Cross-Coupling Reactions

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Straightforward Synthesis of CF_3-Substituted Triarylethenes by Stereoselective Threefold Cross-Coupling Reactions**

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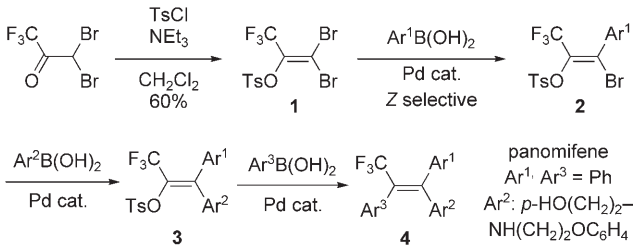
The incorporation of fluorine atoms into organic molecules has been a powerful strategy for the improvement of parent compounds in the fields of pharmaceuticals, agrochemicals, and organic materials.[1] The preparation of panomifene[2] is an example of the application of the strategy to triarylethenes, which constitute an important class of nonsteroidal antiestrogens.[3] Although a few stereoselective syntheses of CF_3-substituted triarylethenes are known, the availability of the CF_3-containing starting substrates and/or the use of organolithium or organomagnesium reagents limit their scope and versatility.[4] We report herein that the threefold cross-coupling reaction of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene (**1**)[5] with three kinds of aryl boronic acids provides a simple and straightforward approach to the synthesis of CF_3-substituted triarylethenes **4** (Scheme 1). The presence of a



Scheme 1. Approach for the synthesis of CF_3-substituted triarylethenes **4**. Ts = toluene-4-sulfonyl.

CF_3 group is essential for both high chemical yields and high *Z* selectivity in the first coupling reaction. This approach is highly versatile, since any stereoisomers of **4** can be arbitrarily synthesized in a stereochemically pure form simply by changing the order of the coupling partners, and, furthermore, a one-pot synthesis can also be achieved.

The twofold cross-coupling reaction of 1,1-dihalo-1-alkenes ($RHC{=}CX_2$) with organometallic compounds constitutes an efficient method for the stereoselective synthesis of trisubstituted alkenes.[6] Meanwhile, the threefold cross-coupling reaction of $R(X^2)C{=}C(X^1)_2$ (X^1, X^2 = (pseudo)halogens) leading to unsymmetrical tetrasubstituted alkenes has no precedent, presumably because of the difficulty in discriminating between the three leaving groups (X^1 and X^2) in the first coupling reaction.[7] However, we anticipated that the steric and/or electronic nature of a CF_3 group might overcome this difficulty.[8] Thus, we studied the palladium-catalyzed reaction of **1** with an equimolar amount of $PhB(OH)_2$ to prove the viability of the approach.[9] Initial experiments disclosed that both the stereoselectivity of **2** and the production of dicoupled and side products were critical issues to be solved.[5] After extensive optimization, we found that monocoupled product **2a** could be isolated in 94% yield with high diastereoselectivity (92:8) when the reaction was conducted in the presence of $[PdCl_2(PPh_3)_2]$ (5 mol%), P(*m*-tolyl)$_3$ (5 mol%), and 5 M aqueous Cs_2CO_3 in toluene at 80°C (Table 1, entry 1). The stereochemistry of the major product

Table 1: Coupling reaction of **1** with $Ar^1B(OH)_2$.[a]

Entry	Ar^1	**2**	Yield [%][b]	*Z*/*E*[c]
1	C_6H_5	**2a**	94	92:8
2	*p*-$MeOC_6H_4$	**2b**	74	90:10
3	*p*-MeC_6H_4	**2c**	73	89:11
4	*p*-$CF_3C_6H_4$	**2d**	89	87:13
5	*p*-BrC_6H_4	**2e**	85	88:12
6	*p*-PhC_6H_4	**2f**	96	88:12
7	2-naphthyl	**2g**	78	89:11
8	*m*-FC_6H_4	**2h**	87	89:11
9[d]	3-thienyl	**2i**	80	90:10

[a] Reaction conditions: **2** (0.50 mmol), $Ar^1B(OH)_2$ (0.55 mmol), $[PdCl_2(PPh_3)_2]$ (25 μmol), P(*m*-tolyl)$_3$ (25 μmol), 5 M aq Cs_2CO_3 (1.0 mmol), toluene (5 mL), 80°C, 24 h. [b] Yield of isolated product. [c] The *Z*/*E* ratio was determined by ^{19}F NMR spectroscopic analysis of the crude products. [d] (3-Thienyl)$B(OH)_2$ (0.75 mmol) and 5 M aq K_3PO_4 (1.0 mmol) as a base were used.

