An efficient route to biaryl bisbenzocyclobutene monomers based on Suzuki coupling reaction at room temperature

Jun-xiao Yang[a], Kuo-yan Ma[a], Fang-hua Zhu[a], Wen Chen[a], Bo Li[b], Lin Zhang[b] and Ru-gang Xie[a]*

[a]*Department of Chemistry, Sichuan University, Chengdu 610064, P. R. China*

[b]*China Academy of Engineering Physics, Mianyang, Sichuan 621900, P. R. China*

An efficient and practical preparation of the bisbenzocyclobutene monomers has been developed via the room temperature Suzuki couplings of phenyl-1, 4-diboronic ester with 4-bromobenzocyclobutene or benzocyclobutene-4-boronic acid with aryl dibromides.

Keywords: benzocyclobutene, Suzuki coupling, room temperature

Benzocyclobutenes (BCBs) are a family of thermally polymerisable monomers for high-performance polymers, which have been widely used in the microelectronics industry because of their low dielectric constant, low dispersion factor, low water up-take, high thermal and chemical stability, and ease of processing.[1] Homopolymers and copolymers of aryl bridged bisbenzocyclobutene monomers (bisBCB) also exhibit excellent properties.[2] However, a practical method for the synthesis of bisBCB monomers in good yield has not been reported. In general, these monomers have been prepared via phosphine-catalysed cross-coupling reactions of aryl dihalides with Grignard reagents of 4-bromobenzocyclobutene (4-BrBCB **2**) in very low yields (about 20–30 %).[2a-c] Products from 4-BrBCB are difficult to obtain on a large scale,[3] which makes it necessary to find an efficient route to these bisBCB monomers.

Suzuki cross-coupling is one of the most efficient methods for the carbon–carbon bond formation in biaryls.[4] In principle, this approach could provide an alternative strategy to bisBCB monomers from the cross-coupling of aryl diboronic acids (esters) with aryl halides or aryl boronic acids with aryl dihalides. To the best of our knowledge, no synthetic method for bisBCB monomers based on Suzuki couplings has been reported. Usually, effective Suzuki coupling reactions require phosphine or amine palladium complexes as catalyst precursors or high temperatures. Recently, some methodologies conducted without ligands or (and) at room temperature have been developed.[5] Our current interest has been focused on ligand-free catalysed C–C and C–N bond formation reactions. Very recently, our group reported a particularly effective simple copper salt catalysed *N*-arylation from arylboronic acids.[6] Herein, we describe a simple, efficient and practical synthesis of bisBCB monomers in one pot from 4-BrBCB or benzocyclobutene-4-boronic acid (4-BBCB, **4**) by employing ligand-free Suzuki couplings in the presence of a less-toxic solvent at room temperature.

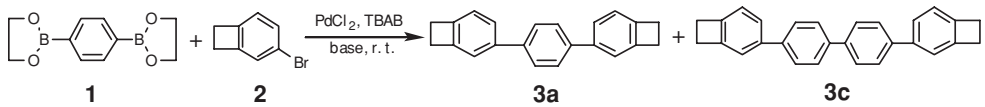
Generally, the related cross-coupling reactions of aryl diboronic acids or esters are limited to the use of more reactive aryl halides such as aryl iodides and aryl bromides with electron-withdrawing substituents,[7] presumably because diboronic acids or esters may be deboronated easily in the presence of relative strong bases. Recently, Chaumeil *et al.* reported that the cross-coupling between phenyl-1,4-diboronic acid bis-pinacol ester and electron-rich aryl bromides failed to the corresponding terphenyl, even in the presence of a phosphine ligand at reflux.[7b] Our initial exploration of reaction conditions focused on the coupling of phenyl-1,4-diboronic ester **1** with relatively unactivated 4-bromobenzocyclobutene **2** (Scheme 1).

