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Synthesis of 4,4′-Bisaryl-2,2′-bisbenzimidazoles as Building Blocks for Supramolecular Structures

Yoshizumi Yasui,† Derik K. Frantz, and Jay S. Siegel*

*Organic Chemistry Institute, University of Zurich, Winterthurerstrasse 190,
8057 Zurich, Switzerland*

jss@oci.unizh.ch

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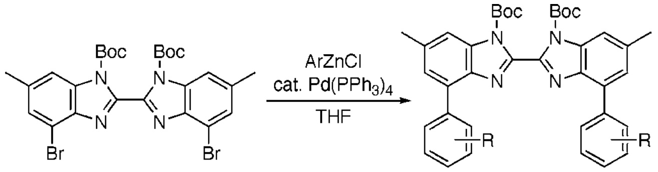
ABSTRACT



A series of 4,4′-bisaryl-2,2′-bisbenzimidazoles has been synthesized from the corresponding 4,4′-dibromo-2,2′-bisbenzimidazoles by Negishi coupling reactions. This procedure affords highly substituted bisbenzimidazoles.

Applications of supramolecular assemblies as molecular machines[1] or molecular devices[2] are routinely comprised of coordination metal complexes. Higher-order metal complexes have shared a dominant position in this field, owing to their rich photochemical and electrochemical properties.[3] 2,2′-Bisbenzimidazoles (BBI) are in a unique class of ligands that show high binding affinity to a wide range of transition metals: early transition metals (Ti,[4] Mo[5]); middle transition metals (Mn,[6] Re,[7] Fe,[8] Ru,[9] Os,[10] Co,[11] Rh,[12] Ir[12b]); and late transition metals (Ni,[13] Pd,[14] Pt,[15] Cu,[16] Ag,[17] Au[18]). Moreover, stable polymetallic complexes are known to be formed through bridging of monoanionic and dianionic BBIs, which are generated by deprotonation of the amino nitrogens.[19] BBI's ability to form polymetallic species was applied to

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† Current address: Graduate School of Pharmaceutical Sciences, Kyoto University. Email: yasui@pharm.kyoto-u.ac.jp.

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make a molecular sensor; emission switching of a BBI−ruthenium complex was shown in the presence of various metal ions.[20] Additionally, it was demonstrated that supramolecular assemblies of BBI complexes could be formed through hydrogen bonding in the solution[21] and solid phases.[22]

Although the chemistry of simple BBIs has been studied widely, the knowledge of substituted BBIs, such as aryl derivatives, is limited.[23] From our own experience with supramolecular metal complexes,[24] the extent of study for a given system depends on the ease of the synthesis of a series of derivatives.[25]

4,4′-Bisaryl-BBI has the potential to be a building block for a variety of more complex ligands (Figure 1). Taking a schematic approach, 4,4′-bisaryl-BBI can adopt a U-shaped conformation which has two differentiated binding sites, namely, the exo binding sites [N(1) and N(1′)] and the endo binding sites [N(3) and N(3′)].[26] The schematic lines made by two aromatic moieties are parallel, and the distance between these should be ca. 8 Å.[27] This cleftlike structure creates the possibility of controlling complex formations at the exo or endo sites. Less sterically congested complexes, such as tetrahedral complexes, may be formed at either the exo or endo binding sites (**A**). In contrast, only the exo binding sites could participate in sterically congested complexes, such as octahedral complexes (**B**). Addition of aryl substituents will allow for further structural elaboration. Introduction of heterocyclic aromatics may form multidentate ligands (**C**). Ring closure between the two ends of the aryl groups may generate a new class of macrocyclic ligands (**D**). Moreover, a series of large, macrocyclic ligands may be generated by fusion of more than one 4,4′-bisaryl-BBI (**E**).

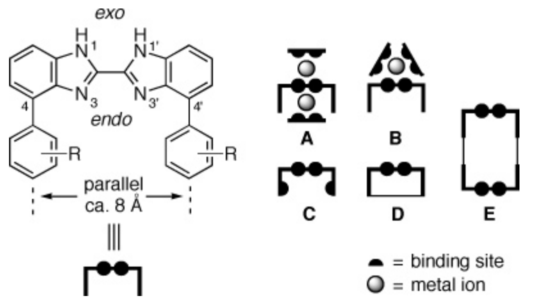
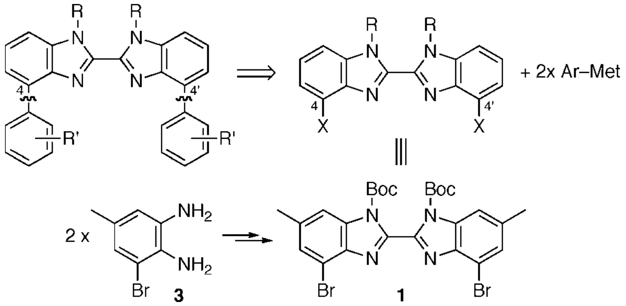


Figure 1. Schematic representation of 4,4′-bisaryl-BBI and its derived complexes and structures.

