

Synthesis of Substituted Indoline and Carbazole by Benzyne-Mediated Cyclization—Functionalization

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ABSTRACT



A benzyne-mediated synthesis of substituted indolines and carbazoles was developed. The reaction includes generation of benzyne using $\text{Mg(TMP)}_2 \cdot 2\text{LiCl}$ as a base, cyclization, and trapping the resulting organomagnesium intermediate with an electrophile to provide a series of substituted indolines and carbazoles in a regiospecific manner. This was applied to a concise five-pot total synthesis of heptaphylline.

Multisubstituted benzo-fused nitrogen heterocycles, such as indolines, indoles, and carbazoles, are found in biologically and medicinally important natural products (Figure 1).¹ Despite tremendous synthetic efforts to develop regioselective installation of substituents on these heterocycles, a general and efficient method is still limited. Functionalization of the benzene ring at the para position of the nitrogen atom can be easily executed by a conventional electrophilic aromatic substitution reaction. In contrast, regioselective introduction of a substituent at the ortho position is not always an easy task. The lateral directed metalation and trapping of the resultant anion species with an electrophile has often been used; however, this protocol has limited scope of the substrates and electrophiles due to the requirement of a strong base such as *s*-BuLi.²

Cyclization of a tethered amide anion to benzyne is one of the conventional methods to form benzo-fused heterocycles (Scheme 1).³ Nucleophilic addition of the tethered nitrogen anion should give a cyclization product. If the transient carbanion **3** can be trapped with an electrophile, substituted indoline/carbazole **4** should be generated in a regiospecific manner.

However, there are few reports on trapping the anion intermediate **3** with an electrophile,⁴ possibly because benzyne generation has been generally conducted using a strong base, such as alkyl lithium or lithium amide, leading to highly reactive organolithium species **3**, which could hamper smooth functionalization. We describe herein a construction of multisubstituted indolines and carbazoles by the benzyne-mediated cyclization—functionalization sequence, in which use of $\text{Mg(TMP)}_2 \cdot 2\text{LiCl}$ as a base is

(1) (a) Joshi, B. S.; Kamat, V. N.; Saksena, A. K.; Govindachari, T. R. *Tetrahedron Lett.* **1967**, 8, 4019. (b) Nakamura, T.; Kodama, N.; Arai, Y.; Kumamoto, T.; Higuchi, Y.; Chaichantipyuth, C.; Ishikawa, T.; Ueno, K.; Yano, S. *J. Nat. Med.* **2009**, 63, 21. (c) Thongthoom, T.; Promsuwan, P.; Yenjai, C. *Eur. J. Med. Chem.* **2011**, 46, 3755. (d) Enomoto, Y.; Furutani, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *Agric. Biol. Chem.* **1978**, 42, 1331. (e) Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, 68, 2765.

(2) (a) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, 5, 1899. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, 15, 306. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, 43, 2206.

(3) (a) Huisgen, R.; König, H.; Lepley, A. R. *Chem. Ber.* **1960**, 93, 1496. (b) Huisgen, R.; Sauer, J. *Angew. Chem.* **1960**, 72, 91. (c) Bunnett, J. F.; Hrutfiord, B. F. *J. Am. Chem. Soc.* **1961**, 83, 1691. (d) Kessar, S. V.; Pal, D.; Singh, M. *Tetrahedron* **1973**, 29, 177. (e) Kessar, S. V. *Acc. Chem. Res.* **1978**, 11, 283. (f) Mukherjee, C.; Biehl, E. *Heterocycles* **2004**, 63, 2309.

(4) Cyclization—functionalization of a benzyne-tethered nitrogen nucleophile: (a) Sielecki, T. M.; Meyers, A. I. *J. Org. Chem.* **1992**, 57, 3673. Cyclization—functionalization of a benzyne-tethered carbon nucleophile: (b) Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, 47, 2804. (c) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Tetrahedron Lett.* **1999**, 40, 1049. (d) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *J. Org. Chem.* **2006**, 71, 6291.

