Bi Reagents for C-C Cross-Coupling

5,6,7,12-Tetrahydrodibenz[*c,f*][1,5]azabismocines: Highly Reactive and Recoverable Organobismuth Reagents for Cross-Coupling Reactions with Aryl Bromides**

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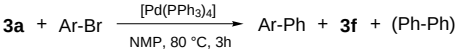
Transition-metal-catalyzed cross-coupling reactions of organometallic reagents, such as organotin, -boron, -silicon, -zinc, and -magnesium compounds, with organic halides and triflates is one of the most powerful methods to form C–C bonds.[1] Recently, tremendous effort has been devoted to the improvement of efficiency and applicability of the cross-coupling reaction by the development of highly active catalyst systems as well as by the modification of the structure of the organometallic reagents.[2] We believe that another important direction of research should be to explore the applicability of other organometallic reagents, which would broaden the scope of the cross-coupling methodology. Recently, organoindium,[3] -manganese,[4] and -titanium[5] compounds have been disclosed to be useful.

Bismuth is a nontoxic element[6] and its organic compounds are potentially useful, low-toxicity reagents for organic synthesis.[7] We have demonstrated that the organobismuth compounds 2,6-Py$(CR_2O)_2BiR^1$ (**1**: R^1 = Ph or Me, R = alkyl) and Ar_3Bi (**2**) can be utilized for the cross-coupling reaction with organic electrophiles such as bromides, iodides, and triflates catalyzed by a palladium complex.[8] However, compounds **1** and **2** suffer from a drawback in that their applicability has considerable limitation. In particular, they do not couple with electron-rich substrates efficiently, even in the presence of stoichiometric amounts of activators. Herein we report that the readily obtainable hypervalent organobismuth compounds, 5,6,7,12-tetrahydrodibenz[*c,f*][1,5]azabismocine derivatives **3a**–**3e**, can couple with electron-deficient, electron-neutral, and even electron-rich aryl bromides efficiently in the absence of any additional activator by using a simple commercially available Pd catalyst, $[Pd(PPh_3)_4]$. There are additional advantages to reagents **3a**–**3e**: 1) Selective one-pot multicoupling reactions by the combination of compounds **3a**–**3e** and bromophenylboronic esters enabled the construction of up to nine bonds in good yields in one pot. 2) Bismuth compounds, such as bromide **3f** and chloride **3g**, are recovered almost quantitatively after the reaction and can be reused as the precursors to **3a**–**3e**.



In the cross-coupling reactions with **1** and **2**, yields were highly dependent on the electronic nature of the organic electrophiles. Additives such as K_2CO_3, Cs_2CO_3, and CsF considerably improved the reactivities of **1** and **2**. Nevertheless, the reactions of **1** and **2** with electron-rich substrates were not satisfactory. We assumed that the reactivity enhancement by the additives was derived from the formation of the "ate complex", electron-rich, higher-coordinated reactive species by coordination of the anionic part of the additives to the bismuth center. Accordingly electron-rich, hypervalent organobismuth compounds are expected to be more reactive than **1** and **2**.

The synthesis and structure of 6-methyl-5,6,7,12-tetrahydrodibenz[*c,f*][1,5]azabismocine derivatives **4** were reported by Akiba and co-workers.[9] We introduced a *t*Bu group in place of the methyl group on the N atom to increase the

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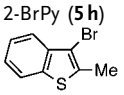
electron-donating ability of the N atom and to protect the N atom from being involved in undesirable side reactions by the steric bulk of the *t*Bu group. Similarly to the synthesis of **4**,[9] compound **3g** was prepared by the reaction of $BiCl_3$ with $(2\text{-}LiC_6H_4CH_2)_2tBuN$, which was generated in situ by the lithiation of $(2\text{-}BrC_6H_4CH_2)_2tBuN$ with *n*BuLi.[10] A third organic group was introduced at the bismuth atom by the reaction of **3g** with organolithium or Grignard reagents.[9,11]