Table 1 Synthesis of 1,4-bis (benzocyclobuten-4-yl) benzene **3a** using phenyl-1,4- diboronic ester **1** and 4-bromobenzocyclobutene **2**[a]

Entry	Solvent	Base	Yield/%[b]
1	Ethanol	$K_3PO_4{\cdot}3H_2O$	78
2[c]	Ethanol	$K_3PO_4{\cdot}3H_2O$	75
3[d]	Ethanol	$K_3PO_4{\cdot}3H_2O$	63
4	95% aqueous ethanol	$K_3PO_4{\cdot}3H_2O$	68
5	Toluene	$K_3PO_4{\cdot}3H_2O$	Trace
6	Toluene/H_2O [4/1 (v)]	$K_3PO_4{\cdot}3H_2O$	Trace
7	Ethanol	$Na_2HPO_4{\cdot}12H_2O$	No
8	Ethanol	Li_2CO_3	51
9	Ethanol	Na_2CO_3	57
10	Ethanol	$LiOH{\cdot}H_2O$	88
11	Ethanol	$Na_2B_4O_7{\cdot}10H_2O$	85
12	Ethanol	$Ba(OH)_2{\cdot}8H_2O$	71
13	Ethanol	NaOH	63

[a]Reaction conditions: 0.2 mmol of **1**, 0.46 mmol of **2**, 0.016 mmol of $PdCl_2$, 0.02 mmol of TBAB and 0.42 mmol of base in 10 ml of solvent at room temperature under N_2 for 16–22 h. [b]Isolated yield (average of two runs) based on **1**. [c]$Pd(OAc)_2$ as catalyst. [d]Phenyl-1,4-diboronic acid was used as substrate.

Firstly, we investigated this model reaction in the presence of $PdCl_2$/Bu_4NBr (TBAB)/K_2CO_3 by using THF/H_2O as solvent under N_2 atmosphere at reflux. Unfortunately, 1, 4-bis(benzocyclobuten-4-yl)benzene **3a** was obtained in a low yield (about 40%) and a significant amount of 4,4'-bis (benzocyclobuten-4-yl)biphenyl **3c** was isolated with a molar ratio of 1:4 to **3a.** However, it was gratifying to discover that the $PdCl_2$/TBAB/ethanol/$K_3PO_4{\cdot}3H_2O$ system effectively facilitated this cross-coupling to the expected bisBCB **3a** in 78 % yield at room temperature (Table 1, entry 1). $Pd(OAc)_2$ also proved to be an effective palladium precursor and afforded the desired **3a** in 75 % yield (entry 2). The yield of **3a** decreased to 68% in 95% aqueous ethanol (entry 4). When toluene was used as solvent, only a trace amount of cross-coupling product was obtained, even after extending periods of



1 **2** **3a** **3c**

Scheme 1

* Correspondent. E-mail: schemorg@mail.sc.cninfo.net

Table 2 Synthesis of biaryl bisBCB **3** using benzocyclobutene-4-boronic acid **4** and aryl dibromides **5** [a]

Entry	Br–Ar–Br **5**	Base	Time/h	Yield of **3**/%[b]
1	**5a**	$K_3PO_4·3H_2O$	6	**3a**, 92
2	**5b**	$K_3PO_4·3H_2O$	4	**3b**, 90
3	**5c**	$K_3PO4·3H_2O$	16	**3c**, 94
4	**5a**	Li_2CO_3	22	**3a**, 82
5	**5a**	Na_2CO_3	22	**3a**, 95
6	**5a**	$LiOH·H_2O$	6	**3a**, 98
7	**5b**	$LiOH·H_2O$	6	**3b**, 98
8	**5c**	$LiOH·H_2O$	8	**3c**, 95
9	**5a**	$Na_2B_4O_7·10H_2O$	6	**3a**, 98
10	**5b**	$Na_2B_4O_7·10H_2O$	3	**3b**, 98
11	**5c**	$Na_2B_4O_7·10H_2O$	8	**3c**, 98
12	**5a**	$Ba(OH)_2·8H_2O$	22	**3a**, 95

[a]Reaction conditions: 0.20 mmol of **5**, 0.42 mmol of **4**, 0.008 mmol of $PdCl_2$ (4 mol % to **5**), 0.02 mmol of TBAB (10 mol %) and 0.44 mmol of base (2.2 equiv) in 10 ml of ethanol at room temperature under N_2. [b]Isolated yield (average of two runs) based on **5**.

reaction (entries 5 and 6). In addition, the nature of the cation and the strength of base or the pH value of the reaction system have a significant effect on the product yield.[8] After screening a variety of bases (*e.g.*, $K_3PO_4·3H_2O$, $Na_2HPO_4·12H_2O$, Li_2CO_3, Na_2CO_3, $LiOH·H_2O$, $Na_2B_4O_7·10H_2O$, $Ba(OH)_2$ and NaOH), we found that $LiOH·H_2O$ and $Na_2B_4O_7·10H_2O$ gave the best results in 88% and 85% yields, respectively (entries 10 and 11).