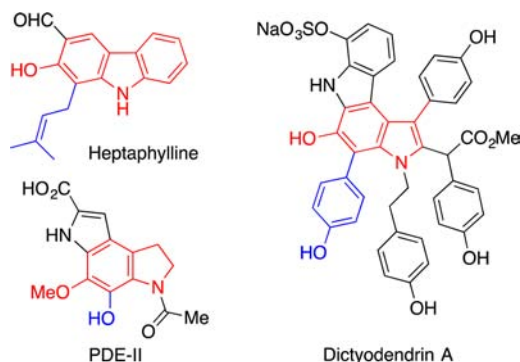
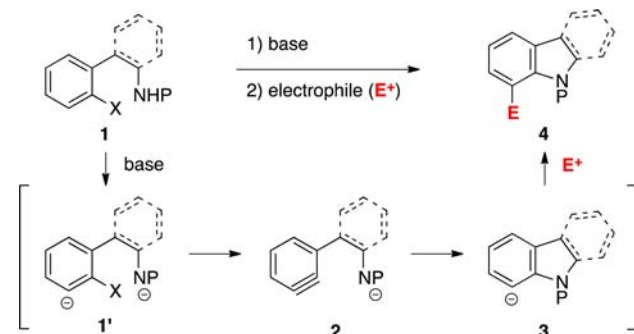


Figure 1. Highly substituted indoline and carbazole alkaloids.

Scheme 1. Our Initial Plan for the Benzyne-Mediated Cyclization–Functionalization Providing Indoline/Carbazole



crucial. Furthermore, the utility of this method is fully demonstrated by a five-pot total synthesis of heptaphylline.

In order to explore a suitable base for the benzyne-mediated sequential cyclization and trapping, a test substrate, **5a**, was treated with various bases (Table 1). First, **5a** was treated with LiTMP (lithium 2,2,6,6-tetramethylpiperidide)⁵ at -78 to 0 °C. After recooling to -78 °C, the reaction was terminated by addition of DCl/D₂O. The desired compounds **6** and **7** were obtained in good combined yields but in a moderate D/H ratio (entry 1). We then tested Mg(TMP)₂·2LiBr,⁶ which we previously found to be useful for the benzyne generation.⁷ However, the desired products were isolated in low yields with recovery of the starting material (entry 2). During further investigations,

we observed the considerable effect of lithium salt. Significantly, reactions using Mg(TMP)₂·2LiCl⁸ gave the cyclization product in quantitative yield and acceptable D/H ratio (entry 3). It is also notable that Mg(TMP)·Cl·LiCl⁹ and Mg(TMP)₂^{6c} provided only a minute amount of the desired products with recoveries of 89% of starting **5a** (entries 4 and 5). The reaction of a substrate without a methoxy group was sluggish, indicating that the methoxy group is necessary for the smooth metalation and cyclization.¹⁰

Table 1. Optimization of Amide Base^a

entry	base	6 + 7 (%) ^b	D/H ^c	5a (%)
1	LiTMP	80	62:38	^d
2	Mg(TMP) ₂ ·2LiBr	34	54:46	58
3	Mg(TMP) ₂ ·2LiCl	quant	79:21	^d
4	Mg(TMP)Cl·LiCl	9	67:33	89
5	Mg(TMP) ₂	8	54:46	89

^a Conditions: Mg(TMP)₂·2LiCl (5.0 equiv), THF, -78 to 0 °C, 1 h; DCl/D₂O, -78 to 0 °C, 1 h. ^b Isolated yield. ^c The ratio was determined by ¹H NMR. ^d Substrate **5a** was completely consumed.

Having established optimal conditions for the benzyne-mediated cyclization and trapping sequence, scope and limitation of the protective group on the nitrogen and the introducible substituent was investigated (Table 2). A bromo group was introduced in good yield when the reaction was terminated by addition of Br(CCl₂)₂Br¹¹ (entry 1). Trisylamide **5b** also served as a suitable substrate, and the desired bromoindoline **8b** was obtained in comparable yield to that of Boc carbamate **5a** (entry 2). However, the reaction of unprotected phenylethylamine **5c** gave a complex mixture (entry 3). Other substituents such as iodine and chlorine atoms were installed using I(CH₂)₂I and CITf¹² to give the 7-haloindolines in 47 and 83% yields (**8d,e**) (entries 4 and 5).¹³ In addition to acetyl and cyano

(5) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.

