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Preparation of differentially 1,3-disubstituted indolines by intramolecular carbolithiation

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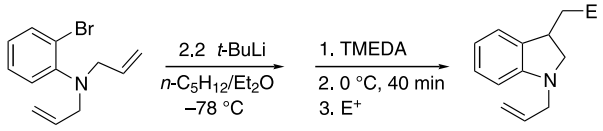
Abstract—The ether-soluble dilithio species (**2**), derived from *N*-allyl-2-bromoaniline (**1**) upon treatment with *t*-BuLi at −78°C, cyclizes when warmed to +5°C in the presence of TMEDA to give a (1-lithio-3-indolinyl)methyllithium (**3**) that may be differentially functionalized by sequential addition of electrophiles. The cyclization of **2** to **3** proceeds enantioselectively when conducted in the presence of (1*S*,2*S*)-(+)-*N*,*O*-dimethylpseudoephedrine.

Some time ago, we[1] and the Liebeskind group[2] reported, as shown below, that the aryllithium derived from an *N*,*N*-diallyl-2-bromoaniline cyclizes upon warming to 0°C in the presence of TMEDA to give a (1-allyl-3-indolinyl)methyllithium that may be trapped with any of a variety of electrophiles to deliver 1-allyl-3-substituted indolines in good yield. More recently it was disclosed that these ring-closures proceed in an enantiofacially selective fashion when conducted in the presence of (−)-sparteine to give an R-configured (indolinyl)methyllithium in high ee.[3]

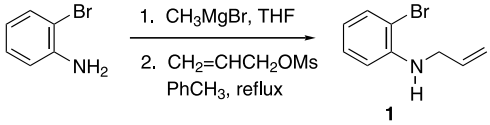


It occurred to us that significant synthetic advantage would derive from development of a more general route to indolines that allows for selective functionalization at both the 1- and 3-positions subsequent to the cyclization step. Herein we report that the dilithio species generated from *N*-allyl-2-bromoaniline (**1**) upon treatment with *tert*-butyllithium (*t*-BuLi) in diethyl ether solvent cyclizes in good yield when allowed to warm in the presence of TMEDA to give a (1-lithio-3-indolinyl)methyllithium that may be differentially functionalized by sequential addition of electrophiles.

The preparation of previously reported *N*-allyl-2-bromoaniline[4] (**1**) was most efficiently accomplished by the general method of Yoshida and Tanabe[5] as illustrated in Scheme 1. It might be noted that more traditional allylation procedures afforded **1** accompanied by significant quantities of the *N*,*N*-diallyl analog.

It was anticipated that treatment of a solution of **1** in dry diethyl ether at −78°C with 3 molar equivalents of *t*-BuLi in *n*-heptane would rapidly and uneventfully effect both deprotonation of the amine nitrogen and lithium–bromine exchange[6] to give a dilithio species (**2**). Somewhat unexpectedly, the exchange reaction was found to proceed rather slowly: after 15 min at −78°C, ~25% of **1** was recovered following quench with MeOH. For this reason, the reaction time was extended to 1 h to ensure complete conversion of **1** to **2**.

Cyclization of **2** to give (1-lithio-3-indolinyl)methyllithium (**3**) was accomplished, as indicated in Scheme 2, by addition of 3 molar equivalents of dry TMEDA to the reaction flask and allowing the homogeneous solution to then warm and stand at +5°C for 2 h under an atmosphere of argon. Addition of an excess of MeOH to the resulting bright-yellow solution of **3** afforded 3-methylindoline in 71% isolated yield



1
64 %

Scheme 1.

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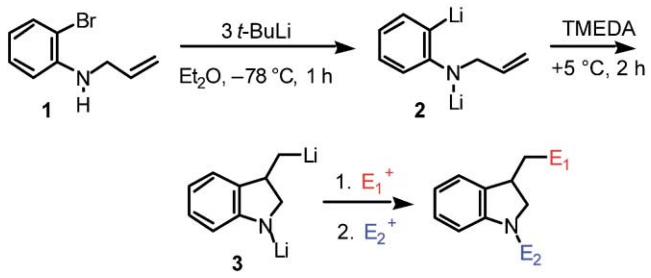


Scheme 2.