One alternative strategy to bisBCB monomers is to use benzocyclobutene-4-boronic acid **4** (4-BBCB) and aryl dibromides (**5a–c**) as substrates (Scheme 2). As shown in Table 2, in most cases, the products were achieved in excellent yields under standard condition. After optimising the reaction conditions, we investigated the couplings of *p*-dibromobenzene, *m*-dibromobenzene and 4,4′-dibromobiphenyl with benzocyclobutene-4-boronic acid **4** and were pleased to find that all of them worked very well. We also examined a relatively large scale preparation (4-BBCB, 6.8 mmol) of these monomers using $Na_2B_4O_7·10H_2O$ as base and found that the products could be isolated with a quite simple procedure. After the mixture was poured into water, the precipitate could be collected by filtration, washed with water and purified by recrystallisation to afford excellent yields of **3a** (95%), **3b** (94%) and **3c** (94%).

Additionally, the conditions of the reaction were equally effective for the cross-coupling reaction of 4-BrBCB **2** with 4-BBCB **4**. Using $LiOH·H_2O$ or $Na_2B_4O_7·10H_2O$ as base, the corresponding cross-coupling product **6** was afforded almost exclusively in 92% and 96% yields, respectively (Scheme 3).

In summary, we have developed the practical preparation of bisbenzocyclobutene monomers via an efficient ligand-free Suzuki coupling under very mild reaction conditions and simple procedures. The reaction comprising a simple palladium salt, inorganic base and less-toxic solvent gave excellent yields. The protocol can be applicable in a relatively large scale and open a new door to the practical preparation of bisbenzocyclobutene monomers. The study of polymer properties will be reported elsewhere.

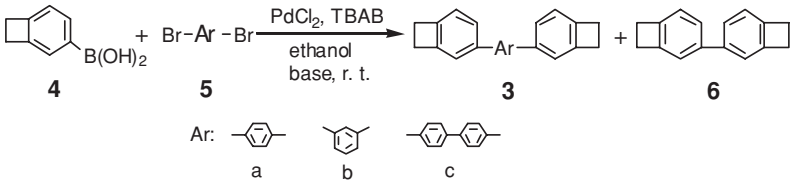
Experimental

THF was freshly distilled from sodium/benzophenone. Ethanol was refluxed under N_2 atmosphere for 2–3 hours and distilled under N_2. *p*-Dibromobenzene, *m*-dibromobenzene and 4, 4'-dibromobiphenyl were purchased from the Acros Company. Benzocyclobutene and 4-bromobenzocyclobutene were prepared according to literature procedures.[3] Phenyl-1,4-diboronic acid was prepared according to literature procedures.[9] All the bases and the other reagents were commercially available and used without further treatment. Melting points were taken on a micro-melting point apparatus (uncorrected). IR spectra were obtained with a Perkin-Elmer 16 PC FIT- IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Unity Varian INOVA-400/54 or an Avance Bruker-300 instrument and chemical shifts in ppm reported with TMS as the internal standard. Mass spectra were measured on a Finnigan MAT4510 instrument. Elemental analyses were performed on a Carlo Erba 1106 instrument.

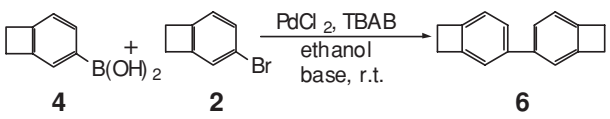
Synthesis of phenyl-1,4-diboronic ethylene glycol ester **1**[10]: Phenyl-1,4-diboronic acid (10 g, 60.2 mmol) was suspended in 250 ml of toluene and 180 mmol (11.2 g) of ethylene glycol was added. The mixture was stirred and refluxed for 2 h and then about 125 ml azeotrope of toluene and water was distilled out. The reaction mixture was cooled and the solvent was removed. The residue was recrystallised from toluene to provide the diboronic ester as colourless crystal. Yield: 96%. m.p. (decon position) 160–164 °C; ^{1}H NMR (400MHz, DMSO–d_6): 4.33 (s, 8H, CH_2CH_2), 7.74 (s, 4H, ArH).

