of the reaction when quenched with DMF.

Since a lithium organic compound (**2**) is formed after halogen–metal exchange, this lithium organic compound might be stabilized and put in a more rigid, sterically stable complex with the assistance of a chelating donor in the side chain of the allylic moiety. Therefore, the *N*-allyl-*N*-benzyl-2-bromoanilines **5a–e** were prepared [R = OH, OMe, OTHP, OTIPS, $(CH_2)_2OMe$; Scheme 2] and their intramolecular carbolithiation was studied. Deprotonation of *N*-allyl-*N*-benzyl-2-bromoaniline (**5a**) with two equivalents of *t*-BuLi afforded the bisanion which after aqueous workup gave the indoline **6a** in 33% yield with 30% ee (Table 2, entry 1).[16,17] Once again the main product was the debrominated starting material obtained by protonation of the lithiated intermediate. Therefore we decided to protect the hydroxyl group with various protecting groups which were different in their steric demand. Good results were obtained with the methyl-protected compound **5b** affording indoline **6b** (Table 2, entry 2). The effect of the chelating donor was significant since the enantioselectivity could be enhanced from 72% ee to 88% ee compared with **4a** whereas the yield was similar to that of **4a** (81% instead of 75%).

When the side chain was extended by two CH_2 groups (Table 2, entry 5) the enantioselectivity was comparable with that obtained for the unsubstituted methyl derivative **4a**, while the chemical yield was low. In this case no chelating effects was observed.



5a–h **6a–h**

Scheme 2 *Reagents and conditions*: (a) *t*-BuLi, (–)-sparteine, toluene; (b) MeOH.

The sulfur- and nitrogen-substituted anilines **5f–h** (Scheme 2, R = CH_2SPh, CH_2SMe, CH_2NMe_2) also showed significant chelating effects which were comparable to the methoxy or OTHP group (Table 3).

The dimethylamino derivative **6h** was obtained in 83% yield with 85% ee (Table 3, entry 3) whereas the yield for the benzylmethylamino derivative was very low (22%).

Table 2 Oxygen-Containing Derivatives

Entry	**5**, R	Temp (°C)	Time (h)	Yield (%) of **6**	ee (%) of **6**
1	**5a**, OH	–80	20	33	30
2	**5b**, OMe	–80	14	81	88
3	**5c**, OTHP	–80	8	34	93
4	**5d**, OTIPS	25	3.5	57	60
5	**5e**, $(CH_2)_2OMe$	25	6	30	72

Table 3 Sulfur- and Nitrogen-Containing Derivatives

Entry	**5**, R	Temp (°C)	Time (h)	Yield (%) of **6**	ee (%) of **6**
1	**5f**, SPh	–80	12	75	87
2	**5g**, SMe	–80	10	81	91
3	**5h**, NMe_2	–80	14	83	85

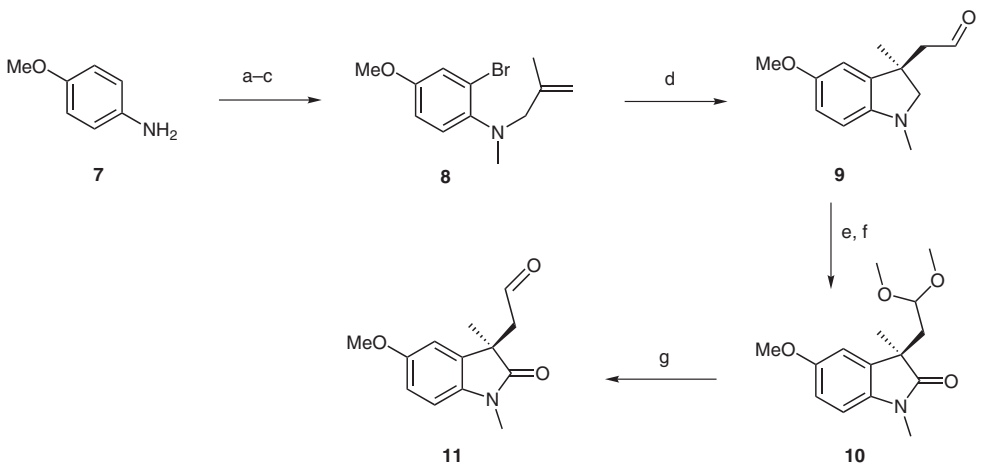
Indolines **6f–h** could be used as intermediates in natural product synthesis.

