

A REGIOSPECIFIC SYNTHESIS OF CARBAZOLES VIA CONSECUTIVE PALLADIUM-CATALYZED CROSS-COUPLING AND ARYNE-MEDIATED CYCLIZATION¹

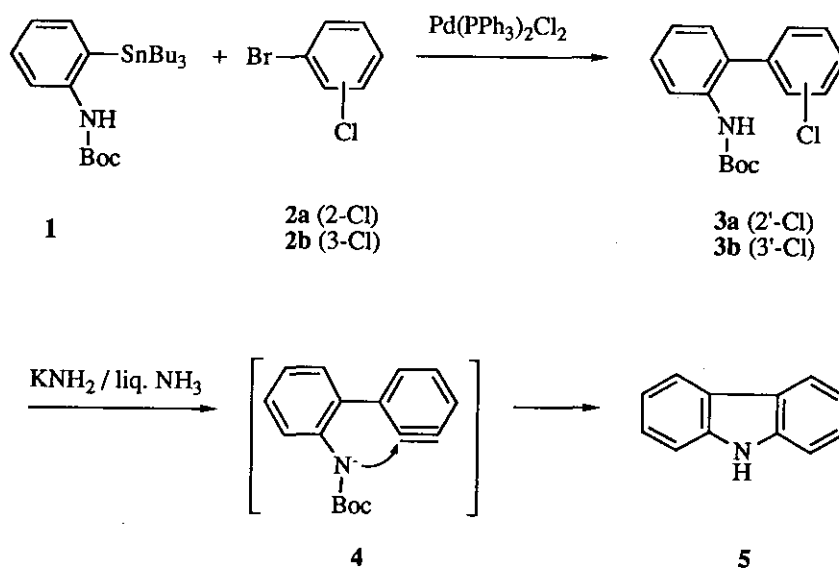
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Abstract- A regiospecific synthesis of carbazoles has been developed using palladium-catalyzed cross-coupling of *N*-(*tert*-butoxycarbonyl)-2-tributylstannylanilines with 2- or 3-bromochlorobenzene followed by aryne-mediated cyclization as the key reactions. The carbazole alkaloids, glycozoline and glycozolidine, were synthesized using this procedure.

Since the first discovery of murrayanine in 1965,² a number of carbazole alkaloids have been isolated from higher plants, microorganisms, and marine sources.³ Some of the alkaloids and their synthetic analogues exhibit significant biological activities, such as antimicrobial,⁴ antiviral,⁵ and cytotoxic properties.⁶ Major synthetic approaches to the carbazole skeleton include a) reductive cyclization of 2-nitrobiphenyls,⁷ b) thermal,⁸ photolytic,⁹ and palladium-promoted¹⁰ cyclization of diphenylamines, c) dehydrogenation of 1,2,3,4-tetrahydrocarbazoles which are usually prepared by Fischer indole synthesis,¹¹ and d) syntheses from indole precursors.¹² In the syntheses of highly substituted carbazole alkaloids, however, many of these methods have problems, such as lengthy steps in the preparation of appropriate precursors, non-regioselectivity of the cyclization steps, and harsh reaction conditions. In this communication, we report a short and regiospecific synthesis of the carbazoles¹³ from easily accessible stannylaniline and bromochlorobenzene precursors using palladium-catalyzed cross-coupling¹⁴ and aryne-mediated cyclization¹⁵ as key reactions.

