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

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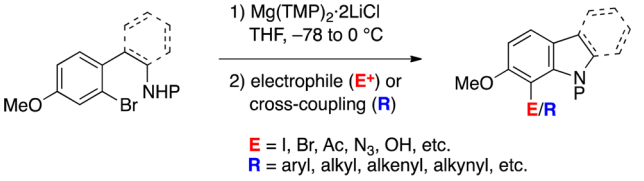
ABSTRACT



A benzyne-mediated synthesis of substituted indolines and carbazoles was developed. The reaction includes generation of benzyne using $Mg(TMP)_2 \cdot 2LiCl$ 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 $Mg(TMP)_2 \cdot 2LiCl$ 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.; Fernádnez, 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.

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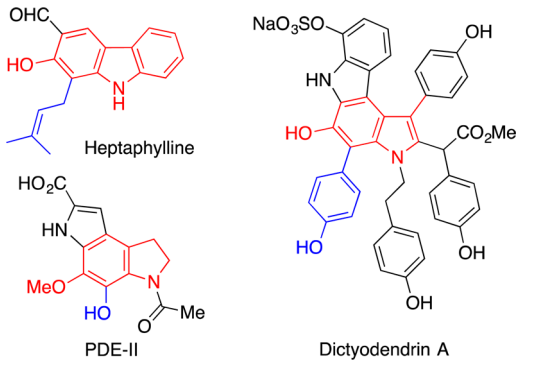
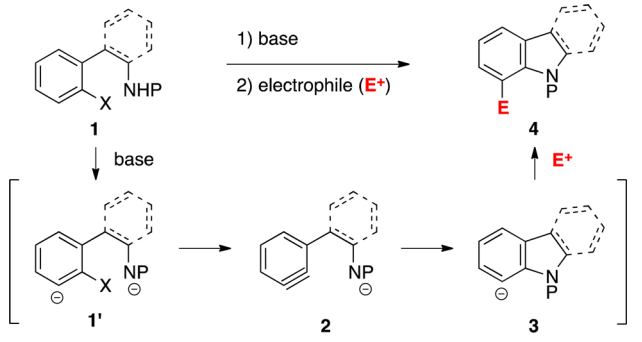


Figure 1. Highly substituted indoline and carbazole alkaloids.

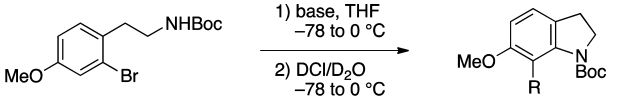
Scheme 1. Our Initial Plan for the Benzyne-Mediated Cyclization–Functionalization Providing Indoline/Carbazole



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/D_2O. The desired compounds **6** and **7** were obtained in good combined yields but in a moderate D/H ratio (entry 1). We then tested $Mg(TMP)_2\cdot 2LiBr$,[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 $Mg(TMP)_2\cdot 2LiCl$[8] gave the cyclization product in quantitative yield and acceptable D/H ratio (entry 3). It is also notable that $Mg(TMP)Cl\cdot LiCl$[9] 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	$Mg(TMP)_2\cdot 2LiBr$	34	54:46	58
3	$Mg(TMP)_2\cdot 2LiCl$	quant	79:21	[d]
4	$Mg(TMP)Cl\cdot LiCl$	9	67:33	89
5	$Mg(TMP)_2$	8	54:46	89

[a] Conditions: $Mg(TMP)_2\cdot 2LiCl$ (5.0 equiv), THF, −78 to 0 °C, 1 h; DCl/D_2O, −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 $Br(CCl_2)_2Br$[11] (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 $I(CH_2)_2I$ and ClTf[12] 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.

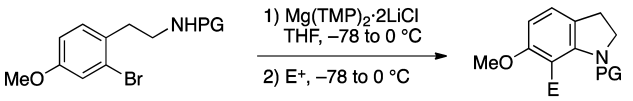
(12) Hakimelahi, G. H.; Just, G. *Tetrahedron Lett.* **1979**, *20*, 3643.

(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.

groups[14] (entries 6 and 7), azide and hydroxyl groups were also introduced with TsN_3[15] and $B(OMe)_3$/basic aqueous H_2O_2, respectively (entries 8 and 9). The use of LiTMP significantly diminished the yields of the products, demonstrating the broader scope of $Mg(TMP)_2 \cdot 2LiCl$ over LiTMP (entries 6 and 8).

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



5 8

entry	PG	E^+	E	product	yield (%)[b]
1	Boc	$Br(CCl_2)_2Br$	Br	**8a**	67
2	trisyl[c]	$Br(CCl_2)_2Br$	Br	**8b**	70
3	H	$Br(CCl_2)_2Br$	Br	**8c**	[d]
4	Boc	$I(CH_2)_2I$	I	**8d**	47
5	Boc	ClTf	Cl	**8e**	83
6	Boc	Ac_2O	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: $Mg(TMP)_2 \cdot 2LiCl$ (5.0 equiv), THF, −78 to 0 °C, 1 h; E^+ (10 equiv), −78 to 0 °C, 1 h. [b] Isolated yield. [c] trisyl = 2,4,6-triisopropylbenzenesulfonyl. [d] Complex mixture. [e] Instead of $Mg(TMP)_2 \cdot 2LiCl$, LiTMP was used as a base. [f] The reaction was quenched with aqueous NaOH and aqueous H_2O_2.