Scheme 1. Synthetic Plan of 4,4′-Bisaryl-BBI



3 **1**

Transition-metal-catalyzed coupling reactions have been shown to be an efficient method to synthesize functionalized heteroaromatic ligands.[28] These methods have advantages for the synthesis of 4,4′-bisaryl-BBI (Scheme 1). Retrosynthetically, a biaryl linkage at the 4,4′-positions is disconnected to 4,4′-dihalo-BBI and aryl organometals. Our plan was to substitute these halogens with a variety of aryl groups via coupling reactions at the latter stage of the synthesis. In this context, Boc-protected 4,4′-dibromo-BBI **1** was chosen as a

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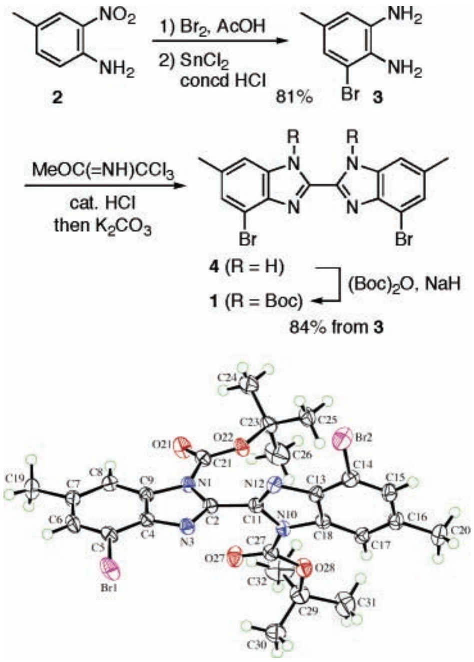
(26) The discussion on the topology of 4,4′-bisaryl-BBI is based on an assumption that two aryl groups are pointing the same direction (syn conformation), though it is known that the anti conformer is dominant in the solid state and likely preferred in the solution phase as well. See: Rath, N.; Mohanty, R. R.; Jena, S.; Hemling, H. *Indian J. Heterocycl. Chem.* **1997**, *6*, 303. Torsional studies of 1,1′-dimethyl-2,2′-bisbenzimidazole have calculated the difference in the heats of formation from the anti to the syn conformer to be 12.3 kcal/mol, giving an indication in related systems. Studies of *N*1,*N*1′-bridged-4,4′-bisaryl-BBIs are currently under investigation.

(27) The distance between C(4) and C(7′) of trans-oriented 4,4′-dibromo-6,6′-dimethyl-2,2′-bisbenzimidazole was measured from its X-ray structure.

(28) For selected examples, see: (a) ref 24. (b) Tzalis, D.; Tor, Y. *Tetrahedron Lett.* **1995**, *36*, 6017. (c) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048. (d) Lehmann, U.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3483. (e) Goeb, S.; Nicola, A. D.; Ziessel, R. *J. Org. Chem.* **2005**, *70*, 6802.

Scheme 2. Preparation of BBI **1** and X-ray Crystal Structure of **1**

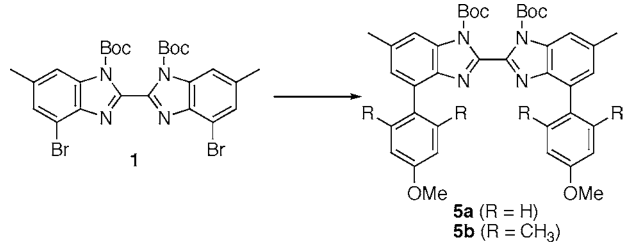


convenient dihalide. Compound **1** can be prepared by dimerization of the corresponding diamine **3**, followed by protection.