was unambiguously confirmed as *Z* by single-crystal X-ray analysis,[5] which indicated that a bromine atom *cis* to the CF_3 group was selectively substituted by a Ph group. Considering that the steric parameters (*A* values) of CF_3 and OTs groups are 2.4–2.5 and 0.5 kcal mol^{-1}, respectively,[10] it should be noted that the coupling, in other words, an oxidative addition of **1** to a Pd center, occurs at the more hindered site. The optimized conditions were applicable to various aryl boronic acids, thus giving rise to **2b–i** in good to excellent yields (Table 1, entries 2–9). In the case of thienylboronic acid, the use of aqueous K_3PO_4 in place of aqueous Cs_2CO_3 resulted in

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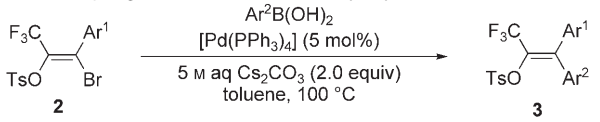
a better yield of **2i** (Table 1, entry 9). The *Z*/*E* selectivity ranged from 87:13 to 92:8, and in all cases the *E* and *Z* isomers of **2** could be easily separated by column chromatography on silica gel or by recrystallization from hexane.

With stereochemically pure **2** in hand, we carried out the second coupling reaction with $Ar^2B(OH)_2$ by using [Pd(PPh_3)$_4$] (5 mol%) and aqueous Cs_2CO_3 (2.0 equiv) in toluene. The coupling reaction proceeded chemoselectively with the remaining bromine atom rather than the tosyloxy group at 100 °C to give rise to **3** as a single diastereomer in good to excellent yields (Table 2).

Table 2: Coupling reaction of **2** with $Ar^2B(OH)_2$.[a]



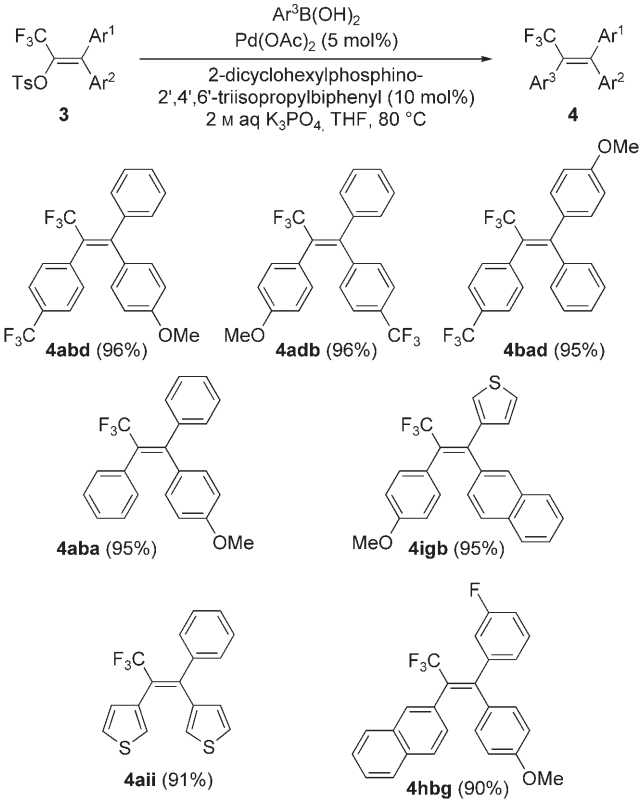
Entry	**2**	Ar^1	Ar^2	**3**	Yield [%][b]
1	**2a**	C_6H_5	C_6H_5	**3aa**	97
2	**2a**	C_6H_5	*p*-$MeOC_6H_4$	**3ab**	88
3	**2a**	C_6H_5	*p*-$CF_3C_6H_4$	**3ad**	83
4[c]	**2a**	C_6H_5	3-thienyl	**3ai**	60
5	**2b**	*p*-$MeOC_6H_4$	C_6H_5	**3ba**	82
6	**2b**	*p*-$MeOC_6H_4$	*p*-$CF_3C_6H_4$	**3bd**	70
7	**2d**	*p*-$CF_3C_6H_4$	C_6H_5	**3da**	97
8	**2h**	*m*-FC_6H_4	*p*-$MeOC_6H_4$	**3hb**	90
9	**2i**	3-thienyl	2-naphthyl	**3ig**	88

[a] Reaction conditions: **2** (0.20 mmol), $Ar^2B(OH)_2$ (0.24 mmol), [Pd(PPh_3)$_4$] (10 μmol), 5 M aq Cs_2CO_3 (0.40 mmol), toluene (2 mL), 100 °C, 24 h. [b] Yield of isolated product. [c] (3-Thienyl)$B(OH)_2$ (0.40 mmol) and 5 M aq K_3PO_4 (1.0 mmol) as a base were used.

