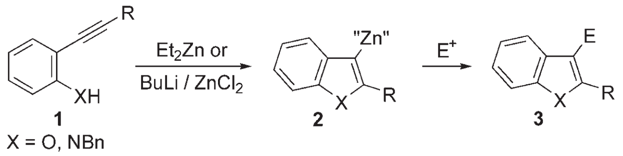
Heterocycles

DOI: 10.1002/ange.200502920

3-Zinciobenzofuran and 3-Zincioindole: Versatile Tools for the Construction of Conjugated Structures Containing Multiple Benzoheterole Units**

Masaharu Nakamura, Laurean Ilies, Saika Otsubo, and Eiichi Nakamura**

Functionalized benzoheteroles, such as benzofuran and indole, form the core of natural products and serve as promising units in materials science.[1] In the latter applications, conjugated compounds containing one or more benzoheterole units are attracting particular attention.[2] A potentially general approach to this class of compounds is the cyclization of a metal 2-ynyl phenolate or 2-ynyl anilide **1** to a 3-metallobenzoheterole intermediate **2** that reacts further with an electrophile to produce the corresponding heterole **3** (Scheme 1). We report herein the virtually quantitative cyclization of **1** into a zinc compound **2** and its use in the concise synthesis of a variety of new benzoheterole conjugated systems (cf. Table 2). Such a cyclization has been known for the synthesis of some 3-metallobenzofuran intermediates (metal = Li, Hg,[3] and Pd[4]), but not in the indole series.[5] The value of the present zinc-mediated chemistry resides in the high yield of the cyclization and the versatility of the resulting zinc compounds **2** in synthesis of a library of new multiple benzoheterole conjugated systems.



Scheme 1. Cyclization of a 2-alkynyl phenol or aniline to a 3-zinciobenzoheterole. Bn = benzyl; E^+ = electrophile.

The incorporation of a zinc atom to obtain **2**, which is stable yet reactive in the presence of a catalyst, was critical to

---

[*] Prof. Dr. M. Nakamura, L. Ilies, S. Otsubo, Prof. Dr. E. Nakamura
Department of Chemistry
The University of Tokyo
and Nakamura Functional Carbon Cluster Project ERATO
Japan Science and Technology Agency
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
Fax: (+81) 3-5800-6889
E-mail: masaharu@chem.s.u-tokyo.ac.jp
nakamura@chem.s.u-tokyo.ac.jp

[**] We thank the Ministry of Education, Culture, Sports, Science, and Technology of Japan for financial support, a scholarship (L.I.) and for the 21st Century COE Program for Frontiers in Fundamental Chemistry.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

success, as it was for the addition of a zinc enamide and enolate to an unactivated alkene or alkyne.[6] Deprotonation of a 2-alkynyl phenol **1a**–**f** with 0.5 equivalents of Et_2Zn followed by heating in the presence of a catalytic amount of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in refluxing toluene effected smooth cyclization into 2-substituted benzofurans **3a**–**f** (E = H), which were isolated after quenching the reaction mixture with aqueous ammonium chloride. We observed 97% deuterium incorporation (R = Ph) after quenching the reaction mixture with deuterium chloride. The reaction afforded 2-aryl, heteroaryl, vinyl, and alkoxymethyl benzofurans in almost quantitative yields (Table 1, entries 1–6), except sterically hindered 2-*tert*-butylbenzofuran (**3c**), which was obtained in 50% yield. Zinc phenoxides are known to form oligomeric aggregates,[7] and therefore TMEDA is thought to activate the aggregate by partially breaking the coordination between the oxygen and zinc atoms. We have so far been unable to cyclize either phenol **1**, in which R = H, likely because of the high acidity of the free acetylenic proton, or the phenol in which R = Me_3Si, as it resists cyclization and premature loss of the silyl group results. We have previously shown that a silicon group retards the reaction taking place with such regiochemistry.[8]

Table 1: Cyclization of a 2-alkynyl phenol or aniline to form a benzoheterole **3** (E = H).

