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Facile synthesis of multisubstituted buta-1,3-dienes *via* Suzuki–Miyaura and Kumada cross-coupling strategy of 2,4-diiodo-buta-1-enes with arylboronic acids and Grignard reagents†

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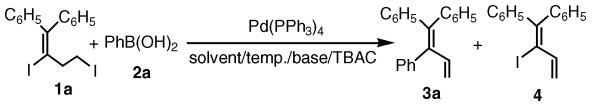
One-pot Suzuki–Miyaura-type and Kumada-type cross-coupling reactions of 2,4-diiodo-buta-1-enes with arylboronic acids and alkyl/aryl magnesium bromides were carried out in the presence of accessibly simple catalysts under mild conditions. As a result, some 1,1,2-trisubstituted buta-1,3-dienes were obtained including the Tamoxifen-type, which have potential adjuvant therapy in women who have suffered from breast cancer and cyclooxygenase-2-type (COX-2-type) inhibitors, some of which have been proved to elicit efficient anti-inflammatory analgesic activities and less adverse gastrointestinal side effects and to be very useful in the prophylactic treatment of a wide variety of cancers and neurodegenerative disorders.

Conjugated dienes constitute an important functionality among organic compounds and are widely distributed among natural products.[1–11] In recent years, they have emerged as a distinct class by themselves due to their increasing utility in organic synthesis and also due to their interesting physical properties. Dienes have attracted a great deal of attention as they exhibit exceptional reactivity in cycloadditions and electrocyclic reactions. The most common use of dienes is in Diels–Alder reactions (both inter- and intramolecular) and in thermal and photochemical reorganization to furnish diverse carbo- and heterocyclic frameworks, which find application in synthesis of natural products and non-natural products.[12] In view of such diverse applications and future potential, newer synthetic methods for assembling dienes under mild and efficient reaction conditions are being continually explored. Indeed, in the last few years, synthetic activity directed towards these substrates has witnessed explosive growth,[13] in which transition metal-catalyzed carbon–carbon bond-forming reactions are one of the most important reactions.[14] As part of our program on the transformation of 2,4-diiodo-buta-1-enes derived from the ring-opening of methylenecyclopropanes (MCPs) with iodine,[15] we have synthesized some cross-conjugated products in moderate to high yields *via* a Heck-type reaction[16–18] under simple conditions.[19] In fact, 2,4-dihalobutenes have attracted considerable attention because of their versatility as a building block or starting substrate in organic synthesis[20] and in the pharmaceutical industries.[21] In order to consummate the transformation of the corresponding diiodides, we also carried out the Suzuki–Miyaura-type reaction[22] and Kumada-type reaction[23] in which some multisubstituted buta-1,3-dienes, including the 1,1,2-triarylsubstituted buta-1,3-dienes which are mimics of Tamoxifen[24] having potential adjuvant therapy in women who have suffered from breast cancer and cyclooxygenase-2-type (COX-2-type) inhibitors,[25] some of which have been proved to elicit efficient anti-inflammatory analgesic activities and less adverse gastrointestinal side effects[26–27] and to be very useful in the prophylactic treatment of a wide variety of cancers and neurodegenerative disorders,[28] can be obtained conveniently. Herein we wish to report the results in detail.

Firstly, we carried out the typical Suzuki–Miyaura-type cross-coupling reactions of diiodides **1** with some arylboronic acids **2** in the presence of a palladium catalyst. For our optimization studies, we chose to focus on the Suzuki–Miyaura coupling reaction of 1,1-diphenyl-2,4-diiodo-buta-1-ene **1a** (0.25 mmol) with phenylboronic acid **2a** (0.30 mmol) in the presence of $Pd(PPh_3)_4$ catalyst (0.025 mmol) and various bases and solvents. Parts of these results are summarized in Table 1. After several trials and errors, we were pleased to find out that the reaction of **1a** with **2a** in a mixed solvent of THF–H_2O (3 : 1) under reflux in the presence of KOH as a base proceeded smoothly to give the coupling product **3a** in 82% yield as the sole product (Table 1, entry 7). Coupling product **3a** was also obtained in somewhat lower yields, either in the case of K_2CO_3–Ag_2O, Cs_2CO_3–Ag_2O as the base (Table 1, entries 5 and 6) or in the combination of other solvents such as DME–H_2O, toluene–H_2O, DMF–H_2O, benzene–H_2O, 1,4-dioxane–H_2O (Table 1, entries 10–14). In the presence of other bases such as K_2CO_3, $NaHCO_3$, K_3PO_4, KF, CsOH, CsF, the coupling product **3a** was obtained in much