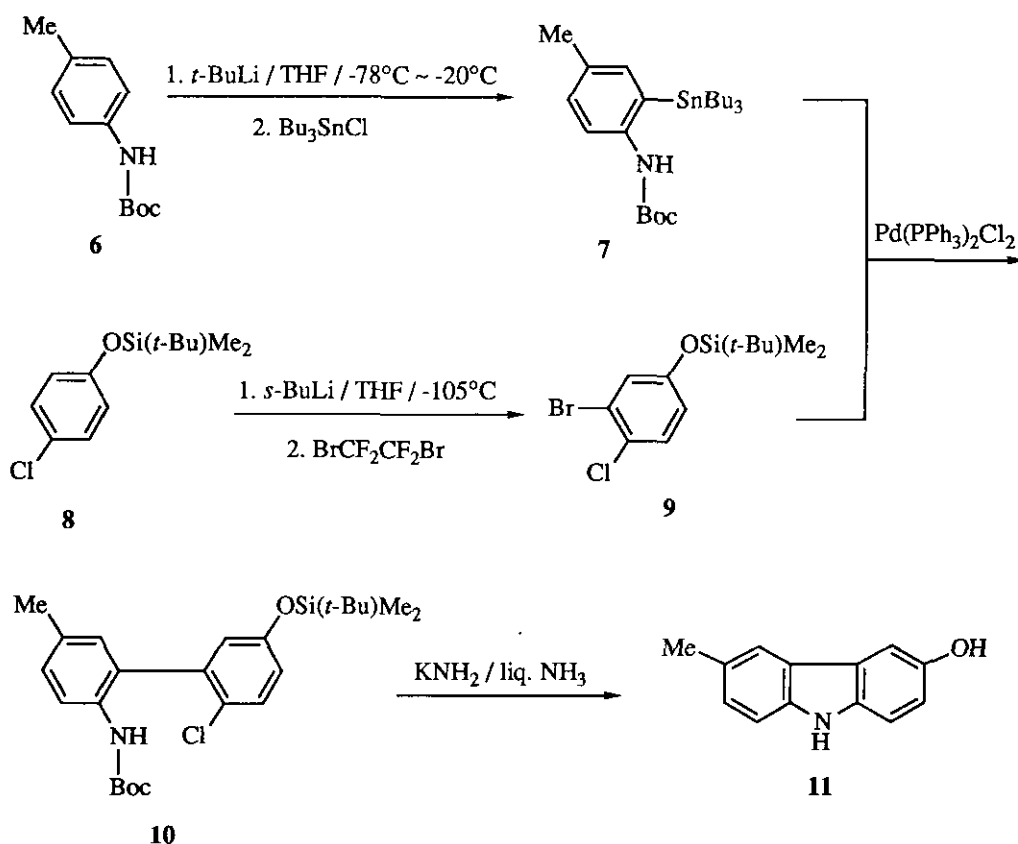
The stannane (**1**),¹⁶ which was prepared in 80% yield by *ortho*-lithiation of *N*-(*tert*-butoxycarbonyl)aniline under the standard conditions¹⁷ (2.5 equiv. *t*-BuLi / THF / -78°C ~ -20°C) followed by stannylation with Bu₃SnCl, was coupled with 2-bromochlorobenzene (**2a**) in the presence of 5 mol % of Pd(PPh₃)₂Cl₂ in toluene at 110°C for 25 h to give *N*-(*tert*-butoxycarbonyl)-2-(2'-chlorophenyl)aniline (**3a**) in 74% yield (Scheme 1). The reaction proceeded in DMF under milder conditions (90°C, 25 h) affording **3a** in 76% yield. In a similar manner (5 mol % of Pd(PPh₃)₂Cl₂ / DMF / 90°C / 25 h), **1** was coupled with 3-bromochlorobenzene (**2b**) to furnish *N*-(*tert*-butoxycarbonyl)-2-(3'-chlorophenyl)aniline (**3b**) in 80% yield. Treatment of **3a** with excess KNH₂ (10 equiv.) in liq. NH₃ at -33°C for 3 h afforded carbazole (**5**) in 99% yield *via* the aryne intermediate (**4**). The *tert*-butoxycarbonyl group was cleaved under the highly nucleophilic reaction conditions. Under similar reaction conditions, **3b** cyclized to **5** in 70% yield. The lower yield of the cyclization of **3b** compared to **3a** may be due to simultaneous formation of the isomeric aryne intermediate (3',4'-aryne).



Scheme 1

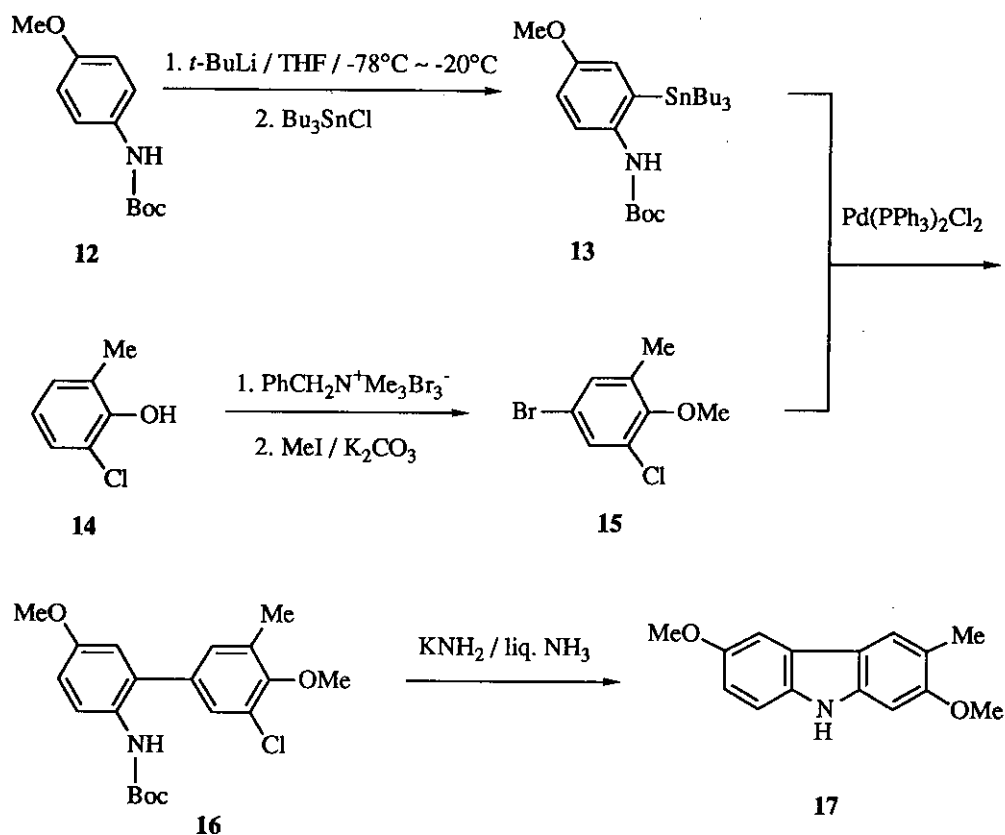
The utility of this carbazole synthesis was demonstrated in the preparation of carbazole alkaloids, glycozolinine (**11**)¹⁸ and glycozolidine (**17**).¹⁹ The synthesis of glycozolinine (**11**) is shown in Scheme 2. *Ortho*-lithiation of *N*-(*tert*-butoxycarbonyl)-4-methylaniline (**6**) followed by a reaction with Bu₃SnCl afforded the stannane (**7**)¹⁶ in 62% yield. Another *ortho*-lithiation of 1-(*tert*-butyldimethylsilyloxy)-4-chlorobenzene (**8**) (1.2 equiv. *s*-BuLi / THF / -105°C / 2 h)²⁰ and subsequent reaction with 1,2-dibromo-1,1,2,2-tetrafluoroethane²¹ gave the bromide