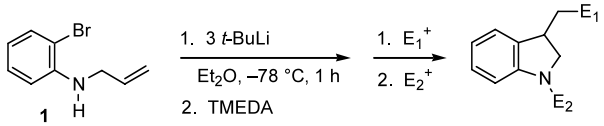
(Table 1, entry 1). In a similar vein, **3** was trapped by addition of an excess of dimethyl sulfate or allyl bromide to give 1-methyl-3-ethylindoline (Table 1, entry 2) and 1-allyl-3-(3-butenyl)indoline (Table 1, entry 3), respectively, in good yield. Thus, although cyclization of **2**→**3** is somewhat slower than is the analogous ring closure of the aryllithium derived from *N*,*N*-diallyl-2-bromoaniline,[1,2] the generation of **2** and its isomerization to **3** proceeds in reasonable overall yield.

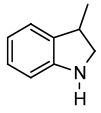
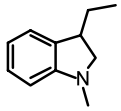
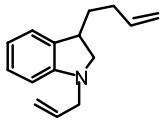
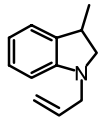
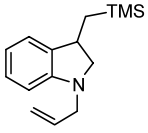
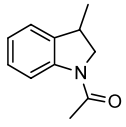
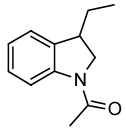
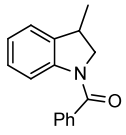
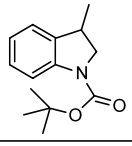
The synthetically more interesting possibility of effecting selective, differential functionalization of **3** was investigated in a series of experiments involving sequential addition of two different electrophiles (Scheme 2, $E_1^+ \neq E_2^+$).[7] As might be anticipated, there is a major limitation to this approach: introduction of a ketone (Scheme 2, $E_1^+ = EtOAc$) or an ester (Scheme 2, $E_1^+ = ClCO_2Et$) at the 3-position results in rapid enolization, and subsequent condensation reactions when reaction mixtures are warmed, due to proton abstraction by the basic N–Li function prior to the introduction of the second electrophile. Nonetheless, as illustrated by the results summarized in Table 1 (entries 4–9), a variety of electrophile combinations may be used to trap **3** to give differentially 1,3-disubstituted indolines.[8] It should be noted that acyl chlorides are less efficient than esters or anhydrides for introduction of an amide function (Table 1, entries 6–9): the use of AcCl as E_2^+ (Scheme 2) leads to variable quantities of product resulting from electrophilic aromatic substitution.

In light of the fact that this one-pot route involves four discrete steps (deprotonation–exchange, cyclization, and trapping with two electrophiles), the 60–70% isolated yield of chromatographically pure product (Table 1) implies that each step in the sequence is quite efficient.

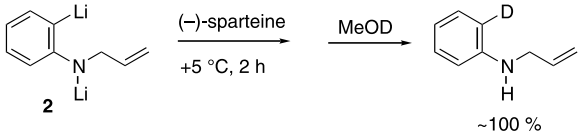
Attempts to accomplish an asymmetric cyclization of **2** in the presence of 3 molar equivalents of dry (–)-sparteine led to the unexpected result depicted below: *N*-allyl-2-deuterioaniline was the exclusive product of the reaction following addition of MeOD. The high deuterium content of the product belies inadvertent quench of the **2** as an explanation for the failure to observe cyclization. More likely, the proximity of the two bulky, rigid sparteine ligands, which are presumably associated with the Li-atoms of **2**, may have disrupted the Li–π interaction essential for the ring closure.[9]