The *N*-benzyl-*N*-methallyl-2-bromoanilines **1a–c** and **5a–h** were also cyclized in the presence of TMEDA instead of (–)-sparteine to afford racemic indolines **4a–c** and **6a–h**. The yields were comparable or even higher and the reactions could be performed at lower temperatures.

The enantiomeric excesses were determined as follows: Indoline **6b** was demethylated with BBr_3 to indoline **6a**. Indolines **6c**,**d** were deprotected to compound **6a** by treatment with HCl in MeOH. Enantiomeric excesses of indolines **6a**,**f**,**g**,**h** were determined by NMR experiments using (–)-binaphthylphosphoric acid as chiral solvating agent.[18] Indolines **4a**,**b**, and **6e** were debenzylated by treatment with 1-chloroethyl chloroformate, sodium iodide, and acetone followed by methanol.[19] Enantiomeric excesses were determined by chiral GC–MS.[20]

In order to determine the absolute configuration of the generated quaternary stereocenter we synthesized a known compound, which is the major intermediate towards the synthesis of physostigmin, which was prepared enantioselectively by Overman and co-workers.[21] After the synthesis of the cyclization precursor **8** from the readily available *p*-anisidine (**7**) the indoline core was generated by intramolecular carbolithiation by treatment with *t*-BuLi in the presence of (–)-sparteine. The lithium intermediate was trapped with DMF and the desired aldehyde **9** was isolated and subsequently protected as its acetal. Oxidation to the 2-oxoindole **10** by $Hg(OAc)_2$–EDTA[22] and deprotection yielded the desired product **11** with an enantiomeric excess of 60%, the negative sign of the optical rotary power revealed *R*-configuration of the starting indoline **9** (Scheme 3).

In summary, we have developed the first method for direct and highly enantioselective synthesis of 3,3-disubstituted indolines via a (–)-sparteine-mediated asymmetric in-



Scheme 3 *Reagents and conditions*: (a) Br_2, AcOH, 3 h, 35%; (b) *n*-BuLi, MeI, 3 h, 60%; (c) methallyl chloride, K_2CO_3, 90%; (d) (–)-sparteine, *t*-BuLi, 20 h, then DMF, 31%, 60% ee; (e) MeOH, *p*-TsOH, 82%; (f) $Hg(OAc)_2$, EDTA, 48%; (g) amberlyst-15, acetone, 24 h, 68%.

tramolecular carbolithiation process. As substituents at the aromatic system do not effect the cyclization and it is possible to trap the lithium organic species **3** with other electrophiles, significant utility and broad application of the present methodology may be anticipated.

Acknowledgment

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(16) **General Procedure for the Carbolithiation**: All experiments were carried out under an argon atmosphere using Schlenk techniques. A solution of substrate **5** (0.83 mmol) and (–)-sparteine (1.5 equiv) in toluene (10 mL) was cooled to –78 °C and *t*-BuLi (2.2 equiv, 1.5 M in pentane) was added. The reaction mixture was stirred for 16 h at this temperature. MeOH (5 mL) was added to quench the lithium

intermediate. After addition of sat. NH_4Cl solution (10 mL) and H_2O (10 mL) the aqueous layer was extracted using EtOAc (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired indoline **6**.