(6) (a) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (b) Eaton, P. E.; Xiong, Y.; Gilardi, R. *J. Am. Chem. Soc.* **1993**, *115*, 10195. (c) Henderson, K. W.; Kerr, W. J. *Chem.—Eur. J.* **2001**, *7*, 3430. (d) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794.

(7) (a) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925. (b) Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T. *Chem. Asian J.* **2011**, *6*, 560.

(8) (a) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (b) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503. (c) Rohbogner, C. J.; Wagner, A. J.; Clososki, G. C.; Knochel, P. *Org. Synth.* **2009**, *86*, 374.

(9) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

(10) If necessary, the methoxy group is directly removed by a nickel-catalyzed reductive hydrogenation: (a) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, *332*, 439. Reduction via aryl triflates: (b) Kotsuki, H.; Datta, P. K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, 1348. The triflates are also transformed to alkyl, alkenyl, acyl groups: (c) James, C. A.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4080. (d) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341.

(11) Beak, P.; Kempf, D. J.; Wilson, K. D. *J. Am. Chem. Soc.* **1985**, *107*, 4745.

(12) Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, *20*, 3643.

(13) 6-Methoxy-7-haloindoles (**8a'**, **8d'**, and **8e'**) were also isolated in low yields. For a plausible mechanism for the formation of the indoles, see the Supporting Information.

(14) (a) van Leusen, A. M.; Iedema, A. J. W.; Strating, J. *Chem. Commun.* **1968**, 440. (b) van Leusen, A. M.; Jagt, J. C. *Tetrahedron Lett.* **1970**, *11*, 967.

groups¹⁴ (entries 6 and 7), azide and hydroxyl groups were also introduced with TsN₃¹⁵ and B(OMe)₃/basic aqueous H₂O₂, respectively (entries 8 and 9). The use of LiTMP significantly diminished the yields of the products, demonstrating the broader scope of Mg(TMP)₂·2LiCl over LiTMP (entries 6 and 8).

Table 2. One-Pot Synthesis of 7-Substituted Indolines^a

entry	PG	E ⁺	E	product	yield (%) ^b
1	Boc	Br(CCl ₂) ₂ Br	Br	8a	67
2	trityl ^c	Br(CCl ₂) ₂ Br	Br	8b	70
3	H	Br(CCl ₂) ₂ Br	Br	8c	^d
4	Boc	I(CH ₂) ₂ I	I	8d	47
5	Boc	ClTf	Cl	8e	83
6	Boc	Ac ₂ O	Ac	8f	78 (47 ^e)
7	Boc	TsCN	CN	8g	47
8	Boc	TsN ₃	N ₃	8h	76 (33 ^e)
9 ^f	Boc	B(OMe) ₃	OH	8i	88

^a Conditions: Mg(TMP)₂·2LiCl (5.0 equiv), THF, –78 to 0 °C, 1 h; E⁺ (10 equiv), –78 to 0 °C, 1 h. ^b Isolated yield. ^c trityl = 2,4,6-trisopropylbenzenesulfonyl. ^d Complex mixture. ^e Instead of Mg(TMP)₂·2LiCl, LiTMP was used as a base. ^f The reaction was quenched with aqueous NaOH and aqueous H₂O₂.

The sequential reaction is also applicable for installing sp³ carbon substituents. While the direct methylation after Mg(TMP)₂·2LiCl-mediated cyclization gave no methylated indoline **8j**, we have found that transmetalation of the organomagnesium intermediate to copper species drastically promoted the methylation reaction to provide the desired compound **8j** in 71% yield (Table 3, entry 1). An allyl group was also introduced in 93% (entry 2).

