Enantioselective Synthesis of 3-Substituted Indolines by Asymmetric Intramolecular Carbolithiation in the Presence of (−)-Sparteine

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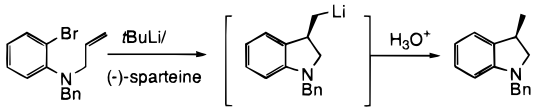
3-Substituted indolines are incorporated in many biologically active compounds and natural products such as (+)-CC-1065, the most potent cytotoxic drug until today.[1] Here we wish to report the first direct and highly enantioselective synthesis of 3-substituted indolines via a (−)-sparteine-mediated asymmetric intramolecular carbolithiation process.[2]

Classical approaches to such racemic compounds, which typically involve reduction of the corresponding indole,[3] radical[4] or ionic[5] cyclization, have been extensively reviewed. Although methods for the effective enantioselective preparation of 2-substituted indolines have been reported,[6] syntheses of enantiomerically pure 3-substituted indolines are still scarce and include resolution of racemic intermediates.[7] Liebeskind[8] and Bailey[9] reported an experimentally simple route to racemic 3-substituted indolines starting from 2-bromo-*N,N*-diallylanilines. After halogen−metal exchange by treatment with *t*BuLi/TMEDA an intramolecular carbo-lithiation takes place to yield 3-lithiomethylindolines which can be trapped with different electrophiles. However, until now, no enantioselective version of this method has been described. The scarcity of enantioselective carbometalation is due to the difficulty in enantiofacial differentiation of an unactivated alkene.[10] In 1989 Hoppe[11] demonstrated that (−)-sparteine is an effective ligand for high asymmetric induction in lithiation-substitution reactions. Later on Beak[12] used this methodology successfully for the generation of 2-substituted *N*-Boc-pyrrolidines. On the basis of these results, Marek and Normant[13] recently reported that (−)-sparteine can serve as a promoter for the enantioselective carbolithiation of cynnamyl derivatives by adding organolithium compounds. This observation led us to consider the enantioselective intramolecular carbolithiation of 2-(*N*-allyl-*N*-benzyl)-aryllithiums in the presence of the chiral diamine (−)-sparteine.

Table 1. Effect of Solvent on the Yield and Enantioselectivity of Formation of (*R*)-3-Methyl-*N*-benzylindoline (**3a**)



1a **2** (*R*)-**3a**

entry	solvent	*T*, °C	yield **3a**, %[a]	ee,%[b]
1	Et_2O	−78	60	65
2	THF	−78	80	0
3	toluene	−78	90	80
4	toluene	−90	85	87
5	cumene	−90	84	75

[a] Yields refer to isolated products. [b] Determined by capillary chiral GC.

In view of the importance of indolines in asymmetric catalysis,[14] as auxiliaries in enantioselective synthesis[15] and their presence in many pharmacologically active compounds, significant utility and broad application of the present methodology may be anticipated.

Initial attempts to effect the intramolecular carbolithiation with *tert*-butoxycarbonyl and *p*-toluenesulfonyl as protecting groups were unsuccessful. The *N*-allyl-*N*-benzyl-2-bromoaniline (**1a**) was selected to optimize the reaction conditions. First we decided to study the effect of the solvent on the yield and enantioselectivity of this reaction. Thus, addition of *N*-allyl-*N*-benzyl-2-bromoaniline (**1a**) to a solution of 2.2 equiv. of *t*BuLi in Et_2O at −78 °C in the presence of 1.5 equiv of (−)-sparteine generates the lithium intermediate **2** which upon quenching with MeOH, followed by warming to room temperature, and standard aqueous NH_4Cl workup afforded the *N*-benzyl-3-methylindoline (**3a**) in 60% chemical yield and 65% ee (Table 1). As byproduct (30%) the *N*-allyl-*N*-benzyl-aniline was observed presumably through competitive protonation by the solvent. The same procedure in THF leads to a racemic product, which is in agreement with results published by Hoppe.[16] Sparteine shows the most pronounced effect in apolar donor solvents such as toluene or cumene. As shown in Table 1, the use of toluene at −90 °C was found to be the most effective system to obtain high enantioselectivity. Under these conditions 3-methylindoline (*R*-**3a**) was obtained in 85% chemical yield and 87% ee.

In contrast to these results the carbolithiation of unsubstituted olefines in an intermolecular version leads to racemic products.[13] The enantiomeric excess was established by chiral GC analysis of the deprotected indolines.[17] These data were compared with the data obtained from racemic material being prepared by carbolithiation in toluene in the presence of TMEDA instead of

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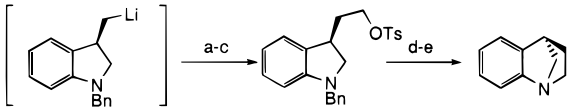
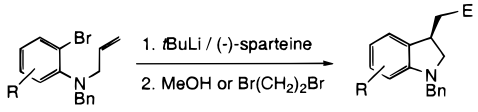
Scheme 1. Correlation of 3-lithiomethylindoline (2)[a]



[a] (a) DMF, toluene, −78 °C, 70%. (b) $NaBH_4$, MeOH, −10 °C, 90%. (c) TsCl, Et_3N, CH_2Cl_2, 0 °C, 80%. (d) $ClCO_2CH(Cl)CH_3$, NaI, acetone, 20 °C/MeOH, reflux, 65%. (e) NaOH, H_2O, 100 °C, 30%.