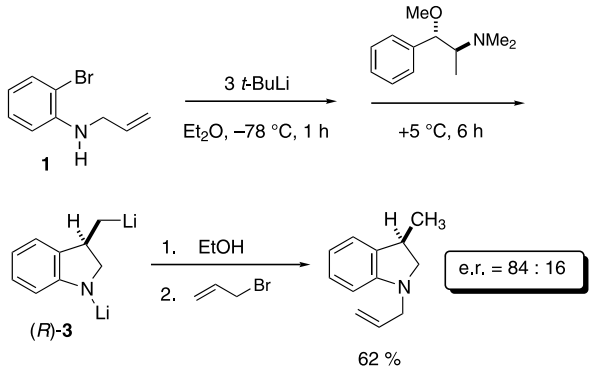
Table 1. Preparation of differentially 1,3-disubstituted indolines



entry	E_1^+	E_2^+	product	% yield[a]
1	MeOH	MeOH		71
2	$(CH_3O)_2SO_2$	$(CH_3O)_2SO_2$		60
3				66
4	EtOH			69
5	TMSCl			64
6	EtOH	EtOAc		62
7	$(CH_3O)_2SO_2$	EtOAc		59
8	EtOH	EtOBz		66
9	EtOH	$(Boc)_2O$		61

[a]Isolated yields of chromatographically pure product.





Scheme 3.

Indeed, conducting the isomerization of **2** in the presence of 3 molar equivalents of dry (1*S*,2*S*)-(+)-*N*,*O*-dimethylpseudoephedrine,[10] a ligand that is considerably more conformationally flexible than is (–)-sparteine,[11] effected an asymmetric ring closure. Thus, as illustrated in Scheme 3, (*R*)-(–)-1-allyl-3-methylindoline, of known absolute configuration,[3] is produced in 62% isolated yield with e.r. of 84:16 when (*R*)-**3** is trapped by sequential addition of EtOH and allyl bromide.[12]

In summary, the chemistry described above provides an experimentally convenient one-pot route to differentially 1,3-disubstituted indolines from readily available *N*-allyl-2-bromoaniline. The ability to effect the cyclization of **2** to **3** in an asymmetric fashion using a derivative of commercially available, enantiopure pseudoephedrine allows for the preparation of enantiomerically enriched indolines.

Acknowledgements

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6. On a molecular scale, deprotonation of **1** likely occurs more rapidly than does the exchange. For a detailed discussion of the relative rates of such processes in a related system, see: Gallagher, D. J.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 7984.
7. Experimental procedure: An approximately 0.1 M solution of *N*-allyl-2-bromoaniline, **1**, (typically 2–3 mmol) in anhydrous diethyl ether was cooled under argon to −78°C, 3.3 molar equiv. of *t*-BuLi in heptane was added, and the resulting solution was allowed to stir at −78°C for 1 h prior to the addition of 3.3 molar equiv. of TMEDA. The reaction flask was then equipped with an argon-filled balloon, submerged in a +5°C bath, and allowed to stir for 2 h at +5°C. The bright-yellow solution was then recooled to −78°C and 0.9 molar equiv. of the first electrophile (E_1) was added dropwise (typically as a solution in Et_2O) followed by dropwise addition of the second electrophile (E_2). The reaction mixture was removed from the cooling bath and allowed to warm and stir at room temperature for 1 h before being poured into water. The organic layer was washed with water, dried ($MgSO_4$), concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel.
8. With the exception of 1-methyl-3-ethylindoline (Table 1, entry 2), all of the indolines prepared in this study are known compounds whose physical and spectroscopic properties were in accord with those reported in the literature. Data for 1-methyl-3-ethylindoline (Table 1, entry 2): colorless oil: ^{1}H NMR δ 1.00 (t, J=7.43 Hz, 3H), 1.49–1.60 (m, 1H), 1.80–1.91 (m, 1H), 2.74 (s, 3H), 2.93 (t, J=8.05 Hz, 1H), 3.05–3.15 (m, 1H), 3.46 (t, J=8.47 Hz, 1H), 6.48 (d, J=7.75 Hz, 1H), 6.78 (t, J=7.34 Hz, 1H), 7.08 (apparent q, J=7.62 Hz, 2H); ^{13}C NMR δ 12.16, 26.94, 36.43, 42.67, 62.15, 107.48, 117.91, 123.71, 127.76, 134.32, 153.43; HRMS calcd for $C_{11}H_{15}N$ 161.1204, found 161.1222.
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11. Wiberg, K. B.; Bailey, W. F. *J. Mol. Struct.* **2000**, *556*, 2.
12. It might be noted that we have not attempted to optimize the enantioselectivity of the cyclization by modification of the pseudoephedrine-derived ligand.