(17) All products have been fully characterized by ^1H NMR and ^{13}C NMR. The analyses of known compounds are in agreement with the published data. The characteristics of selected compounds are as follows:
Compound **6b**: $[\alpha]_D^{20}$ +32.4° (*c* = 1.15, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, CMe), 3.01, 3.39 [2 × d, *J* = 8.2 Hz, 2 × 1 H, N(Bn)CH_2], 3.33 (s, 3 H, OMe), 3.35, 3.59 (2 × d, J_{AB} = 10 Hz, 2 H, CH_2OMe), 4.24, 4.31 (2 × d, *J* = 15.0 Hz, 2 × 1 H, NCH_2Ph), 6.49 (d, *J* = 7.8 Hz, 1 H, ArH), 6.68 (t, *J* = 7.4 Hz, 1 H, ArH), 7.03–7.10 (m, 2 H, ArH), 7.24–7.35 (m, 5 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.8 (C*Me*), 44.9 (*C*Me), 52.7 (*C*H_2Ph), 59.3 (OMe), 63.1 [N(Bn)*C*H_2], 79.0 (CH_2O), 106.9, 117.5, 122.9, 127.0, 127.7, 128.0, 128.4 (7 × CH_{Ar}), 135.0 ($CMeC_{Ar}$), 138.4 ($C_{q,Ph}$), 151.5 (NC_{Ar}). MS (EI, 70 eV): *m*/*z* = 267 [M^+], 222 [$M^+ - CH_2 - OMe$], 91 [$C_7H_7^+$]. IR (film): 3026, 2922, 2869, 2823, 1605, 1494, 1453, 1118 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.60; H, 7.82; N, 5.20.
Compound **6e**: $[\alpha]_D^{20}$ +19.6° (*c* = 0.52, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, CMe), 1.42–1.78 (m, 2 × 2 H, CH_2CH_2CH_2OMe), 3.00, 3.18 (2 × d, *J* = 8.6 Hz, 2 × 1 H, NCH_2CMe), 3.27 (s, 3 H, OMe), 3.30 (t, *J* = 7.8 Hz, 2 H, CH_2OMe), 4.17, 4.29 (2 × d, *J* = 15.2 Hz, 2 × 1 H, NCH_2Ph), 6.47 (d, *J* = 7.8 Hz, 1 H, ArH), 6.64–6.69 (m, 2 H, ArH), 6.98–7.34 (m, 6 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.1, 25.9, 37.2, 43.3, 53.1, 58.5, 65.7, 73.2, 106.9, 117.6, 122.5, 127.1, 127.6, 127.8, 128.5, 137.4, 138.6, 151.5. MS (EI, 70 eV): *m*/z = 295 [M^+], 222 [M + $CH_2CH_2CH_2OMe$], 91 [$C_7H_7^+$].
Compound **6g**: $[\alpha]_D^{20}$ +21.3° (*c* = 0.92, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CMe), 2.02 (s, 3 H, SMe), 2.73, 2.78 (2 × d, *J* = 12.8 Hz, 2 × 1 H, CH_2SMe), 3.02, 3.38 [2 × d, *J* = 9.0 Hz, 2 × 1 H, N(Bn)CH_2], 4.18, 4.33 (2 × d, *J* = 14.8 Hz, 2 × 1 H, NCH_2Ph), 6.50 (d, *J* = 7.8 Hz, 1 H, ArH), 6.70 (t, *J* = 7.4 Hz, 1 H, ArH), 7.06–7.09 (m, 2 H, ArH), 7.24–7.37 (m, 5 H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.9 (CMe), 24.3 (SMe), 45.0 (CMe), 45.7 (CH_2SMe), 52.9 (CH_2Ph), 64.9 [N(Bn)CH_2], 107.2, 117.7, 122.6, 127.1, 127.8, 128.1, 128.5 (7 × CH_{ArH}), 136.3 ($C_{q,ArH}$), 138.3, 151.2 (C_qN). GC–MS (EI, 70 eV): *m*/*z* = 283 [M^+], 222 [$M^+ - CH_2 - SMe$], 91 [$C_7H_7^+$]. Anal. Calcd for $C_{18}H_{21}NS$: C, 76.28; H, 7.47; N, 4.94. Found: C, 76.20; H, 7.47; N, 5.29.

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