Synthesis of benzocyclobutene-4-boronic acid **4**: The Grignard reagent from 4-bromobenzocyclobutene (6.00 g, 33 mmol), magnesium (0.99 g, 41 mmol) and THF (30 ml) was added by a syringe during 2 h to a solution of trimethyl borate (5.62 ml, 49.5 mmol) in dry THF (40 ml) at –78 °C. The mixture was stirred for 2 h at –78 °C, then the temperature was slowly elevated to room temperature and kept at that value for 2 days. The mixture was then diluted with ether (100 ml) and added to a stirred mixture of crushed ice (150 g) and concentrated sulfuric acid (2 ml). The addition of ether (150 ml) and water (100 ml) facilitate the separation of the organic and the aqueous layers. The aqueous layers were extracted repeatedly with ether (3 × 150 ml) and the combined organic phase was evaporated on a water-bath. The residue was washed with petroleum ether (60–90 °C, 100 ml) and dried at 100 °C for 2 h and afforded the crude product (slightly yellow solid) 4.15 g. Further recrystallisation from water gave white solid or white needle crystals 3.56 g. Yield: 73%. m.p. >220 °C; MS (*m/z*, %): 148 (100). ^{1}H NMR (400MHz, DMSO-d_6): 3.13 (s, 4H, CH_2CH_2), 7.04 (d, 1H, *J*=6.8 Hz, ArH). 7.48 (s, 1H, ArH), 7.65 (d, 1H, *J*=7.2 Hz, ArH), 7.89 (s, 2H, B-OH). Elemental analysis was believed to be thworted by ease of dehydration.[9,11]

General procedure for the coupling reaction: A mixture of phenyl-1,4-diboronic acid or ester (0.2 mmol), 4-BrBCB (85 mg, 0.46 mmol), TBAB (0.02 mmol) and $PdCl_2$ (0.016 mmol) in 10 ml of ethanol was stirred for 30–60 min under N_2 at room temperature.



Scheme 2



Scheme 3

The base (solid, 0.42 mmol) was then added and the mixture was stirred vigorously for 16–22 hours. The reaction mixture was poured into 15 ml of water and then extracted with $CHCl_3$ (3 × 20 ml). The combined organic phase was washed with 30 ml of water and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a grey-white solid, which could be purified by chromatography on silica gel using petroleum ether (60–90 °C) as eluent to recover excess 4-BrBCB first, then using a mixture of petroleum ether: toluene [25:1 (v)] to afford colourless needle crystals **3a**. The products were characterised by MS, ^{1}H NMR and element analysis.

1,4-bis(benzocyclobuten-4-yl)benzene **3a**: m.p. 171–172 °C (Lit. 170 °C)[2d]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (s, 8 H, CH_2CH_2), 7.15 (d, 2 H, *J*= 7.6 Hz, ArH), 7.33 (s, 2 H, ArH), 7.47 (d, 2 H, *J*= 7.6 Hz, ArH), 7.61 (s, 4 H, ArH). MS (*m/z*, %): 282 (M^+, 100). Anal. Calcd. For $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.5; H, 6.4.

1,3-bis(benzocyclobuten-4-yl)benzene **3b**: m.p. 95–96 °C (Lit. 94.5–96 °C)[2c]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (s, 8 H, CH_2CH_2), 7.14 (d, 2H, *J*= 7.6 Hz, ArH), 7.33 (s, 2 H, ArH), 7.57 (m, 5 H, ArH), 7.71 (s, 1 H, ArH). MS (*m/z*, %): 282 (M^+, 100). Anal. Calcd. For $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.5; H, 6.3.

4,4′-bis(benzocyclobuten-4-yl)biphenyl **3c**: Melting at 229 °C and polymerising (detected by DSC). IR (KBr): 2923, 1500, 1455, 1425, 1296, 1230, 1206, 1004, 888, 814. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (s, 8 H, CH_2CH_2), 7.14 (d, 2H, *J*= 7.6 Hz, ArH), 7.33 (s, 2 H, ArH), 7.47 (d, 2 H, *J*= 7.6 Hz, ArH), 7.70 (d, 4 H, *J*=8.1 Hz, ArH), 7.63 (d, 4 H, *J*= 8.3 Hz, ArH). ^{13}C NMR (300 MHz, $CDCl_3$) δ_c: 29.46, 29.52, 121.46, 122.84, 126.05, 127.29, 127.68, 139.25, 139.84, 141.32, 145.11, 146.35 ppm. MS (*m/z*, %): 358 (M^+, 100). Anal. Calcd. For $C_{28}H_{22}$: C, 93.8; H, 6.2. Found: C, 93.7; H, 6.3.