Table 1 Suzuki–Miyaura-type reaction of **1a** (0.25 mmol) with **2a** (0.30 mmol) under different reaction conditions



Entry[a]	Solvent	Base[b]	Temp./Time	Yield (%)[c] 3a	4
1	THF–H_2O	K_2CO_3	Reflux/24 h	27	29
2	THF–H_2O	$NaHCO_3$	Reflux/24 h	11	23
3	THF–H_2O	K_3PO_4	Reflux/24 h	30	35
4	THF–H_2O	KF	Reflux/24 h	71	17
5	THF–H_2O	K_2CO_3–Ag_2O[d]	Reflux/24 h	47	—
6	THF–H_2O	Cs_2CO_3–Ag_2O[d]	Reflux/24 h	50	—
7	THF–H_2O	KOH	Reflux/58 h	82	—
8	THF–H_2O	CsOH	Reflux/32 h	21	31
9	THF–H_2O	CsF	Reflux/32 h	—	22
10	DME–H_2O	KOH	Reflux/58 h	68	—
11	Toluene–H_2O	KOH	100 °C/48 h	67	—
12	DMF–H_2O	KOH	100 °C/48 h	17	—
13	Benzene–H_2O	KOH	Reflux/58 h	75	—
14	Dioxane–H_2O	KOH	100 °C/58 h	65	—

[a] Tetrabutylammonium chloride (TBAC) (0.25 mmol) as the additive. [b] Otherwise specified, 1.2 mmol base was used. [c] Isolated yields. [d] M_2CO_3–Ag_2O (1.2 mmol–0.3 mmol).

† Electronic supplementary information (ESI) available: Spectroscopic data (^1H, ^{13}C, and NOESY NMR spectra data), HRMS for all the new compounds and detailed descriptions of the experimental procedures. See http://www.rsc.org/suppdata/ob/b5/b504071j/

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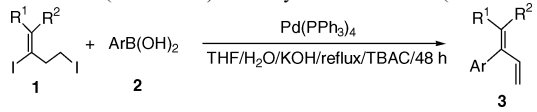
Table 2 Suzuki–Miyaura-type reaction of diiodides **1** (0.25 mmol) with arylboronic acids **2** (0.30 mmol) under the optimized conditions



Entry	Diiodides **1** (R^1/R^2)	**2**, Ar	Yield (%)[a]
1	**1a** (C_6H_5/C_6H_5)	**2b** (p-ClC_6H_4)	**3b**, 72
2	**1a**	**2c** (p-$CH_3C_6H_4$)	**3c**, 68
3	**1a**	**2d** (o-$CH_3C_6H_4$)	**3d**, 99
4	**1a**	**2e** (2-Benzo[1,3]dioxol-5-yl)	**3e**, 70
5	**1b** (p-$MeOC_6H_4/C_6H_5$)[b]	**2a** (C_6H_5)	**3f**, 88 (1 : 1)[c]
6	**1c** (p-MeC_6H_4/p-MeC_6H_4)	**2c**	**3g**, 67
7	**1c**	**2a**	**3h**, 70
8	**1c**	**2d**	**3i**, 78
9	**1c**	**2e**	**3j**, 70
10	**1d** (p-ClC_6H_4/p-ClC_6H_4)	**2b**	**3k**, 83
11	**1d**	**2a**	**3l**, 82
12	**1d**	**2c**	**3m**, 75
13	**1d**	**2d**	**3n**, 77
14	**1d**	**2e**	**3o**, 73
15	**1e** (C_6H_3/H)[d]	**2a**	**3p**, 79
16	**1f** (Me/p-$EtOC_6H_4$)[e]	**2a**	**3q**, 85
17	**1g** (p-$CH_3OC_6H_4$/H)[d]	**2a**	**3r**, 59

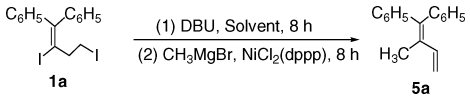
[a] Isolated yields. [b] $E : Z = 1 : 1$. [c] $E : Z$ ratio [d] **1e** and **1g** were used as Z-isomer (Supporting Information†).[33] [e] **1f** were used as E-isomer (Supporting Information†)

lower yields along with the uncoupled product **4** in most cases (Table 1, entries 1–4, 8, 9).