Next, we focused on the introduction of sp² carbon by a one-pot sequential reaction (Table 4). After transmetalation to copper species, one-pot cross-coupling of aryl iodide with both electron-donating –OMe and electron-withdrawing –CF₃ groups proceeded smoothly even at room temperature (entries 1 and 2). When using *p*-bromoiodobenzene, the reaction proceeded exclusively at the iodine group, and the bromo group remained intact (entry 3). Alkenyl halides were also feasible for providing the corresponding 7-octenyl indoline **10c** in good yield (entry 4).

A stepwise cross-coupling reaction was also carried out through a borylated intermediate. Thus, after Mg(TMP)₂·2LiCl-mediated cyclization and borylation, Suzuki–Miyaura cross-coupling¹⁶ proceeded to introduce an anisyl group in 53% yield (Scheme 2).

Furthermore, a sp carbon substituent was introduced under the Knochel oxidative cross-coupling conditions.¹⁷

(15) (a) Dimroth, O. *Justus Liebigs Ann. Chem.* **1910**, 373, 336. (b) Smith, P. A. S.; Rowe, C. D.; Bruner, L. B. *J. Org. Chem.* **1969**, 34, 3430.

(16) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457.

(17) Dubbaka, S. R.; Kienle, M.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, 46, 9093.

Table 3. One-Pot Introduction of sp³ Carbon via Transmetalation with CuI^a

entry	E ⁺	E	product	yield (%) ^b
1	MeI	Me	8j	71 (0) ^c
2		allyl	8k	93 ^d

^a Conditions: Mg(TMP)₂·2LiCl (5.0 equiv), THF, –78 to 0 °C, 1 h; CuI (10 equiv), –78 °C, 1 h; E⁺ (10 equiv), –78 to 0 °C, 1 h. ^b Isolated yield. ^c In the absence of CuI. ^d The yield was determined by ¹H NMR.

Table 4. One-Pot Cross-Coupling Reaction^a

5a

9/10

entry	R-I	R	product	yield (%) ^b
1			R' = OMe 9	70
2			R' = CF ₃ 10a	96
3			R' = Br 10b	83
4			10c	83

^a Conditions: Mg(TMP)₂·2LiCl (5.0 equiv), THF, –78 to 0 °C, 1 h; CuI (10 equiv), –78 °C, 1 h; RI (5.0 equiv), Pd(PPh₃)₄ (20 mol %), –78 °C to rt, 3 h. ^b Isolated yield.

Thus, after formation of the indoline, transmetalation with CuCl·2LiCl and subsequent addition of alkynyl lithium followed by oxidation with chloranil gave **11** having a phenylethynyl group in 51% yield (Scheme 3).¹⁸

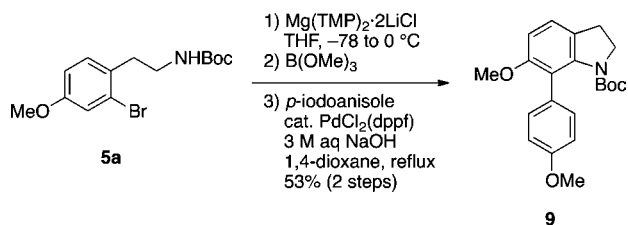
This methodology is also applicable to construction of functionalized carbazoles (Scheme 4). After cyclization, treatment of the resulting anion with aqueous hydrogen chloride gave the desired carbazole **13a** in 95% yield. Bromination and cross-coupling reaction led to the formation of the corresponding carbazoles **13b** and **13c** in 88 and 81% yields, respectively.

Finally, the utility of this methodology was fully demonstrated by application to a total synthesis of the carbazole alkaloid heptaphylline (Scheme 5). The only example of total synthesis reported by Joshi¹⁹ has two regiochemical problems in the attachment of formyl and prenyl groups by

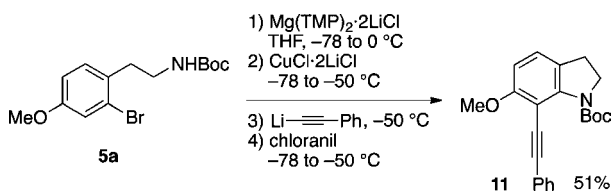
(18) Under our cross-coupling conditions with iodophenylacetylene, the undesired 7-iodoindoline **8d** was obtained in 56% yield. For iodination of aryl lithium using iodophenylacetylene, see: Boger, D. L.; Brunette, S. R.; Garbaccio, R. M. *J. Org. Chem.* **2001**, 66, 5163.