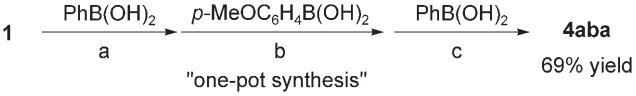
The final coupling of **3** with $Ar^3B(OH)_2$ to give **4** was accomplished by applying the conditions developed by Buchwald and co-workers.[11] We succeeded in isolating diverse compounds **4** as single stereoisomers in high to excellent yields (Scheme 2). Since it has been reported that **4aba** can be converted into panomifene,[4c] its preparation is equivalent to the formal synthesis of panomifene. The striking versatility of the present strategy is that both the *E* and *Z* isomers as well as any olefinic constitutional isomers of **4** can be synthesized at will simply by changing the order of the three aryl boronic acids employed, as demonstrated by the preparation of **4abd**, **4adb**, and **4bad**.

Another advantage of the designed sequence is the feasibility of a one-pot synthesis. Thus, panomifene precursor **4aba** was obtained from **1** in 69% yield without isolation of **2a** or **3ab**, although the conditions have not been optimized (Scheme 3).

To gain insight into the effect of the CF_3 group on the first coupling reaction we carried out the reaction of **5a–c** with $PhB(OH)_2$ under the optimum conditions (Table 3). The reaction of non-fluorinated dibromoalkene **5a** resulted in a lower yield of the isolated product and a lower *Z*/*E* selectivity of the monocoupled product **6a** (Table 3, entry 1). Ethoxycarbonyl-substituted ethene **5b** gave **6b** in moderate yield together with fair amounts of the dicoupled product **7b** and acetylene **8** as by-products (Table 3, entry 2). In the case of **5c**, diphenylated ethene **7c** was formed as the major product (Table 3, entry 3). Thus, these results indicate the high *Z* selectivity of **2** can be attributed to the presence of a CF_3 group, while both the CF_3 and tosyloxy groups are indispensable for suppressing the second coupling reaction. While elucidation of the origin of the stereochemical outcome

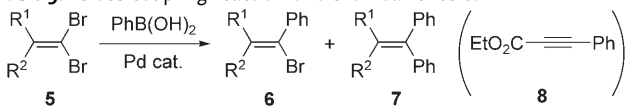


Scheme 2. Synthesis of CF_3-substituted triarylethenes **4**.



Scheme 3. Reagents and conditions: a) [$PdCl_2$(PPh_3)$_2$] (5 mol%), P(*m*-tolyl)$_3$ (5 mol%), 5 M aq Cs_2CO_3, toluene, 80 °C, 24 h; b) 5 M aq Cs_2CO_3, 100 °C, 24 h; c) $Pd(OAc)_2$ (5 mol%), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (10 mol%), 2 M aq K_3PO_4, 80 °C, 12 h.

Table 3: Cross-coupling reaction of dibromoalkenes **5**.[a]



Entry	**5**	R^1	R^2	**6** (*Z*/*E*)[b]	**7**[b]	**8**[b]
1	**5a**	CH_3	OTs	70 (68:32)	0	–
2	**5b**	EtO_2C	OTs	57 (96:4)	16	21
3[c]	**5c**	CF_3	$(CH_2)_2Ph$	15 (81:19)	47	–

[a] Reaction conditions: **5** (1.0 equiv), $PhB(OH)_2$ (1.1 equiv), [$PdCl_2$(PPh_3)$_2$] (5 mol%), P(*m*-tolyl)$_3$ (5 mol%), 5 M aq Cs_2CO_3, toluene, 80 °C, 24 h. [b] Yield of isolated product. [c] **5c** was recovered in 31% yield.

awaits further study, a Pd···F interaction in the oxidative addition step may be operative.[12]

In summary, we have developed a straightforward stereocontrolled synthesis of CF_3-substituted triarylethenes. Further study of the coupling reactions of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene with other kinds of nucleophiles is in progress.

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