To survey the generality of this transformation, we next investigated the reaction using other diiodides **1** and a variety of arylboronic acids **2** under the optimized conditions. The results are summarized in Table 2. As can be seen from Table 2, for the diaryl substituted substrate **1**, the reactions proceeded smoothly to give the corresponding 1,1,2-triaryl-buta-1,3-dienes **3b–o** in good to high yields (Table 2, entries 1–14). The substituents on the benzene ring of diiodides **1** and arylboronic acids **2** did not significantly affect the yields of the coupling products, namely, the reaction could tolerate various functional groups for the synthesis of the skeleton of 1,1,2-triaryl-buta-1,3-dienes. It should be noted that these triaryl substituted buta-1,3-dienes have a core structure of triarylethylene many of which have been tested with regard to their mammary tumor inhibiting properties.[29] Tamoxifen, which is now widely used for the treatment of advanced breast cancer, also can be synthesized from product **3f** in a shorter way.[30–32] For the unsymmetrical disubstituted diiodides **1** (one is hydrogen or methyl group and the other is aryl group), the reactions also gave the corresponding products **3p–r** in good to high yields (Table 2, entries 15–17).

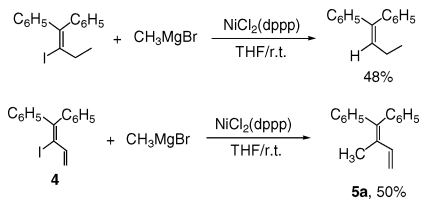
On the other hand, for our investigation on the Kumada-type cross-coupling reaction, we initially chose diiodide **1a** (0.25 mmol) and methylmagnesium bromide as the substrates using $NiCl_2$(dppp) (0.025 mmol) as the catalyst, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base[34] and Et_2O as the solvent. Preliminary studies showed that the reaction gave the product **5a** in 53% yield when a solution of **1a**, DBU and the solvent was stirred at room temperature in the presence of Na_2SO_4 for 8 h, then $NiCl_2$(dppp) and 3 equiv. of methylmagnesium bromide were added successively and the resulting mixtures were stirred for a further 8 h (Table 3, entry 1). Further studies showed that the addition sequence of the reactants, the base, and the amount of methylmagnesium bromide affected the reaction dramatically. When the steps described above were reversed, the reaction was disordered (low yielding) (Table 3, entry 2). When the reaction was carried out in a one-pot procedure in the presence of the base, the coupling product **5a** was obtained in 31% yield (Table 3, entry 3). These results suggest that in order to get a higher yield of **5a**, the elimination of the homoallylic iodide by DBU is essential before Kumada-coupling reaction takes place, *i.e.* only the Kumada-type coupling reaction of **4** with methylmagnesium bromide proceeds efficiently. This is the difference between Suzuki–Miyaura type cross-coupling reaction and Kumada-type cross-coupling reaction in the transformation of diiodides **1**. The control experiments shown in Scheme 1 disclosed that the reaction of 2-iodo-1,1-diphenyl-buta-1-ene with methylmagnesium bromide gave the product 1,1-diphenyl-buta-1-ene in 48% yield rather than the desired coupling product and the reaction of **4** with methylmagnesium bromide gave the desired product **5a** in 50% yield.[35] We believe that the buta-1,3-diene derivative **4** may act as a promoter in the subsequent Kumada-type coupling reaction.[36] Another strong evidence for this speculation is that

Table 3 The optimization of the Kumada-type cross-coupling reaction



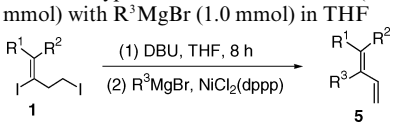
Entry	CH_3MgBr [equiv.]	Solvent	Yield (%)[a] **5a**
1	3	Et_2O	53
2[b]	3	Et_2O	disordered
3[c]	3	Et_2O	31
4[d]	3	Et_2O	disordered
5	4	Et_2O	99
6	4	THF	99
7	4	CH_3CN	87
8	4	DCE	71

[a] Isolated yields. [b] The two steps were reversed. [c] The reaction was carried out in a one-pot procedure. [d] The reaction was carried out in a one-pot procedure in the absence of DBU.