The cross-coupling reaction of **3a** with 1-bromonaphthalene **5a** proceeded smoothly in the absence of any additives to give 1-phenylnaphthalene quantitatively (NMP, 80 °C, 3 h, $[Pd(PPh_3)_4]$ (2 mol %); Table 1, entry 1). The same reaction of

Table 1: Cross-coupling reaction of **3a** with aryl bromides.[a]

3a + Ar-Br $\xrightarrow[\text{NMP, 80 °C, 3h}]{[Pd(PPh_3)_4]}$ Ar-Ph + **3f** + (Ph-Ph)

Entry	ArBr[b]	$[Pd(PPh_3)_4]$ [mol %]	Ar-Ph [%][c]	Ph-Ph [%][d]
1	1-BrNpt (**5a**)	2	97(100)	3
2	**5a**	0.5	(98)	4
3	2-BrAnt (**5b**)	2	91	nd[e]
4	$4\text{-}AcC_6H_4Br$ (**5c**)	2	97	3
5	$4\text{-}NCC_6H_4Br$ (**5d**)	2	91	9
6	$4\text{-}MeC_6H_4Br$ (**5e**)	10	89	6
7	$4\text{-}MeOC_6H_4Br$ (**5f**)	10	93	5
8	$4\text{-}Me_2NC_6H_4Br$ (**5g**)	10	76	nd[e]
9[f]	2-BrPy (**5h**)	2	86(93)	2
10[g]	 (**5i**)	10	74	0

[a] **3a** (0.30 mmol), ArBr (0.25 mmol), 1-methyl-2-pyrrolidinone (NMP; 3 mL). [b] Nap = naphthalene, Ant = anthracene, Py = pyridine. [c] Yield of isolated product based on ArBr. Yields determined by GC with *n*-hexadecane as an internal standard are shown in parentheses. [d] Yield determined by GC based on **3a**. [e] Not determined. [f] Reaction time: 6 h. [g] Reaction time: 10 h.

$2,6\text{-}Py(CMe_2O)_2BiPh$ and Ph_3Bi with **5a** under similar reaction conditions produced 1-phenylnaphthalene only in 15 % and 2 % yields, respectively, in the absence of additives and in 88 % and 76 % yields in the presence of Cs_2CO_3 (2 equiv) and CsF (8 equiv), respectively.[8b,c] The performance of compound **3a** clearly seen in Table 1 can be summarized as follows. All electron-deficient, electron-neutral, and even electron-rich aryl bromides smoothly reacted in the presence of $[Pd(PPh_3)_4]$ as a catalyst without any additives. Sterically hindered substrate **5i**, which has a Me group at the position adjacent to Br, also gave the cross-coupled product in a good yield although a longer reaction time was required (Table 1, entry 10). The amount of catalyst can be decreased to 0.5 mol % as shown in the reaction of **5a** (Table 1, entry 2). In most cases, a small amount of biphenyl was also formed as a by-product (Table 1).

The reactivity of azabismocines **3** with a substituted aryl or alkenyl group toward aryl bromides is summarized in Table 2. Electron-deficient and -rich aryl bismuth compounds **3b**–**3d** as well as isopropenylbismuth compound **3e** efficiently reacted with electron-deficient, -neutral, and -rich aryl bromides **5d, 5a** and **5f**. Notably, sterically demanding **3d**,

Table 2: Cross-coupling reaction of **3b**–**3e** with aryl bromides.[a]

3b – 3e + Ar-Br $\xrightarrow[\text{NMP, 80 °C, 3h}]{[Pd(PPh_3)_4]}$ Ar-R + **3f** + (R-R)

Entry	**3**	ArBr	$[Pd(PPh_3)_4]$ [mol %]	Ar-R [%][b]	R-R [%][c]
1	**3b**	**5d**	2	87	8
2		**5a**	5	96	3
3		**5f**	10	87	3
4	**3c**	**5d**	2	91	4
5		**5a**	10	93	nd[d]
6		**5f**	10	91	11
7[e]	**3d**	**5a**	2	87	0
8[e]		**5f**	10	78	0
9	**3e**	**5d**	5	90	nd[d]
10		**5a**	5	80	nd[d]
11		**5f**	5	81	nd[d]