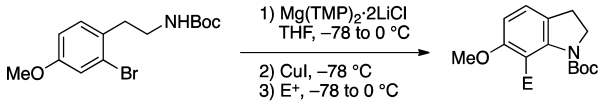
The sequential reaction is also applicable for installing sp^3 carbon substituents. While the direct methylation after $Mg(TMP)_2 \cdot 2LiCl$-mediated cyclization gave no methylated indoline **8j**, we have found that transmetalation of the oragnomagnesium intermediate to copper species drastically 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 sp^2 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 $-CF_3$ 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 $Mg(TMP)_2 \cdot 2LiCl$-mediated cyclization and borylation, Suzuki–Miyaura cross-coupling[16] 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]

Table 3. One-Pot Introduction of sp^3 Carbon via Transmetalation with CuI[a]

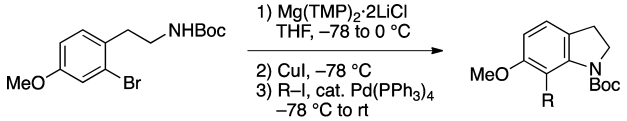


5a 8

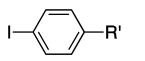
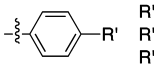
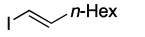
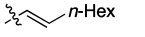
entry	E^+	E	product	yield (%)[b]
1	MeI	Me	**8j**	71 (0)[c]
2			**8k**	93[d]

[a] Conditions: $Mg(TMP)_2 \cdot 2LiCl$ (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: $Mg(TMP)_2 \cdot 2LiCl$ (5.0 equiv), THF, −78 to 0 °C, 1 h; CuI (10 equiv), −78 °C, 1 h; RI (5.0 equiv), $Pd(PPh_3)_4$ (20 mol %), −78 °C to rt, 3 h. [b] Isolated yield.

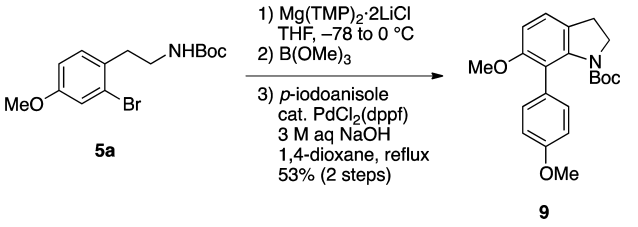
Thus, after formation of the indoline, transmetalation with $CuCl \cdot 2LiCl$ and subsequent addition of alkynyl lithium followed by oxidation with chloranil gave **11** having a phenylethynyl group in 51% yield (Scheme 3).[18]

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.

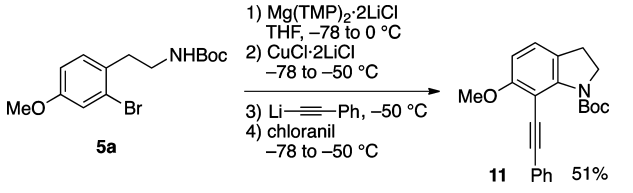
Finally, the utility of this methodology was fully demonstrated by application to a total synthesis of the carbazole alkaloid heptaphylline (Scheme 5). The only example of total synthesis reported by Joshi[19] has two regiochemical problems in the attachment of formyl and prenyl groups by

(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.
(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.

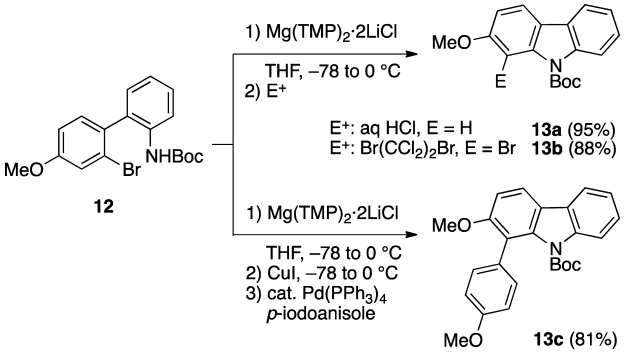
Scheme 2. Stepwise Synthesis of 7-Anisyl Indoline



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



Scheme 4. Application to the Synthesis of Carbazole



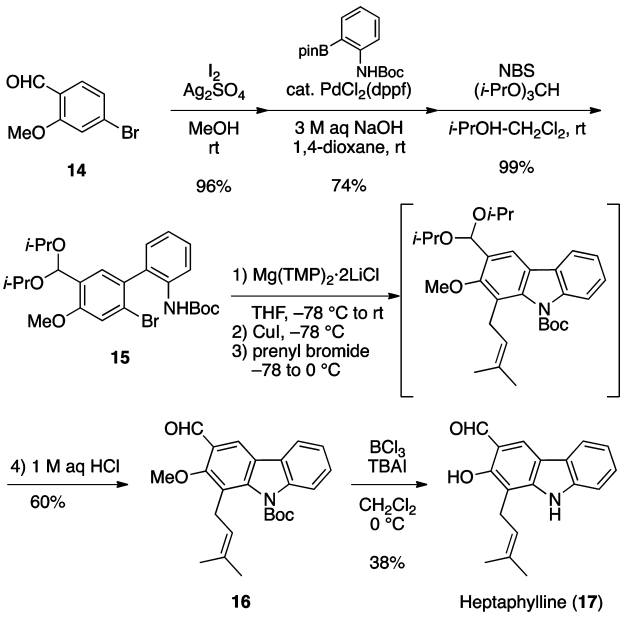
conventional methods. Our synthesis started from commercially available bromoanisaldehyde **14**, which was converted to biaryl **15** in three steps.[20,21] Gratifyingly, one-pot carbazole formation–prenylation and removal of the acetal moiety upon acidic workup provided the

(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.

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 TBAI[22] 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 $Mg(TMP)_2 \cdot 2LiCl$ 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.