Scheme 1 Control experiments on the reaction of 2-iodo-1, 1-diphenyl-but-1-ene and 2-iodo-1, 1-diphenyl-buta-1,3-diene with methylmagnesium bromide (3.0 equiv.).

Table 4 The Kumada-type reaction of diiodides **1** (0.25 mmol) with R^3MgBr (1.0 mmol) with R^3MgBr (1.0 mmol) in THF



1 **5**

Entry	Diiodides **1** (R^1/R^2)	R^3	Yield (%)[a] **5**
1	**1c** (*p*-MeC_6H_4/*p*-MeC_6H_4)	Me	**5b**, 82
2	**1d** (*p*-$C1C_6H_4$/*p*-ClC_6H_4)	Me	**5c**, 67
3	**1h** (*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$)	Me	**5d**, 81
4	**1a** (C_6H_5/C_6H_5)	Et	**5e**, 68
5	**1c**	Et	**5f**, 78
6	**1h**	Et	**5g**, 80
7	**1e** (C_6H_5/H)[b]	Me	**5h**, 82(1 : 1)[c]
8	**1f** (Me/*p*-$EtOC_6H_4$/H)[b]	Me	**5i**, 61
9	**1g** (*p*-$CH_3OC_6H_4$/H)[b]	Me	**5j**, 67(1 : 1)[c]
10	**1a** (C_6H_5/C_6H_5)	*p*-$MeSC_6H_4$	**5k**, 61
11	**1c**	*p*-$MeSC_6H_4$	**5l**, 56
12	**1d**	*p*-$MeSC_6H_4$	**5m**, 47

[a] Isolated yields. [b] **1e** and **1g** were used as *Z*-isomer (Supporting Information†).[33] [c] The ratio of *E*- and *Z*-isomers (Supporting Information†). [d] **1f** was used as *E*-isomer (Supporting Information†).

when no base was used, the reaction was disordered (low yielding) (Table 3, entry 4). In the presence of DBU (1.0 equiv), a nearly quantitative yield of **5a** was obtained when 4 equiv. of methylmagnesium bromide was used (Table 3, entry 5). Further screening of the solvent showed that a variety of solvents such as THF, CH_3CN, and 1,2-dichloroethane (DCE) were also suitable for this coupling reaction (Table 3, entries 6–8). The best solvents are Et_2O and THF. Considering the volatility of Et_2O at room temperature, THF was chosen as the solvent for the following reactions.

To extend the present reaction, a wide array of diiodides **1** was allowed to react with alkyl/aryl magnesium bromide under the optimized conditions as in entry 6 in Table 3. The results are elucidated in Table 4. For the diaryl substituted diiodides **1**, the coupling reactions with methyl and ethyl magnesium bromides gave the multisubstituted buta-1,3-dienes **5** in good to high yields (Table 4, entries 1–6, 10–12). For the unsymmetrical disubstituted diiodides **1** (one is hydrogen or methyl and the other is aryl), the reactions also gave the corresponding products **5h–5j** in good yields (Table 4, entries 7–9). The structures of **5** were also determined by their ^1H NMR and ^{13}C NMR spectroscopic data. It should be noted that for the coupling reactions between diaryl substituted diiodides **1** with *p*-thioanisole magnesium bromide, the corresponding products **5k–m** have the formal structure of COX-2, which is a novel class of triaryl olefins that may provide a clinically acceptable anti-inflammatory-analgesic agent that is non-ulcerogenic and may also exhibit anticancer activity (Fig. 1).[37]

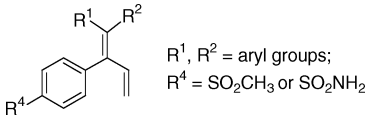


Fig. 1 Cyclooxygenase-2-type (COX-2-type) inhibitors.