Among various known methods to construct the BBI framework, condensation of phenylene diamine with methyl 2,2,2-trichloroacetimidate, which was initially discovered by Holan et al.[29] and recently improved by Parker et al.,[23c,e] was chosen.[30] The intermediate phenylene diamine **3** was synthesized by bromination of commercially available 4-methyl-2-nitroaniline **2**,[31] followed by reduction of the nitro group with $SnCl_2$ (Scheme 2). Diamine **3** was converted to BBI **1** by treatment with half a molar equivalent of methyl 2,2,2-trichloroacetimidate in the presence of a catalytic amount of concentrated HCl to form 2-trichloromethylbenzimidazole,[29] which, after basification with K_2CO_3, reacts in situ with the residual diamine **3** to afford **4**. Finally, Boc groups were selectively introduced to the less-hindered nitrogen atoms of **4** to give dibromide **1** in 84% overall yield from diamine **3**. X-ray crystallography analysis of **1** confirmed the position of the Boc groups.

With dibromide **1** in hand, interest focused on the Negishi coupling reaction[32] to introduce aryl groups at the 4,4′-positions. Reaction conditions were optimized with 4-methoxyphenyl and 4-methoxy-2,6-dimethylphenyl as aryl groups (Table 1). Initial trials under typical coupling conditions (3.0 equiv of 4-$MeOC_6H_4ZnCl$, 10 mol % of $Pd(PPh_3)_4$, in THF, reflux, 18 h) gave disappointing results (entry 1). However, the use of excess 4-$MeOC_6H_4ZnCl$ (4.5 equiv) gave the desired bisaryl-BBI **5a** in 67% isolated yield (entry 2). Attempting to reduce the amount of zincate, we had the idea of replacing the excess zincate with $ZnCl_2$. When 2.5 equiv of $ZnCl_2$ was employed, the arylation was completed with 2.5 equiv of 4-$MeOC_6H_4ZnCl$, though cleavage of the Boc group took place and the isolated yield was poor (entry 3). It was found that limiting the time of the reaction to 6 h (60 °C), when using 2.5 equiv of ArZnCl/2.5 equiv of $ZnCl_2$, prevented cleavage of the Boc groups and produced **5a** in good yield (entry 5). Under these milder conditions (60 °C, 6 h), the reaction with 4.5 equiv of 4-$MeOC_6H_4ZnCl$ also proceeded in good yield (entry 6). Using 4.5 equiv of sterically hindered 4-MeO-2,6-$Me_2C_6H_2ZnCl$ (60 °C, 18 h) provided good results (entry 7). However, 2.5 equiv of 4-MeO-2,6-$Me_2C_6H_2ZnCl$ with 2.5 equiv of $ZnCl_2$ (60 °C, 6 h) did not produce **5b**, and **1** was recovered in 43% yield (entry 8). The well-known Nolan catalysts were not efficient for 4-$MeOC_6H_4ZnCl$ coupling (entry 9) but provided a good yield for coupling of sterically hindered 4-MeO-2,6-$Me_2C_6H_2ZnCl$ (entry 10).[33] It would appear that self-coupling

Table 1. Optimization of Negishi Arylation of BBI **1**[a]



entry	product	ArZnCl[b] (equiv)	$ZnCl_2$ (equiv)	temp (C°)	time (h)	yield (%)
1	**5a**	3.0	–	reflux	18	32
2[c]	**5a**	4.5	–	reflux	18	67
3	**5a**	2.5	2.5	reflux	18	40[d]
4	**5a**	4.5	–	60	12	69
5	**5a**	2.5	2.5	60	6	76
6	**5a**	4.5	–	60	6	70
7	**5b**	4.5	–	60	18	70
8	**5b**	2.5	2.5	60	6	–[e]
9[f]	**5a**	4.5	–	60	12	7[g]
10[f]	**5b**	4.5	–	60	18	66

[a] Unless otherwise indicated, reactions were run on a 0.6–0.7 mmol scale in THF using 10 mol % of $Pd(PPh_3)_4$. [b] Ar = 4-methoxylphenyl for product **5a** and 4-methoxy-2,6-dimethylphenyl for **5b**. [c] 30 mol % of $Pd(PPh_3)_4$ was used. [d] de-Boc compound, 4,4′-bis(4-methoxyphenyl)-6,6′-dimethyl-2,2′-bisbenzimidazole, was isolated in ca. 35% yield. [e] **1** was recovered in 43% yield. [f] $Pd(OAc)_2$ (10 mol %) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (10 mol %) were used instead of $Pd(PPh_3)_4$. [g] 44% of **1** was recovered.

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(30) For other methodologies to construct BBI, see: (a) Lane, E. S. *J. Chem. Soc.* **1953**, 2238. (b) Vyas, P. C.; Oza, C. K.; Goyal, A. K. *Chem. Ind. (London)* **1980**, 287. (c) Park, S. B.; Alper, H. *Org. Lett.* **2003**, *5*, 3209.