Entry	X	R	**1**	*t*	Yield [%][a]	Product
1	O	Ph	**1a**	1 h	94	**3a**
2	O	*n*Bu	**1b**	1 h	99	**3b**
3	O	*t*Bu	**1c**	3 days	50	**3c**[b]
4	O	*E*-styryl	**1d**	1 h	99	**3d**
5	O	2-thienyl	**1e**	3 h	93	**3e**
6	O	CH_2OMOM[c]	**1f**	1 h	98	**3f**
7	NBn	Ph	**1g**	1 h	99	**3g**

[a] Yield of the isolated product. [b] Starting material **1c** was recovered in 31% yield. [c] MOM = methoxymethyl.

A slightly modified method was found to be useful for the indole synthesis. Deprotonation of *N*-benzyl-protected alkynyl aniline **1g** with butyllithium,[9] followed by treatment with zinc chloride and heating for one hour in toluene quantitatively generated 2-substituted 3-zincioindole, which was quenched with ammonium chloride to give 2-phenylindole in 99% yield (Table 1, entry 7). When the reaction mixture was quenched with deuterium chloride, 95% deuterium incorporation at the mechanistically expected 3 position was observed. TMEDA was not necessary for the cyclization of indoles, presumably because the corresponding zinc anilides tend not to form unreactive aggregates like the related zinc phenoxides.[10]

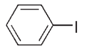
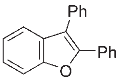
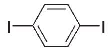
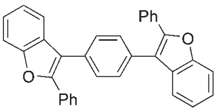
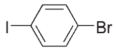
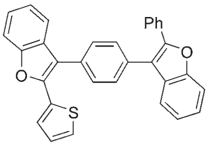
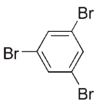
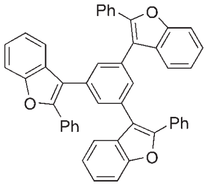
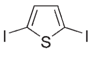
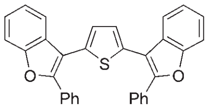
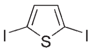
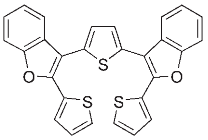
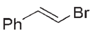
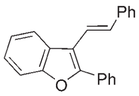
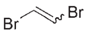
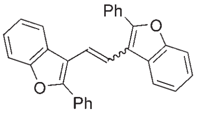
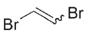
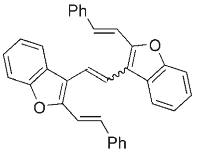
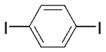
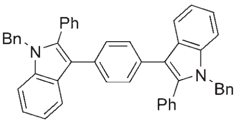
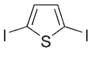
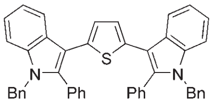
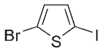
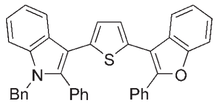
The zinc intermediate **2** is a useful building block for the construction of various conjugated structures with 2,3-disubstituted benzoheteroles as a key structural motif. After screening several catalyst systems, we found that various aryl and alkenyl halides readily couple with **2** in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone; 5 mol%) and $P(tBu)_3$ (20 mol%; Table 2).[11] The reactions of the 3-zinciobenzofuran intermediate are described first: The reaction with iodobenzene and (*E*)-bromostyrene took place quantitatively to give 2,3-diphenylbenzofuran (**4**)[12] and 2-phenyl-3-(*E*)-phenylethenylbenzofuran (**10**; entries 1 and 7, respectively). The synthetic merit of the zinc methodology is demonstrated in the reactions with polyhaloarenes, which afforded compounds inaccessible by known methods. For example, two or three benzofuran moieties can be introduced in a single step to a benzene ring to yield molecules containing seven and ten aromatic rings (**5** and **7**, 87 and 74% yield of the isolated products, respectively; entries 2 and 4). Molecular-modeling studies suggest intrinsic nonplanarity of these compounds owing to the steric repulsion of substituents on the benzofuran rings, which makes a chiral propeller conformation for tribenzofuran **7** favorable (see the Supporting Information). The present method provides easy access to asymmetrically substituted compounds, such as **6**, by using two different zinc benzofuran compounds. Thus, zinc intermediates **2a** and **2e** were treated sequentially with 1-bromo-4-iodobenzene to give a mixed-furan compound **6** in 82% yield (entry 3). Similarly, we synthesized **8** and **9** with benzofuran-thiophene-benzofuran alternating units in 89 and 67% yield, respectively (entries 5 and 6) by starting with 2,5-diiodothiophene. 1,2-Dibromoethene afforded an ethylene-linked benzofuran **11** and a highly conjugated benzofuran **12** in high yield (entries 8 and 9). The olefin geometry in the starting dibromide was retained in the product. Some of these compounds show intense fluorescence both in solution and in the solid state because of the extended conjugation and nonplanarity; this property will be an interesting future subject of materials-related studies.