In summary, we have developed a versatile direct synthesis of some multisubstituted buta-1,3-dienes *via* a Suzuki–Miyaura-type reaction and a Kumada-type reaction under simple and mild reaction conditions with no special ligands between 1,1-disubstituted 2,4-diiodo-buta-1-enes with arylboronic acids and Grignard reagents, respectively. Some of the products such as the Tamoxifen-type and COX-2-type mimics, which may also show biological activities, have been easily synthesized. Efforts are in progress to detect the potential application of the products obtained and the results will be reported in due course.

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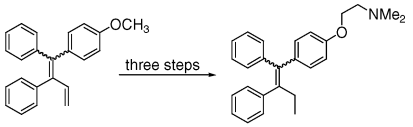


(*E*,*Z*)-**3f** (*E*,*Z*)-*Tamoxifen*

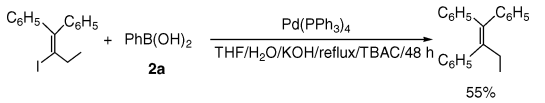
Reagents and conditions:
(a) H_2O_2, N_2H_4-H_2O, -60 °C, then r.t., 5 h.
(b) BBr_3, CH_2Cl_2, -60 °C, then r.t., 5 h.
(c) EtONa, $Me_2NCH_2CH_2Cl$·HCl, EtOH, reflux, 24 h.

32 Though it is of great interest that the *E*-isomer of Tamoxifen shows contrasting biological properties concerning estradiol receptor affinity, uterotrophic and antiuterotrophic activity, and mammary tumor inhibiting effects, many papers are reported for the synthesis of (*E*,*Z*)-isomers of its mimics and many of which also show special biological activities. For some related papers, see: (*a*) M. R. Schneider, E. V. Angerer, H. Schönenberger, R. T. Michel and H. P. Fortmeyer, *J. Med. Chem.*, 1982, **25**, 1070–1077; (*b*) A. B. Foster, M. Jarman, O.-T. Leung, R. McCague, G. Leclercq and N. Derleeschouwer, *J. Med. Chem.*, 1985, **28**, 1491–1497; (*c*) M. J. Meegan, R. B. Hughes, D. G. Lloyd, D. C. Williams and D. M. Zisterer, *J. Med. Chem.*, 2001, **44**, 1072–1084; (*d*) D. W. Robertson and J. A. Katzenellenbogen, *J. Org. Chem.*, 1982, **47**, 2387–2393; (*e*) G. A. Potter and R. McCague, *J. Org. Chem.*, 1990, **55**, 6184–6187; (*f*) S. Gauthier, J. Mailhot and F. Labrie, *J. Org. Chem.*, 1996, **61**, 3890–3893.

33 Note: Substrates **1e** and **1g** were also obtained by the ring-opening reaction of the corresponding MCPs with I_2 as described in Ref. 19. We found that the *E* : *Z*-selectivities were significantly affected by the solvent and the concentration of the ring-opening reaction. For example, for substrate **1g**, when the reaction was carried out in 1,2-dichloroethane (DCE) (2.0 mL) with equal molar amounts of the corresponding MCP (8 mmol) and I_2 (8 mmol), no desired product was obtained. When the above reaction was carried out in THF (3.0 mL), **1g** was obtained as a mixture of *E*- and *Z*-isomers in a ratio of 1 : 1. When the amount of THF was increased to 80 mL, **1g** was also obtained as a mixture of *E*- and *Z*-isomers in a ratio of 5 : 1. The best result was obtained when THF was increased to 120 mL for the above reaction and the *Z*-isomer of **1g** was obtained in 67% yield as a sole product.

34 DBU was a suitable base for the elimination of the homoallylic iodide at room temperature.

35 The reaction of 2-iodo-1,1-diphenylbut-1-ene with phenylboronic acid **2a** took place smoothly in the optimized conditions to give the coupling product 1,1,2-triphenylbut-1-ene in 55% yield.



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