(9) in 95% yield. Cross-coupling of 7 with 9 (5 mol % of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ / DMF / 90°C / 25 h) furnished the biphenyl (10) in 65% yield. Treatment of 10 with KNH_2 (10 equiv.) in liq. NH_3 overnight²² gave glycozoline (11)²³ in 54% yield. During the cyclization both the *tert*-butoxycarbonyl and *tert*-butyldimethylsilyl groups were cleaved.



Scheme 2

The synthesis of glycozolidine (17) is shown in Scheme 3. The stannane (13)¹⁶ was prepared from *N*-(*tert*-butoxycarbonyl)-4-methoxyaniline (12) in 63% yield in a similar manner as described for 1 and 7. The bromide (15) was synthesized from 2-chloro-6-methylphenol (14) by sequential bromination ($\text{PhCH}_2\text{N}^+\text{Me}_3\text{Br}_3^-$ / CH_2Cl_2 -MeOH / room temperature / 5 h)²⁴ and methylation (MeI / K_2CO_3 / acetone / reflux / 4 h) in 96% overall yield. Coupling of 13 with 15 (5 mol % of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ / DMF / 90°C / 25 h) gave the biphenyl (16) in 56% yield. Cyclization of 16 (10 equiv. of KNH_2 / liq. NH_3 / -33°C / 3 h) furnished glycozolidine (17)²⁵ in 99% yield.



Scheme 3

In summary, we have developed a new and efficient route for the regiospecific preparation of substituted carbazoles. Since this is based on the easy availability of the stannane and bromochlorbenzene precursors using directed *ortho*-lithiation and conventional bromination strategies, its further application for the synthesis of a wide range of carbazole alkaloids may be anticipated.

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22. Ammonia was spontaneously evaporated overnight. When the reaction mixture was quenched after 3 h at -33°C, only the desilylated starting material was recovered.
23. Glycozolinine (11): mp 235-238°C (ether) (lit.,^{18a} mp 231-232°C); ir (KBr) 3390, 1615, 1575, 1460, 1400, 1320, 1250, 1200, 1140, 935, 865, 800, 575, 450 cm⁻¹; ¹H nmr (400 MHz, DMSO-*d*₆) δ 2.43 (s, 3H), 6.85 (dd, 1H, *J*=8.7 and 2.5 Hz), 7.13 (d, 1H, *J*=7.9 Hz), 7.23 (d, 1H, *J*=8.7 Hz), 7.28 (d, 1H, *J*=7.9 Hz), 7.35 (d, 1H, *J*=2.5 Hz), 7.75 (s, 1H), 8.87 (s, 1H, exchanged with D₂O), 10.71 (s, 1H, exchanged with D₂O); ms *m/z* 197 (M⁺). *Anal.* Calcd for C₁₃H₁₁NO: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.26; H, 5.61; N, 7.17.
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25. Glycozolidine (17): mp 166-167°C (ether-hexane) (lit.,^{19a,b} mp 161-162°C); ir (KBr) 3400, 3000, 2940, 2830, 1630, 1580, 1490, 1470, 1430, 1320, 1295, 1275, 1220, 1200, 1170, 1135, 1110, 1030, 815, 775, 460 cm⁻¹; ¹H nmr (400 MHz, DMSO-*d*₆) δ 2.27 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 6.88 (dd, 1H, *J*=8.6 and 2.7 Hz), 6.91 (s, 1H), 7.29 (d, 1H, *J*=8.6 Hz), 7.51 (d, 1H, *J*=2.7 Hz), 7.79 (s, 1H), 10.77 (s, 1H, exchanged with D₂O); ms *m/z* 241 (M⁺). *Anal.* Calcd for C₁₅H₁₅NO₂: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.39; H, 6.31; N, 5.78.

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