Next, we examined the scope of this coupling protocol for the 3-zincioindole reagent (Table 2, entries 10–12). Coupling of the zinc intermediate **2g** with 1,4-diiodobenzene and 2,5-diiodothiophene in the presence of the Pd^0 catalyst gave the conjugated bisindoles **13** and **14** in excellent yield. We could also synthesize a indole-thiophene-benzofuran ternary compound **15** by allowing zinciobenzofuran **2a** and zincioindole **2g** to react sequentially in one pot with 2-bromo-5-iodothiophene (entry 12).

In conclusion, we have developed an efficient and general synthetic method for 3-metallated 2-substituted benzoheteroles and their use in the preparation of molecules containing multiple benzofuran and indole units. The rather low reactivity of the zinc phenoxides in the absence of TMEDA is probably due to the propensity of zinc phenoxides to form coordinatively saturated oxygen-bridged aggregates, in contrast to the corresponding zinc anilides. The high reactivity of the 3-metallobenzoheterole reported above suggests that other the standard techniques in organozinc chemistry[13] could contribute to expanding the utility of our heteroaromatic zinc reagents. The nonplanar, multiaromatic ring systems suggest their potential as new chiral scaffolds to be exploited in asymmetric synthesis. We expect the present methodology to be applicable to other heterocyclic systems, such as benzothiophenes and benzosiloles, and to provide a variety of new compounds for various applications.

Received: August 17, 2005

Table 2: Conjugated compounds obtained by Pd-catalyzed coupling with halides.

Entry	Phenol	Electrophile	Coupling product		Yield [%][a]
1	**1a**			**4**	99
2	**1a**			**5**	87
3	**1a** **1e**			**6**	82[b]
4	**1a**[c]			**7**	74
5	**1a**			**8**	89
6	**1e**			**9**	67
7	**1a**			**10**	94
8	**1a**			**11**	92
9	**1d**			**12**	88
10	**1g**			**13**	93
11	**1g**			**14**	91
12	**1a** **1g**			**15**	48

[a] Yield of the isolated products. [b] Symmetric coupling products were obtained in about 15 % yield (GC analysis). [c] 10 mol % of palladium and 40 mol % of P(tBu)$_3$ were used. [d] $E/Z = 43{:}57$, as determined by ^{1}H NMR spectroscopic analysis.

Keywords: benzoheterole · conjugation · cyclization · heterocycles · palladium · zinc

[1] a) A. R. Katritzky, *Comprehensive Heterocyclic Chemistry, Vol. 4*, Part 3, Pergamon, Oxford, **1984**, pp. 658 – 712; b) A. Williams, *Furans, Synthesis and Applications*, Noyes Data Corporation, Park Ridge, NJ, **1973**, pp. 1 – 303.