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(32) Negishi, E. Overview of the Negishi Protocol with Zn, Al, Zr, and Related Metals. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley & Sons: New York, 2002; Vol. 1, pp 229–247.

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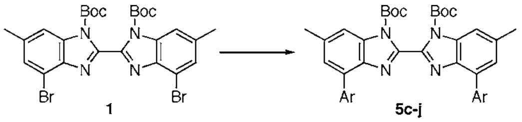
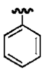
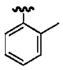
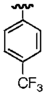
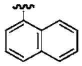
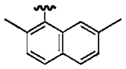
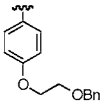
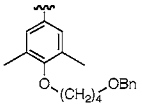
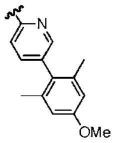
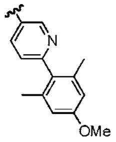
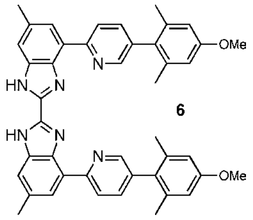
Table 2. Synthesis of 4,4′-Bisaryl-BBI[a]



entry	Ar	method[b]	time (h)	product	yield (%)
1a		A	6	**5c**	60
1b		B	6		60
2a		A	6	**5d**	75
2b		B	6		41
3a		A	6	**5e**	57
3b		B	6		53
4		A	18	**5f**	68
5		A	18	**5g**	63
6		B	6	**5h**	69
7a		A	6	**5i**	73
7b		B	6		53
8		A	6	**6**	21[c]
9		A	24	**5j**	50

[a] Reactions were run on a 0.6−0.7 mmol scale at 60 °C in THF using 10 mol % of $Pd(PPh_3)_4$. [b] Method A: ArZnCl (4.5 equiv). Method B: ArZnCl (2.5 equiv) and $ZnCl_2$ (2.5 equiv). [c] Compound **6** was isolated in 21% yield.



of the organozinc species is the dominant side reaction that reduces yields.

Having established a working set of conditions, we investigated the substitution effect of various aryl zincates (Table 2). Method A (4.5 equiv of ArZnCl) was compared to method B (2.5 equiv of ArZnCl and 2.5 equiv of $ZnCl_2$) in many cases. To prevent deprotection of the Boc groups, trials using method B were confined to 6 h; however, where deprotected products are tolerated, even better yields are possible. The electron density on the aromatic ring affected the success of the reaction. Electron-rich 4-$MeOC_6H_4ZnCl$ (Table 1, entries 5 and 6) gave higher yields than PhZnCl (entries 1a and 1b) and 4-$CF_3C_6H_4ZnCl$ (entries 3a and 3b) for both methods. Method A (4.5 equiv of ArZnCl) was effective for introducing sterically hindered aromatics (entries 2a and 5, Table 2; entry 7, Table 1). Even 1-naphthyl was introduced in good yield (entry 4). It was possible to reduce the amount of zincate and maintain a high yield by using method B when the aromatic is electron rich and sterically unhindered (Table 2, entry 6; Table 1, entry 5).

Compound **5h** possesses interesting potential as a precursor for a macrocyclic ligand. Although 4-alkoxy-3,5-dimethylphenyl zincate provided reasonable yields under both conditions, method A was more effective (entries 7a and 7b). These results could be explained by its moderate nucleophilicity, presumably coming from restricted conjugation of the alkoxy group. Pyridine derivatives were examined to demonstrate the possibility of synthesizing higher-order multidentate ligands. The reaction of 2-pyridyl zincate and **1** produced considerable cleavage of Boc groups (entry 8). From the crude mixture, **6** was isolated in 21% yield. On the other hand, 3-pyridyl zincate reacted smoothly to give a 50% yield of the desired product, though it required longer reaction time due to low solubility of the zincate (entry 9).

In summary, we have developed a synthetic strategy that enables quick and high yield access to a variety of 4,4′-bisaryl-BBIs. These BBIs will be useful as building blocks for functionalized supramolecular assemblies. Metal complexation, luminescence studies, and assembly construction of these BBIs are currently under investigation.

Acknowledgment. We express our gratitude to Dr. Anthony Linden (Organic Chemistry Institute, University of Zurich) for the X-ray crystal structure determination of **1**. Y.Y. thanks the Uehara foundation and the Legerlotz Stiftung for a postdoctoral fellowship.

Supporting Information Available: Detailed experimental procedures and characterization data of all new compounds. The crystal structure for compound **1** and cif data. This material is available free of charge via the Internet at http://pubs.acs.org.

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