Table 2. Enantioselective Carbolithiation of *N*-Allyl-*N*-benzyl-2-bromoanilines **1a**−**e**



entry	aniline	R	*T*, °C	*E*	yield, %[a]	ee, %[b]
1	**1a**	H	−90	Br	70	85
2	**1b**	4-OBn	−78	H	80	87[c]
3			−78	Br	68[d]	85
4	**1c**	5-OBn	−78	H	86	88[c]
5			−78	Br	78[d]	82
6	**1d**	4-Me	−90	H	90	89
7			−90	Br	80	87
8	**1e**	4-F	−90	H	80	90
9			−90	Br	65	88

[a] Yields refer to isolated products unless otherwise noted. [b] The ee was determined after cleavage of the *N*-benzyl group into a secondary amine by capillary chiral GC, unless otherwise noted. [c] The ee was determined directly on the protected indoline by chiral shift ^{1}H NMR spectroscopy using binaphthylphosphonic acid as solvating agent.[20] [d] Determined by GC−MS analysis of the crude reaction mixture.

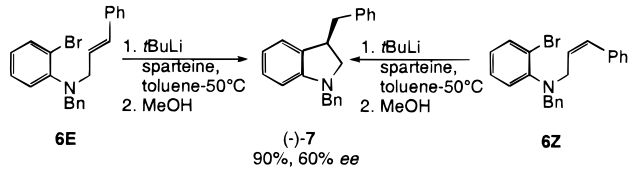
(−)-sparteine followed by cleavage of the benzyl group. The absolute configuration of the stereogenic center was determined through transformation of **2** into the 3,4-dihydro-2*H*-1,4-methanochinoline (**5**) of known configuration,[18] and comparison with the data being reported (Scheme 1). Whereas in the case of Pracejus the optical rotation featured a negative value, our sample showed a positive value. For this reason the absolute stereochemistry of **5** was determined as (+)-*R*, leading us to the conclusion, that in the carbolithiation step (*R*)-lithiomethylindolines **2** are preferably formed.

After optimizing the reaction conditions a variety of substituted *N*-allyl-*N*-benzyl-2-bromoanilines (**1a**−**e**) were used under the improved carbolithiation conditions to demonstrate the scope and limitations of this reaction. As shown in Table 2, substrates with electron-deficient substituents required slightly higher temperatures (−78 °C) to proceed to completion of the reaction. The corresponding enantioenriched 3-methyl substituted indolines were obtained in good yields and 82−89% ee. By quenching of the 3-methyllithioindolines with dibromoethane the corresponding 3-bromomethyl indolines were obtained. The bromine serves as useful functional group for further transformations.

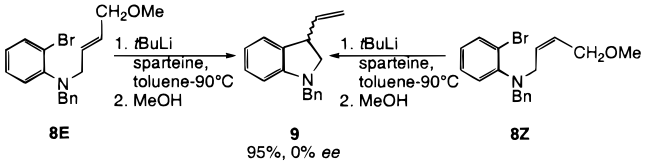
Enantiomeric excess was established by comparison with racemic products,[8,9] by a variety of methods.

To investigate the role of the stereochemistry of the olefin on the enantioselectivity of the carbolithiation, the 2-bromoanilines

Scheme 2



Scheme 3



6E and **6Z** were prepared. The bromo−lithium exchange was carried out at −78 °C; however, the carbolithiation step required slightly higher temperatures (−50 °C) to proceed to completion. We found that the geometry of the double bond has no influence on the stereochemical outcome. Identical indolines exhibiting the same optical rotation and moderated enantiomeric excesses (60%) were obtained (Scheme 2).

We also found that the cyclization of either **8E** and **8Z** proceeded with greater efficiency than the corresponding cyclization into **3a**, according to studies by Broka.[20] The vinylindoline **9** is formed in considerably improved yield, however as a racemic product (Scheme 3).

In summary, a novel procedure for the enantioselective synthesis of 3-substituted indolines has been developed. In contrast to other (−)-sparteine-mediated cyclocarbolithiations[21] the facial selection at the double bond is not effected by a chiral carbanionic center, but exclusively by a chiral lithium−sparteine complex. Current investigation is focused on the use of other C-2 symmetric diamines[22] and the application of this methodology to the preparation of biologically active compounds such as CC-1065.

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Supporting Information Available: Representative experimental procedures for the synthesis of **3a**, **3c**, **8a**, **7**, and **9** as well as ^{1}H- and ^{13}C NMR spectras of **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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