4,4′-bisbenzocyclobutene **6**: m.p. 61–62 °C (Lit. 62 °C)[2d]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (s, 8 H, CH_2CH_2), 7.12 (d, 2 H, *J*=7.7 Hz, ArH), 7.24 (s, 2H, ArH), 7.38 (dd, 2H, *J*= 7.5 and 1.3 Hz, ArH). MS (*m/z*, %): 206 (M^+, 100). Anal. Calcd. For $C_{16}H_{14}$: C, 93.2; H, 6.8. Found: C, 92.8; H, 6.7.

The authors are grateful to the Education Ministry of China and the National Natural Science Foundation of China for grant support.

Received 16 November 2004; accepted 6 January 2005
Paper 04/2875

References

1 (a) R.A. Kirchhoff and K.J. Bruza, *Prog. Polym. Sci.,* 1993, **18**, 85; (b) M.F. Farona, *Prog. Polym. Sci.*, 1996, **21**, 505.
2 (a) L.S. Corley and P.K. Wong, U.S. Patent 5157105, 1992; (b) L.S. Corley, U.S. Patent 5032451, 1991; (c) L.S. Corley, U.S. Patent 4973636, 1990; (d) H.Y. Toride, H.A. Yokohama and T.I. Yokohama et al, U.S. Patent 5388328, 1995.
3 (a) P. Schiess, S. Rutschmann and V.V. Toan, *Tetrahedron Lett.,* 1982, **23**, 3669; (b) J.B.F. Lloyd and P.A. Ongley, *Tetrahedron,* 1965, **21**, 245.
4 (a) N. Miyaura and A. Suzuki, *Chem. Rev.,* 1995, **95**, 2457; (b) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, and M. Lemaire, *Chem. Rev.,* 2002, **102,** 1359.
5 (a) E.M. Campi, W.R. Jackson, S.M. Marcuccio and C.G.M. Naeslund, *J. Chem. Soc., Chem. Commun.,* 1994, 2395; (b) F.E. Goodson, T.I. Wallow and B.M. Novak, *Organic synthesis,* 1997, **75**, 61; (c) Y. Li, X.M. Hong, D.M. Collard and M.A. EI-Sayed, *Org. Lett.,* 2000, **2**, 2385; (d) A.F. Littke, C.Y. Dai and G.C. Fu, *J. Am. Chem. Soc.,* 2000, **122**, 4020; (e) D.W. Old, J.P. Wolfe and S.L. Buchwald, *J. Am. Chem. Soc.,* 1998, **120**, 9722; (f) D. Zim, A.S. Gruber, G. Ebeling, J. Dupont and A.L. Monteiro, *Org. Lett.,* 2000, **2**, 2881; (g) J.C. Anderson, H. Namli and C.A. Roberts, *Tetrahedron,* 1997, **53**, 15123.
6 (a) J.B. Lan; L. Chen, X.Q. Yu, J.S.You and R.G. Xie, *Chem. Commun.,* 2004, 188; (b) J.B. Lan, G.L. Zhang, X.Q. Yu, J.S. You, L. Chen, M. Yan and R.G. Xie, *Synlett,* 2004, 1095.
7 (a) M.H. Todd, S. Balasubramanian and C. Abell, *Tetrahedron Lett.,* 1997, **38**, 6781; (b) H. Chaumeil, C. Le-Drian and A. Defoin, *Synthesis,* 2002, 757; (c) E.G. Ijpeij, F.H. Beijer, H.J. Arts, C. Newton, J.G. De Vries and G.–J.M. Gruter, *J. Org. Chem.,* 2002, **67**, 169.
8 H. Chaumeil, S. Signorrella and C. Le-Drian, *Tetrahedron,* 2000, **56**, 9655; (b) T. I. Wallow and B.M. Novak, *J. Org. Chem.,* 1994, **59**, 5034.
9 I.G.C. Coutts, H.R. Goldschmid and O.C. Musgrave, *J. Chem. Soc.(C),* 1970, 488.
10 P.W. Edmynd, I. Michael, R.S. William, R.R. Garden, T.B. Mark and W. Wu, U.S. Patent 6169163, 2001.
11 P. Linnane, T.D. James, S. Imazu and S. Shinkai, *Tetrahedron Lett.,* 1995, **36**, 8833.