(19) Joshi, B. S.; Kamat, V. N.; Gawad, D. H.; Govindachari, T. R. *Phytochemistry* **1972**, 11, 2065.

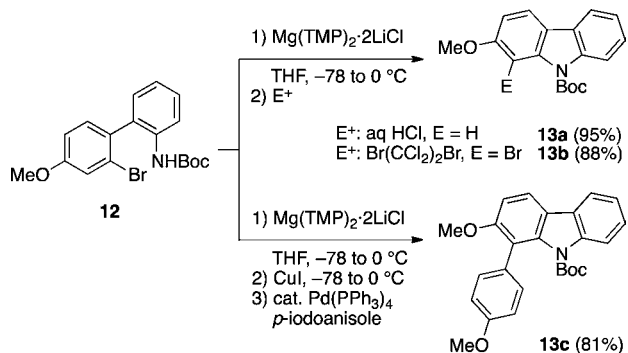
Scheme 2. Stepwise Synthesis of 7-Anisyl Indoline



Scheme 3. One-Pot Oxidative Introduction of a Phenylacetylene Moiety

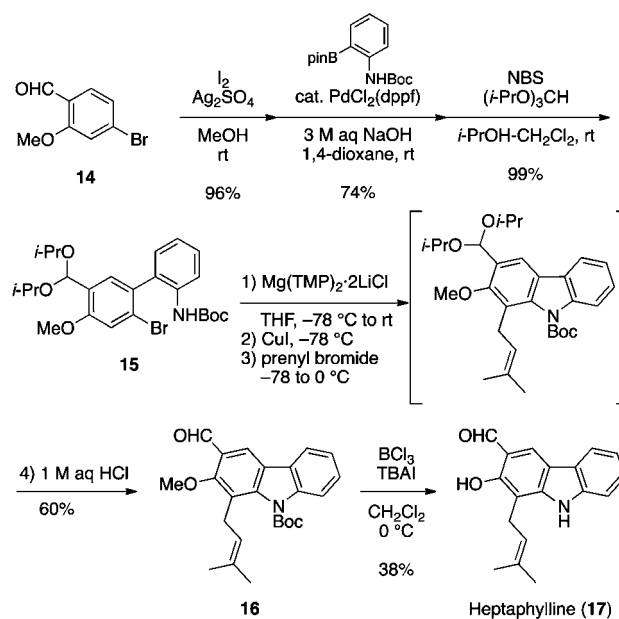


Scheme 4. Application to the Synthesis of Carbazole



conventional methods. Our synthesis started from commercially available bromoanisaldehyde **14**, which was converted to biaryl **15** in three steps.^{20,21} Gratifyingly, one-pot carbazole formation–prenylation and removal of the acetal moiety upon acidic workup provided the

Scheme 5. Five-Pot Synthesis of Heptaphylline



desired product **16** in 60% yield. Finally, the Boc and methyl groups were removed using a combination of BCl_3 and TBAI²² to provide heptaphylline (**17**) in 16% overall yield from bromoanisaldehyde **14**.

In summary, we have developed a synthetic method for substituted indolines and carbazoles by the benzyne-mediated cyclization–functionalization sequence using $\text{Mg}(\text{TMP})_2 \cdot 2\text{LiCl}$ as a base. The synthetic potential of this methodology was demonstrated by a concise synthesis of heptaphylline.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

(20) Iodination with iodine and silver sulfate: Sy, W.-W. *Tetrahedron Lett.* **1993**, 34, 6223.

(21) Ketalization using catalytic NBS and orthoformate: Karimi, B.; Seradj, H.; Ebrahimian, G.-R. *Synlett* **1999**, 1456.

(22) Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, 64, 9719.