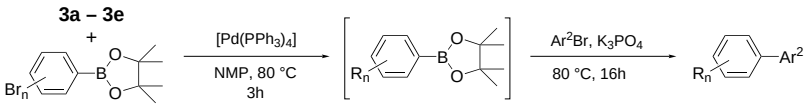
[a] **3b**–**3e** (0.30 mmol), ArBr (0.25 mmol), NMP (3 mL). [b] Yield of isolated product based on ArBr. [c] Approximate values based on **3b**–**3e** calculated from relative peak intensities of Ar-R and R-R by GC analysis. [d] Not determined. [e] Reaction time: 5 h.

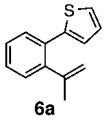
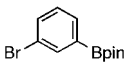
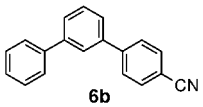
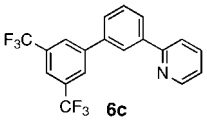
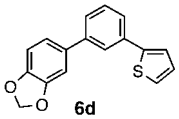
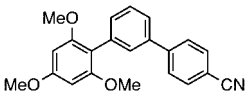
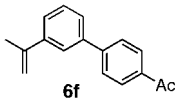
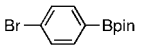
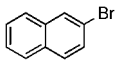
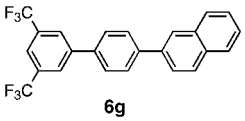
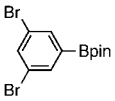
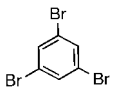
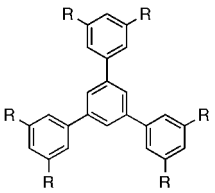
which has two OMe groups *ortho* to the Bi substituent on R, gave the products in good yields, although a slightly longer reaction time was required (Table 2, entries 7–8). As observed in the reaction of **3a** with ArBr, small amounts of self-coupling products of **3b** and **3c**, $(3,5\text{-}(CF_3)_2C_6H_3\text{-})_2$ and $(3,4\text{-}(CH_2O_2)C_6H_3\text{-})_2$, respectively, were also formed, whereas that of **3d** was not observed probably because of the steric bulk of the $2,4,6\text{-}(MeO)_3C_6H_2\text{-}$ group.[12]

After the reaction, the bismuth compound can be recovered almost quantitatively as bromide **3f** or chloride **3g**, which are the precursors for **3a**–**3e**. During the cross-coupling reaction, **3a**–**3e** were converted into bromide **3f**. Since 1.2 equivalents of **3a**–**3e** were used, small quantities of the starting compounds remained unreacted after the reaction. By the aqueous workup with dilute HCl solution, both **3f** and unreacted **3a**–**3e** are quantitatively converted into **3g**. If HBr solution is used instead of HCl solution, the bismuth species can be recovered as bromide **3f**. Both **3f** and **3g** are stable to air and neutral or acidic aqueous conditions.[13] Isolation of **3f** or **3g** from the crude mixture can be performed by solvent extraction of the cross-coupling product,[14] recrystallization, chromatographic separation, or a combination of these methods.

By invoking the difference in the protocols of the new cross-coupling with the bismuth reagents and the well-established Suzuki–Miyaura coupling with aryl boronic acids and esters,[1,15] a one pot multicoupling reaction is readily realized. Generally the latter palladium-catalyzed cross-coupling reaction of aryl boronic compounds with organic halides and triflates requires a base as an activator, whereas the cross-coupling reaction of **3a**–**3e** does not require any additional activators. Accordingly **3a**–**3e** can selectively couple with bromophenylboronic esters without self-condensation of the latter to leave the boronic ester moiety intact. Subsequent addition of a second aryl halide and a base activator affords multicoupling products in one pot as shown in Table 3. All *o*-, *m*-, and *p*-bromophenylboronic esters efficiently underwent cross-coupling in this one-pot

Table 3: One-pot multicoupling reaction of **3a**–**3e** with bromophenylboronic esters and aryl bromides.[a]