[2] a) S. Anderson, P. N. Taylor, G. L. B. Verschoor, *Chem. Eur. J.* **2004**, *10*, 518 – 527; b) K. Nozaki, K. Takahashi, K. Nakano, T. Hiyama, H.-Z. Tang, M. Fujiki, S. Yamaguchi, K. Tamao, *Angew. Chem.* **2003**, *115*, 2097 – 2099; *Angew. Chem. Int. Ed.* **2003**, *42*, 2051 – 2053; c) C. Xu, A. Wakamiya, S. Yamaguchi, *Org. Lett.* **2004**, *6*, 3707 – 3710; d) R. de Bettignies, Y. Nicolas, P. Blanchard, E. Levillain, J.-M. Nunzi, J. Roncali, *Adv. Mater.* **2003**, *15*, 1939 – 1943.

[3] a) M. Inoue, M. W. Carson, A. J. Frontier, S. J. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 1878 – 1889; b) C. R. Larock, L. W. Harrison, *J. Am. Chem. Soc.* **1984**, *106*, 4218 – 4227; c) H. Gilman, D. S. Melstrom, *J. Am. Chem. Soc.* **1948**, *70*, 1655 – 1657.

[4] For example: a) Y. Hu, Y. Zhang, Z. Yang, R. J. Fathi, *Org. Chem.* **2002**, *67*, 2365 – 2368; b) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, *Synlett* **1999**, 1432 – 1434; c) A. Arcadi, S. Cacchi, M. Del Rosario, G. Fabrizi, F. Marinelli, *J. Org. Chem.* **1996**, *61*, 9280 – 9288; d) Y. Kondo, F. Shiga, N. Murata, T. Sakamoto, H. Yamanaka, *Tetrahedron* **1994**, *50*, 11 803 – 11 812.

[5] a) M. Amat, S. Sathyanarayana, S. Hadida, J. Bosch, *Heterocycles* **1996**, *43*, 1713 – 1718; b) C. E. Reck, A. Bretschneider-Hurley, M. J. Heeg, C. H. Winter, *Organometallics* **1998**, *17*, 2906 – 2911; c) J. I. DeGraw, J. G. Kennedy, W. A. Skinner, *J. Heterocycl. Chem.* **1966**, *3*, 67 – 69; d) P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett.* **1997**, *38*, 2405 – 2408; e) M. Amat, S. Hadida, J. Bosch, *Tetrahedron Lett.* **1994**, *35*, 793 – 796.

[6] a) M. Nakamura, T. Fujimoto, K. Endo, E. Nakamura, *Org. Lett.* **2004**, *6*, 4837 – 4840; b) M. Nakamura, C. Liang, E. Nakamura, *Org. Lett.* **2004**, *6*, 2015 – 2017; c) M. Nakamura, T. Hatakeyama, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 11 820 – 11 825; d) M. Nakamura, K. Endo, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 13 002 – 13 003; e) M. Nakamura, T. Hatakeyama, K. Hara, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 6362 – 6363.

[7] a) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 2341 – 2350; b) A. B. Charette, C. Molinaro, C. Brochu, *J. Am. Chem. Soc.* **2001**, *123*, 12 160 – 12 167; c) M. M. Olmstead, P. P. Power, S. C. Shoner, *J. Am. Chem. Soc.* **1991**, *113*, 3379 – 3385.

[8] E. Nakamura, Y. Miyachi, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1992**, *114*, 6686 – 6692.

[9] Diethylzinc is too weak as a base to deprotonate the amine.

[10] A. Erxleben, *Inorg. Chem.* **2001**, *40*, 208 – 213.

[11] a) C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724; b) T. Yamamoto, M. Nishiyama, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 2367–2370.

[12] Y. Hu, K. J. Nawoschik, Y. Liao, J. Ma, R. Fathi, Z. Yang, *J. Org. Chem.* **2004**, *69*, 2235–2239.

[13] a) P. Knochel, P. Jones, *Organozinc Reagents*, Oxford University Press, New York, **1999**; b) E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC, New York, **1996**.