Entry	3	BrArBpin[b]	Ar^2Br	Product	Yield[%][c]
1[d,e]	**3e**			 **6a**	75
2[d]	**3a**		**5d**	 **6b**	84
3[d]	**3b**		**5h**	 **6c**	76
4[d]	**3c**			 **6d**	89
5[d,f]	**3d**		**5d**	 **6e**	72
6[d]	**3e**		**5c**	 **6f**	74
7[g]	**3b**			 **6g**	87
8[e,h]	**3b**			 **7a**: R = 3,5-$(CF_3)_2C_6H_3$ **7b**: R = CH_2=C(Me)−	74[i]
9[h]	**3e**				60[i]

[a] See Supporting Information for details of the reaction procedures. [b] pin = -$OCMe_2CMe_2O$-. [c] Yield of isolated product based on bromophenylboronic esters. [d] Bi/B/Pd/ArBr/K_3PO_4 = 1.1:1.0:0.1:1.1:1.5. [e] Reaction time for the first step: 8 h. [f] Reaction time for the first step: 5 h. [g] Bi/B/Pd/ArBr/K_3PO_4 = 1.1:1.0:0.1:1.5:1.5. Reaction time for the second step: 32 h. [h] Bi/B/Pd/ArBr/K_3PO_4 = 6.7:3.3:0.66:1.0:10. [i] Yield of isolated product based on 1,3,5-tribromobenzene.

synthesis and compounds **6a**–**6g** were obtained in good yields.[16] By using 3,5-dibromophenylboronic ester and 1,3,5-tribromobenzene, nine bonds were efficiently constructed in one pot to give **7a** and **7b** in good yields.[17,18] In all cases except Table 3, entry 5, the first step was nearly quantitative, as judged by GC analysis. The second step, which was performed under typical conditions for the Suzuki–Miyaura reaction, remains to be optimized for further improvement of the yields.

In summary, we have reported that 5,6,7,12-tetrahydrodibenz[*c*,*f*][1,5]azabismocine derivatives **3a**–**3e** are highly efficient and recoverable reagents for the cross-coupling reaction with aryl bromides. Further studies to clarify the scope and the mechanistic aspect of this reaction are underway.

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[11] Compounds **3a**–**3g** were purified by recrystallization and are thermally stable at least up to 110 °C. Compounds **3a, 3b, 3f**, and **3g** also can be purified by silica-gel column chromatography, whereas **3d** seems to decompose by column chromatography on silica gel or alumina. Detail of the synthesis, structure, and some properties of **3a**–**3g** will be reported elsewhere.

[12] In the reaction of **3b** and **3d** with 4-bromoanisole, 3,5-$(CF_3)_2C_6H_3$-Ph and 2,4,6-$(MeO)_3C_6H_2$-Ph were also obtained as a by-product in 4% and 21% yields, respectively. The phenyl group of the by-products probably came from PPh_3 as observed in the related cross-coupling reaction; see: B. E. Segelstein, T. W. Butler, B. L. Chenard, *J. Org. Chem.* **1995**, *60*, 12 – 13.

[13] For example, **3g** was quantitatively recovered when it was stirred in a 1:1 mixture of CH_2Cl_2/1M aqueous HCl at room temperature for 10 h. However, the recovery of **3g** decreased to 70% when it was stirred in a 1:1 mixture of CH_2Cl_2/4M aqueous HCl at room temperature for 2 days.

[14] For an experimental procedure, see Supporting Information.

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[16] Since a slight excess of **3a**–**3e** and Ar^2Br was used, small amounts of direct coupling products between **3a**–**3e** and Ar^2Br were also formed.

[17] Similar compounds have been prepared by multistep procedures: T. M. Miller, T. X. Neenan, R. Zayas, H. E. Bair, *J. Am. Chem. Soc.* **1992**, *114*, 1018 – 1025.

[18] The molecular structure of **7a** was unambiguously confirmed by X-ray analysis. See the Supporting Information for the crystal data as well as a molecular drawing of **7a**. CCDC-192709 (**7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

